

# A Concise Access to (Polyfluoroaryl)allenes by Cu-Catalyzed Direct Coupling with Propargyl Phosphates

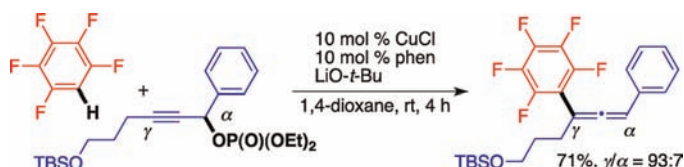
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## ABSTRACT



A copper-based catalyst system for the direct coupling of polyfluoroarenes with propargyl phosphates has been developed. The catalysis can provide a rapid and concise access to (polyfluoroaryl)allenes, which can be important building blocks for the synthesis of fluorinated functional materials.

Allenes are important building blocks in organic synthesis due to their high reactivity associated with two orthogonal  $\pi$ -bonds<sup>1</sup> and frequently occur in natural products and pharmaceuticals.<sup>2</sup> In particular, arene-conjugated allenes constitute an attractive structural class of compounds

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in the synthetic point of view. A metal-catalyzed S<sub>N</sub>2'-type substitution of propargylic electrophiles with arylmetal reagents is one of the most common and reliable approaches to allene functionalities.<sup>3</sup> A variety of catalyst systems based on Pd,<sup>4</sup> Rh,<sup>5</sup> and Cu<sup>6</sup> have been developed to enable aryl–allenyl coupling with organoboron, -magnesium, and -lithium. However, these precedents still suffer from the indispensable preactivation step, stoichiometric metalation, of arenes or halogenated arenes to prepare the starting organometallic compounds. Although the Lewis

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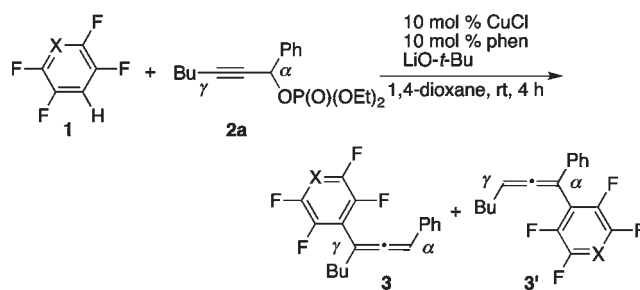
acid promoted Friedel–Crafts type reactions of arenes themselves with propargylic alcohol derivatives appear to be a good alternative, they are generally limited to electron-rich aromatics.<sup>7</sup> Thus, further developments of more efficient and rapid access to the arylallenes are quite appealing.

Meanwhile, recent advances in the metal-mediated C–H functionalization can provide a powerful protocol for the decoration of aromatics to make aryl–aryl, aryl–alkenyl, and aryl–alkyl C–C bonds directly.<sup>8</sup> Very recently, our group<sup>9</sup> and others<sup>10</sup> have succeeded in the copper- and palladium-catalyzed direct allylation of electron-deficient aromatics, polyfluoroarenes,<sup>11</sup> with allylic electrophiles. In the course of the above study, we envisaged that the allylation methodology could be extended to the direct propargylation. Herein, we report a copper-catalyzed direct allenylation of polyfluoroarenes with propargyl phosphates. The copper catalysis allows for a straightforward access to the (polyfluoroaryl)allenes of potentially useful building blocks for the synthesis of fluorinated functional molecules.<sup>12</sup>

On the basis of our previous work,<sup>9</sup> we initially selected pentafluorobenzene (**1a**) and propargyl phosphate **2a** as model substrates and investigated various reaction parameters such as copper salt, ligand, base, and solvent. Pleasingly, a combination of CuCl/phen catalyst (phen = 1,10-phenanthroline) and LiO-*t*-Bu, a similar catalyst system to which has been developed by Daugulis for the direct arylation of polyfluoroarenes,<sup>11b</sup> was observed to be effective for the coupling of **1a** with **2a** in 1,4-dioxane even at room temperature to afford a mixture of the corresponding  $\gamma$ - and  $\alpha$ -substituted allenes (**3aa** and **3aa'**) in a ratio of 92:8 with a good combined yield (Table 1, entry 1).

