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Synthesis of 2-Arylbenzo[*b*]furans via Copper(I)-Catalyzed Coupling of *o*-Iodophenols and Aryl Acetylenes

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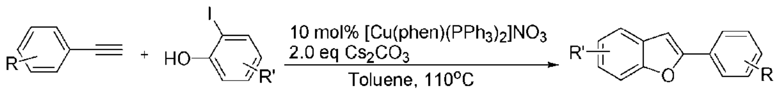
ABSTRACT



We report a copper(I)-catalyzed procedure for the synthesis of 2-arylbenzo[*b*]furans. This protocol can be used to synthesize a variety of 2-arylbenzo[*b*]furans in good to excellent yields. This method can tolerate a variety of functional groups, does not require the use of expensive additives, and is palladium-free.

Benzo[*b*]furans are prevalent in many compounds and natural products that have important biological properties.[1] These include: antitumor properties,[2] inhibition of protein phosphatase 1B,[3] 5-HT$_2$ and 5-HT$_3$ antagonist activity,[4] inhibition of 5-Lipoxygenase (5-LO),[4b] and anti-fungal properties.[5] Pharmaceutically, these properties are relevant in the treatment for cancer, cardiovascular disease, type 2 diabetes, migraines, dementia, and anxiety.[2,4b]

The current methods for the synthesis of benzo[*b*]furans include the dehydrative cyclization of α-(phenoxy)alkyl ketones, cyclofragmentation of oxiranes, acidic dehydration of *o*-hydroxybenzyl ketones, and base-mediated decarboxylation of *o*-acylphenoxyacetic acids and esters.[6] These traditional methods are often multistep reactions, limited to a particular substrate, and do not tolerate a variety of functional groups. More recently, palladium-based cross-coupling reactions with copper iodide as a cocatalyst have been developed for the synthesis of benzofurans.[7] This is accomplished through a tandem Sonagashira coupling/5-*endo-dig* cyclization starting from either *o*-iodophenols or *o*-ethynylphenols. In comparison to the traditional methods, these palladium-based protocols offer increased functional group tolerance and improved yields of the desired benzofuran.

In recent years, the DV group,[8] Buchwald group,[9] and others[10] have been interested in developing copper-catalyzed cross-coupling reactions. In contrast to the traditional Ullmann coupling, these methods are mild and tolerate a wide

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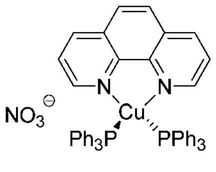
range of functional groups. When compared to noble-metal catalysts, copper-based methods have an economic attractiveness and hence remain the reactions of choice in large and industrial scale reactions. We report here a palladium-free synthesis of 2-arylbenzo[*b*]furans via a copper(I)-catalyzed coupling reaction of *o*-iodophenols and aryl acetylenes using $[Cu(phen)(PPh_3)_2]NO_3$ (**1**) as the catalyst and Cs_2CO_3 as base in toluene.[11]



(**1**)

We have previously shown that $[Cu(phen)(PPh_3)Br]$ can be used as a catalyst for the coupling of phenylacetylene and iodobenzene using K_2CO_3 as the base in toluene.[8c] To study the mechanistic aspects of this reaction, we prepared a variety of copper(I) complexes bearing bidentate nitrogen-based ligands and monitored the formation of diphenylacetylene over time (Figure 1). We discovered that the most active catalyst was $[Cu(phen)(PPh_3)_2]NO_3$ (○ in Figure 1). $[Cu(phen)(PPh_3)Br]$ (●) was slightly less effective and the use of $[Cu(PPh_3)_3Br]$ (▼) resulted in only 40% conversion to the desired product in 24 h. Surprisingly, complexes such as $[Cu(neocup)(PPh_3)Br]$ (▽) (neocup = 2,9-dimethyl-1,10-phenanthroline) and $[Cu(bipy)(PPh_3)Br]$ (■) (bipy = 2,2′-bipyridine) were found to be much less effective at catalyzing this reaction. From Figure 1, it can also be seen that the use of CuI (10 mol %) with 10 mol % of 1,10-phenanthroline (□) as an additive was least effective. On the basis of these findings we chose to use $[Cu(phen)(PPh_3)_2]NO_3$ as the catalyst for the coupling of *o*-iodophenols and aryl acetylenes to synthesize 2-arylbenzo[*b*]furans.

