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Synthesis of 2-(Polyfluoroaryl)benzofurans via a Copper(I)-Catalyzed Reaction of 2-(2,2-Dibromovinyl)phenol with Polyfluoroarene

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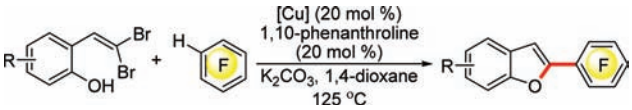
ABSTRACT



A novel and efficient route for the synthesis of 2-(polyfluoroaryl)benzofurans via a copper(I)-catalyzed tandem reaction of 2-(2,2-dibromovinyl)phenol with polyfluoroarene is reported. The corresponding products are generated in good yields. During the reaction process, a copper-catalyzed intramolecular C–O bond formation and a C–H activation are involved.

As a prominent structural motif, compounds with a polyfluorinated aromatic structure have found applications in medicinal chemistry[1] and material science.[2] For example, molecules containing the polyfluoroarene structure serve as active materials in electronic devices, such as organic light-emitting diodes and field-effect transistors.[2] As a privileged scaffold, the benzofuran core structure is found in a wide variety of natural products[3] and biologically important molecules.[4] Additionally, its application in

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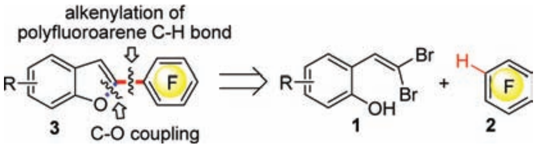
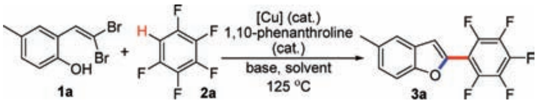
material science has been demonstrated.[5] In our laboratory, we have been interested in the synthesis of natural product-like compounds with privileged scaffolds.[6] Prompted by the importance of polyfluorinated compounds and benzofurans, we envisioned that the benzofuran-incorporated polyfluorinated compounds would be beneficial for various biological assays. Thus, we initiated a program for method development and library construction of 2-(polyfluoroaryl)benzofurans.

Scheme 1. Proposed Route for the Transition-Metal-Catalyzed Reaction of 2-(2,2-Dibromovinyl)phenol **1** with Polyfluoroarene **2**



Recently, the synthesis of polyfluorinated aromatic compounds using a C−H activation strategy[7] has attracted much attention.[8,9] In the meantime, *gem*-dihaloolefins have served as a versatile building block in organic synthesis with good stereoselectivity.[10−12] We also used *gem*-dibromoolefins as substrates for the synthesis of indene derivatives.[11k−m] Encouraged by these results, we conceived that 2-(polyfluoroaryl)benzofurans could be prepared via a transition-metal-catalyzed reaction of 2-(2,2-dibromovinyl)phenol[12l] with polyfluoroarene (Scheme 1). Therefore, we started to explore the possibility of this transformation.

Table 1. Initial Studies for the Copper(I)-Catalyzed Reaction of 2-(2,2-Dibromovinyl)phenol **1a** with Polyfluoroarene **2a**



entry	[Cu] (mol %)	base	solvent	yield (%)[a]
1	CuI (10)	K_3PO_4	1,4-dioxane	40
2[b]	CuI (20)	K_3PO_4	1,4-dioxane	NR
3	CuI (10)	K_3PO_4	DMF	NR
4	CuI (10)	K_3PO_4	DMPU	NR
5	CuI (10)	K_3PO_4	xylene	trace
6[c]	CuI (10)	K_3PO_4	1,4-dioxane	38
7[d]	CuI (20)	K_3PO_4	1,4-dioxane	57
8[e]	CuI (10)	K_3PO_4	1,4-dioxane	52
9[d,e]	CuI (20)	K_3PO_4	1,4-dioxane	72
10[d,e]	CuBr (20)	K_3PO_4	1,4-dioxane	38
11[d,e]	CuCl (20)	K_3PO_4	1,4-dioxane	27
12[d,e]	CuI (20)	Cs_2CO_3	1,4-dioxane	74
13[d,e]	CuI (20)	K_2CO_3	1,4-dioxane	94
14	CuI (20)	Ag_2CO_3	1,4-dioxane	NR

[a] Isolated yield based on 2-(2,2-dibromovinyl)phenol **1a**. [b] Without the addition of 1,10-phenanthroline. [c] In the presence of 4.0 equiv of K_3PO_4. [d] In the presence of 20 mol % of 1,10-phenanthroline. [e] Using 4.0 equiv of pentafluorobenzene **2a**.