The formation of **3aa'** would follow from a base-mediated isomerization of the initially formed  $\alpha$ -substituted alkyne (vide infra). The choice of leaving group was critical: the corresponding propargyl acetate or carbonate gave neither **3aa** nor **3aa'**.<sup>13</sup> Tetrafluorobenzenes that bear electron-donating methyl and methoxy groups showed somewhat lower reactivity and  $\gamma/\alpha$  selectivity (entries 2 and 3). On the other hand, the introduction of trifluoromethyl substitution of electron-withdrawing nature furnished the corresponding allene with higher  $\gamma$ -selectivity (entry 4). A pyridine analogue **1e** could be employed without any difficulties (entry 5). In the case of 1,2,4,5-tetrafluorobenzene (**1f**) that possesses two equivalent reactive C–H bonds, the monoallenylation selectively occurred, albeit with moderate efficiency and regioselectivity (entry 6). The coupling with other fluoroarenes having less than four fluorine atoms completely failed (data not shown), indicating that the step of C–H bond cleavage highly depends on the acidity of C–H.<sup>14</sup>

**Table 1.** Copper-Catalyzed Direct Coupling of Polyfluoroarenes **1** with Propargyl Phosphate **2a** for the Synthesis of (Polyfluoroaryl)allenes<sup>a</sup>



entry	X <b>1</b>	<b>3</b> + <b>3'</b> , yield (%) <sup>b</sup>	<b>3/3'</b> ( $\gamma/\alpha$ ) <sup>c</sup>
1	X = CF <b>1a</b>	<b>3aa</b> + <b>3aa'</b> , 78	92:8
2 <sup>d</sup>	X = CMe <b>1b</b>	<b>3ba</b> + <b>3ba'</b> , 43	70:30
3 <sup>d</sup>	X = COMe <b>1c</b>	<b>3ca</b> + <b>3ca'</b> , 51	75:25
4	X = CCF <sub>3</sub> <b>1d</b>	<b>3da</b> + <b>3da'</b> , 59	98:2
5	X = N <b>1e</b>	<b>3ea</b> + <b>3ea'</b> , 62	99:1
6 <sup>d</sup>	X = CH <b>1f</b>	<b>3fa</b> + <b>3fa'</b> , 45	80:20

<sup>a</sup> Reaction conditions: CuCl (0.050 mmol), phen (0.050 mmol), LiO-*t*-Bu (1.50 mmol), **1** (0.50 mmol), **2a** (1.0 mmol), 1,4-dioxane (3.0 mL), rt, 4 h, N<sub>2</sub>. <sup>b</sup> Yield of isolated product as a mixture of **3** and **3'**. <sup>c</sup> Determined by <sup>1</sup>H NMR or GC. <sup>d</sup> With 30 mol % of CuCl/phen and 1.5 mmol of **2a** at 80 °C.

We next evaluated the scope of propargyl phosphates with pentafluorobenzene (**1a**) (Table 2). The copper catalysis accommodated various aromatic substituents at the  $\alpha$ -position in the propargylic phosphate: chloro-, methyl-, and methoxyphenyl groups were equally tolerated (entries 1–3). A polyfluoroarene/thiophene-conjugated allene was also readily available (entry 4). At the alkyne terminus, smaller methyl and functional primary alkyl groups

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containing chloride and silyl ether moieties were compatible (entries 5–7). In the above cases, a satisfying  $\gamma$ -selectivity was observed. However, the sterically demanding secondary and tertiary alkyl substituents decreased the  $\gamma/\alpha$  selectivity, although the reaction proceeded smoothly (entries 8 and 9). Particularly, the *tert*-butyl-substituted propargyl phosphate **2j** gave the  $\alpha$ -substituted allene **3aj'** as a major regioisomer.<sup>15</sup>

**Table 2.** Copper-Catalyzed Direct Coupling of Pentafluorobenzene (**1a**) with Various Propargyl Phosphates **2<sup>a</sup>**

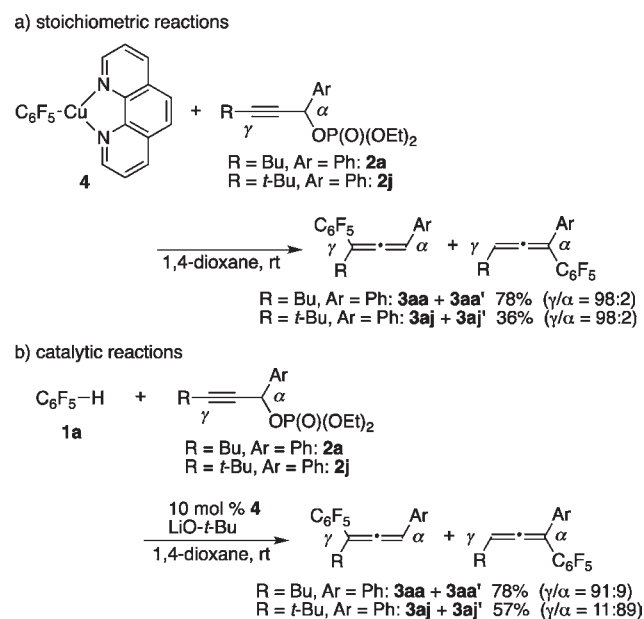
entry	R, Ar <b>2</b>	<b>3</b> + <b>3'</b> , yield (%) <sup>b</sup>	<b>3/3'</b> ( $\gamma/\alpha$ ) <sup>c</sup>
1	R = Bu, Ar = 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>2b</b> )	<b>3ab</b> + <b>3ab'</b> , 67	91:9
2	R = Bu, Ar = 4-MeC <sub>6</sub> H <sub>4</sub> ( <b>2c</b> )	<b>3ac</b> + <b>3ac'</b> , 79	93:7
3	R = Bu, Ar = 3-MeOC <sub>6</sub> H <sub>4</sub> ( <b>2d</b> )	<b>3ad</b> + <b>3ad'</b> , 69	95:5
4	R = Bu, Ar = 3-thienyl ( <b>2e</b> )	<b>3ae</b> + <b>3ae'</b> , 57	98:2
5	R = Me, Ar = Ph ( <b>2f</b> )	<b>3af</b> + <b>3af'</b> , 52	95:5
6	R = (CH <sub>2</sub> ) <sub>4</sub> Cl, Ar = Ph ( <b>2g</b> )	<b>3ag</b> + <b>3ag'</b> , 68	93:7
7	R = (CH <sub>2</sub> ) <sub>3</sub> OTBS, Ar = Ph ( <b>2h</b> )	<b>3ah</b> + <b>3ah'</b> , 71	93:7
8	R = cyclohexyl, Ar = Ph ( <b>2i</b> )	<b>3ai</b> + <b>3ai'</b> , 66	76:24
9	R = <i>t</i> -Bu, Ar = Ph ( <b>2j</b> )	<b>3aj</b> + <b>3aj'</b> , 55	12:88