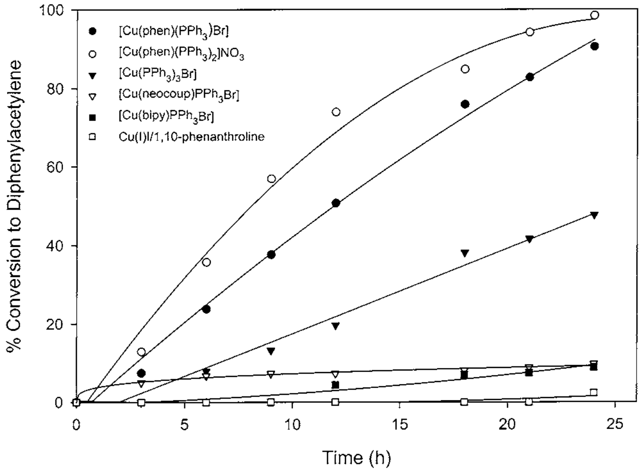
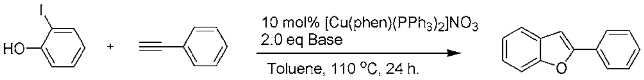


Figure 1. A graph depicting the percent conversion of diphenylacetylene (monitored by GC) from iodobenzene and phenylacetylene using various copper(I) complexes as a catalyst. Reaction conditions: 1.00 mmol of phenylacetylene, 1.00 mmol of iodobenzene, 10 mol % of Cu complex, 2.0 equiv of K_2CO_3, in toluene at 110 °C under Ar atmosphere. Note: Lines are drawn for visual connectivity of the collected data points.

We then screened various bases using *o*-iodophenol and phenylacetylene as the reactants and **1** as the catalyst in toluene (Table 1). We found that Cs_2CO_3 was the most effective base. Other bases such as K_3PO_4, K_2CO_3, NaO*t*-Bu, and KO*t*-Bu were less effective and Et_3N was ineffective.

Table 1. Base Effects on the Copper(I)-Catalyzed Synthesis of 2-Arylbenzo[*b*]furans



base	% conversion (by GC)
Cs_2CO_3	>95
K_3PO_4	67
K_2CO_3	53
KO*t*-Bu	40
NaO*t*-Bu	29
Et_3N	0

Through control experiments we found that CuI, CuBr, or CuCl could not effectively catalyze the reaction and the conversion to 2-phenylbenzo[*b*]furan was 10%, 10%, and 20%, respectively. Finally, 2-phenylbenzo[*b*]furan was not observed by GC when the reaction was run in either the absence of Cs_2CO_3 or **1**. On the basis of these control experiments, we decided to use **1** as the catalyst and Cs_2CO_3 as the base in toluene as the standard protocol to synthesize 2-arylbenzo[*b*]furans from *o*-iodophenols and aryl acetylenes.

Using our protocol, we were able to couple *o*-iodophenol with electron-rich and electron-poor aryl acetylenes in good

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(9) (a) Marcoux, J. F.; Doye, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 10539−10540. (b) Kiyomori, A.; Marcoux, J. F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657−2660. (c) Klapars, A.; Antilla, J. C.; Huang, X. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727−7729. (d) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803−3805. (e) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581−584. (f) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973−976. (g) Hennessy, E. J.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 269−272.

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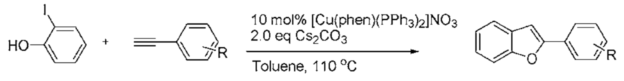
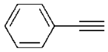
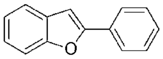
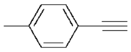
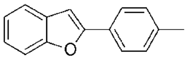
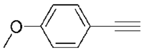
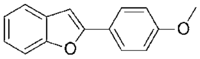
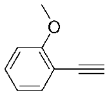
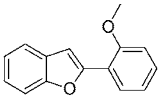
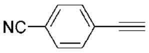
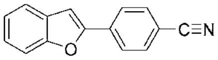
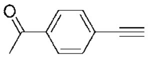
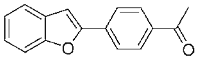
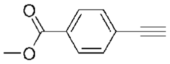
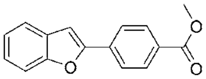
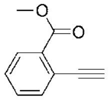
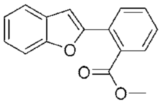
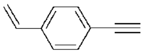
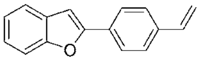
(11) The use of copper has previously been shown to mediate the synthesis of benzofurans. Castro and co-workers synthesized 2-phenylbenzo-[*b*]furan through the coupling reaction of cuprous phenylacetylene and *o*-iodophenol.[a] This procedure, however, requires the use of a stoichiometric amount of the preformed cuprous acetylide and refluxing pyridine. Owen and co-workers[b] modified Castro's procedure using cuprous oxide (63 mol %) and various acetylenes, but this procedure still requires the use of refluxing pyridine and the amount of copper required is still high. The scope and potential of these reactions have not been fully explored: (a) Castro, C. E.; Gauchan, E. J.; Owsley, D. C. *J. Org. Chem.* **1966**, *31*, 4071−4078. (b) Doad, G. J. S.; Barltrop, J. A.; Petty, C. M.; Owen, T. C. *Tetrahedron Lett.* **1989**, *30*, 1597−1598.