Since a copper(I) catalyst showed high efficiency in the C−O coupling reaction[13] as well as in the arylation and alkenylation of polyfluoroarene C−H bonds,[8c,d] at the

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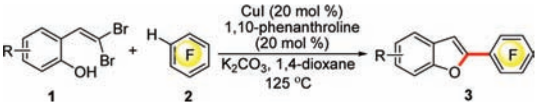
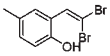
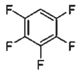
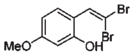
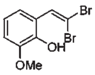
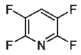
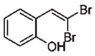
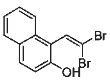
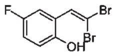
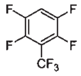
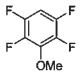
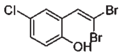
outset we selected copper(I) salts as the catalysts for reaction development. 2-(2,2-Dibromovinyl)phenol **1a** and pentafluorobenzene **2a** were chosen as the model substrates (Table 1). In an initial attempt, the reaction was catalyzed by copper(I) iodide (10 mol %) and 1,10-phenanthroline (10 mol %) in the presence of K_3PO_4 (3.0 equiv) as the base in 1,4-dioxane at 125 °C (Table 1, entry 1). To our delight, the expected 2-(polyfluoroaryl) benzofuran **3a** was formed and isolated in 40% yield. No reaction occurred without the addition of 1,10-phenanthroline in a control experiment (Table 1, entry 2). The reaction could not proceed when the reaction was performed in DMF or DMPU (Table 1, entries 3 and 4). A trace amount of product was detected when the solvent was replaced by xylene (Table 1, entry 5). No better result was generated when the amount of base was increased (38% yield, Table 1, entry 6). The yield could be improved when 20 mol % of copper(I) iodide and 1,10-phenanthroline were employed in the reaction (57% yield, Table 1, entry 7). A similar outcome was observed when the amount of pentafluorobenzene **2a** was increased to 4.0 equiv (52% yield, Table 1, entry 8). Thus, an investigation was conducted for a combination of the above two conditions in the model reaction. As expected, the desired product **3a** was formed in 72% yield (Table 1, entry 9). The result was inferior when the catalyst was changed to copper(I) bromide or copper(I) chloride (Table 1, entries 10 and 11). Other bases were examined subsequently, which showed that K_2CO_3 was the best choice (94% yield, Table 1, entry 13).

With the optimized conditions in hand [CuI (10 mol %), 1,10-phenanthroline (20 mol %), K_2CO_3 (3.0 equiv), 1,4-dioxane, 125 °C], we then investigated the generality of this copper(I)-catalyzed tandem reaction of 2-(2,2-dibromovinyl)phenol **1** with polyfluoroarene **2**. The results are presented in Table 2. Usually, the solution turned black after the reaction was stirred overnight. Noticeably, 2-(2,2-dibromovinyl)phenols **1** with different substitutions on the aromatic ring were all compatible under the standard conditions. For instance, 2-(2,2-dibromovinyl)-5-methoxyphenol **1b** reacted with pentafluorobenzene **2a** leading to the corresponding product **3b** in 93% yield (Table 2, entry 2). An almost quantitative yield was obtained when 2-(2,2-dibromovinyl)-6-methoxyphenol **1c** was used as a substrate in the reaction of pentafluorobenzene **2a** (98% yield, Table 2, entry 3). 2,3,5,6-Tetrafluorobenzonitrile **2b** was a suitable partner as well, which afforded the desired product **3d** in 68% yield (Table 2, entry 4). Interestingly, reaction of 2-(2,2-dibromovinyl)-6-methoxyphenol **1c** with 2,3,5,6-tetrafluoropyridine **2c** worked well to furnish 2,3,5,6-tetrafluoro-4-(7-methoxybenzofuran-2-yl)pyridine **3e** in 92% yield (Table 2, entry 5). 1,2,4,5-Tetrafluoro-3-(trifluoromethyl)benzene **2d** or 1,2,4,5-tetrafluoro-3-methoxybenzene **2e** served as a reactant in the reaction of 2-(2,2-dibromovinyl)phenol **1f** (Table 2, entries 11 and 12). It seems that the reactivity is superior when trifluoromethyl-substituted polyfluoroarene **2d** was employed in the reaction.