Table 2. Synthesis of 2-Arylbenzo[*b*]furans via Copper(I)-Catalyzed Coupling of *o*-Iodophenol and Various Aryl Acetylenes[a]

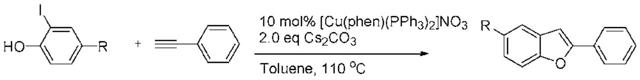


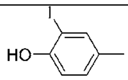
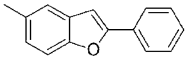
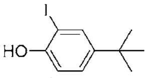
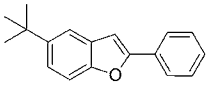
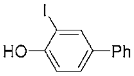
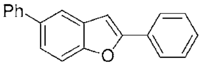
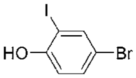
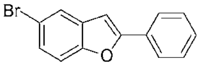
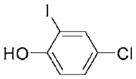
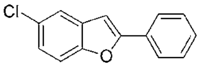
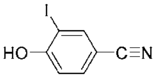
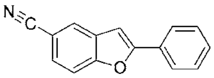
entry	aryl acetylene	product	isolated yield (%)
1			92
2			64
3			62
4			77[b]
5			77
6			69
7			67
8			91
9			68

[a] Reaction conditions: 2.00 mmol of *o*-iodophenol, 2.00 mmol of phenylacetylene, 5.0 mL of toluene, 24 h. [b] Reaction time of 48 h.

to excellent yields (Table 2). Base-sensitive functional groups such as methyl ketones (entry 6, Table 2) and methyl esters (entry 7, Table 2) were tolerated by this protocol. Ortho-substituted aryl acetylenes could also be coupled to *o*-iodophenol in good yields (entries 4 and 8, Table 2). Aryl acetylenes bearing an alkene as a substitutent could also be successfully coupled in good yields with no observed Heck-like coupling; the Heck reaction may be observed if a palladium-based system is used (entry 9, Table 2). Furthermore, we successfully coupled a variety of 4-substituted-*o*-iodophenols with phenylacetylene in good to excellent yields (Table 3). The potential for further functionalization of the benzo[*b*]furan skeleton is made possible by the incorporation of a terminal alkene, bromine, and chlorine groups (entry 9, Table 2 and entries 4 and 5, Table 3, respectively). Our observed yields are comparable to and in some cases better than the yields reported using palladium-catalyzed reactions.[7a,c]

Table 3. Synthesis of 2-Arylbenzo[*b*]furans via Copper(I)-Catalyzed Coupling of Phenylacetylene and Various 4-Substituted-*o*-iodophenols[a]



entry	*o*-iodophenol[b]	product	isolated yield (%)
1			85
2			80
3			79
4			86
5			90
6			96

[a] Reaction conditions: 2.00 mmol of *o*-iodophenol, 2.00 mmol of phenylacetylene, 5.0 mL of toluene, 24 h. [b] 4-Substituted-*o*-iodophenols were synthesized from readily available phenols following the method reported by Edgar and Falling: Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287−5291. See Supporting Information for details.

In summary, we have reported a synthetic protocol for 2-arylbenzo[*b*]furans from *o*-iodophenols and aryl acetylenes using a well-defined copper(I) catalyst. Our protocol tolerates a wide range of functional groups that can be used to further functionalize the benzo[*b*]furan ring. This synthetic route is palladium-free and avoids the use of expensive and/or air-sensitive additives.

Acknowledgment. The University of Massachusetts, Amherst start-up funds provided the financial support for this research. D.V. gratefully acknowledges a Camille and Henry Dreyfus New Faculty Award and an NSF CAREER Award (CHE-0134287). P.S. thanks the Royal Thai Government for financial support. J.M. thanks Bristol-Myers Squibb for an undergraduate fellowship.

Supporting Information Available: Synthetic procedures and crystallographic information files (CIF) for **1** and synthetic procedures and complete characterization data for entries in Tables 2 and 3. This material is available free of charge via the Internet at http://pubs.acs.org.

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