Table 2. Synthesis of 2-(Polyfluoroaryl)benzofurans **3** via a Copper(I)-Catalyzed Reaction of 2-(2,2-Dibromovinyl)phenol **1** with Polyfluoroarene **2**



entry	substrate **1**	substrate **2**	product	yield (%)[a]
1	 **1a**	 **2a**	**3a**	94
2	 **1b**	**2a**	**3b**	93
3	 **1c**	**2a**	**3c**	98
4	**1c**	 **2b**	**3d**	68
5	**1c**	 **2c**	**3e**	92
6	 **1d**	**2a**	**3f**	98
7	 **1e**	**2a**	**3g**	98
8	 **1f**	**2a**	**3h**	90
9	**1f**	**2b**	**3i**	45
10	**1f**	**2c**	**3j**	80
11	**1f**	 **2d**	**3k**	81
12	**1f**	 **2e**	**3l**	46
13	 **1g**	**2a**	**3m**	92
14	**1g**	**2d**	**3n**	90
15	**1g**	**2e**	**3o**	55

[a] Isolated yield based on 2-(2,2-dibromovinyl)phenol **1**.

A similar result was observed when 2-(2,2-dibromovinyl) phenol **1g** was utilized in the reaction of polyfluoroarene **2d** or **2e** (Table 2, entries 14 and 15). Reaction of 2-(2,2-dibromovinyl)phenol **1d** with 1,2,4,5-tetrafluorobenzene **2f** was investigated subsequently (Scheme 2). It was not surprising that two products (compounds **3p** and **3q**) were isolated under the standard conditions. Although we do not have clear evidence to support the mechanism currently, we consider that the reaction may proceed through an initial cupration of polyfluoroarenes by copper(I) iodide,[14] followed by a cross-coupling reaction of the (*E*)-bromoethenyl moiety. Subsequently, the intramolecular copper(I)-catalyzed

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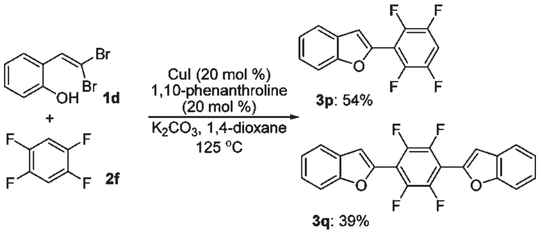
[14] Kanyiva, K. S.; Kashihara, N.; Nakao, Y.; Hiyama, T.; Ohashi, M.; Ogoshi, S. *Dalton Trans.* **2010**, *39*, 10483 and references cited therein.

C–O coupling[13] occurs to afford the benzofuran scaffold.

Scheme 2. Copper(I)-Catalyzed Reaction of 2-(2,2-Dibromovinyl)phenol **1d** with 1,2,4,5-Tetrafluorobenzene **2f**



In conclusion, we have described a novel and efficient route for the generation of 2-(polyfluoroaryl) benzofurans via a copper(I)-catalyzed tandem reaction of 2-(2,2-dibromovinyl)phenol with polyfluoroarene. During the reaction process, a copper-catalyzed intramolecular C–O bond formation and an alkenylation of the polyfluoroarene C–H bond were involved. Currently, using polyfluoroarene as a substrate for the formation of *N*-heterocycles is under investigation in our laboratory, and the results will be reported in due course.

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Supporting Information Available. Experimental procedure, characterization data, ^{1}H and ^{13}C NMR spectra of compounds **3**. This material is available free of charge via the Internet at http://pubs.acs.org.