<sup>a</sup> Reaction conditions: CuCl (0.050 mmol), phen (0.050 mmol), LiO-*t*-Bu (1.50 mmol), **1a** (0.50 mmol), **2** (1.0 mmol), 1,4-dioxane (3.0 mL), rt, 4 h, N<sub>2</sub>. <sup>b</sup> Yield of isolated product as a mixture of **3** and **3'**. <sup>c</sup> Determined by <sup>1</sup>H NMR or GC.

To attain some mechanistic insight, we synthesized a putative organocopper intermediate, (phen)CuC<sub>6</sub>F<sub>5</sub> (**4**),<sup>16</sup> and performed the following stoichiometric and catalytic reactions (Scheme 1). Upon exposure of **2a** to a stoichiometric amount of **4**, the corresponding allenes were obtained in 78% combined yield with 98:2  $\gamma/\alpha$  selectivity. The copper complex **4** also could act as an effective catalyst for the reaction of **1a** with **2a** to afford the same products but with slightly lower regioselectivity ( $\gamma/\alpha = 91:9$ ). On the other hand, the stoichiometric reaction of **4** with **2j** gave the corresponding  $\gamma$ -substituted allene **3aj** as a major product ( $\gamma/\alpha = 98:2$ ), albeit in 36% yield, the regioselectivity of which runs counter to that under optimal conditions ( $\gamma/\alpha = 12:88$ , Table 2, entry 9). In sharp contrast, the catalytic reaction with **4** gave 11:89  $\gamma/\alpha$  selectivity similar to the result of entry 9 in Table 2. These phenomena suggest that the monoarylcopper **4** would give the  $\gamma$ -substituted allene selectively, while an intermediate responsible for the  $\alpha$ -substitution could be another organocopper species derived from **4** under catalytic conditions.

Based on the above outcomes and literature information, we are tempted to assume the reaction mechanism for

**Scheme 1.** Stoichiometric and Catalytic Reactions of (phen)CuC<sub>6</sub>F<sub>5</sub> (**4**) with Propargylic Phosphates **2a** and **2j**



the formation of  $\gamma$ -substituted allene **3aa** to be as follows (Scheme 2). Initial ligand exchange of CuCl with LiO-*t*-Bu and phen forms the (phen)CuO-*t*-Bu (**5**). Subsequent direct cupration of pentafluorobenzene (**1a**) occurs with the aid of an O-*t*-Bu ligand of strongly basic nature to furnish the key intermediate (phen)CuC<sub>6</sub>F<sub>5</sub> (**4**).<sup>16</sup> An addition/elimination sequence<sup>17</sup> in the reaction of **4** with **2a** delivers the corresponding  $\gamma$ -substituted allene **3aa** along with the copper phosphate **6**. Finally, the starting alkoxide complex **5** is regenerated by the action of LiO-*t*-Bu to complete the catalytic cycle. Although the detailed pathway directed toward the  $\alpha$ -substituted allene **3aa'** remains elusive at the present stage, an ate-type organocopper species generated from **4** undergoes oxidative addition of **2a** to form an allenylcopper intermediate. The allenylcopper is in equilibrium to the corresponding propargylcopper, en route to a mixture of  $\gamma$ -substituted allene and  $\alpha$ -substituted alkyne.<sup>18</sup> The formed  $\alpha$ -substituted alkyne is isomerized by LiO-*t*-Bu to the observed  $\alpha$ -substituted allene. The proposed mechanisms can account for the results in Scheme 1: under catalytic conditions, two distinct addition/elimination and oxidative addition pathways are competitive, and thus the  $\gamma$ -selectivity is generally lower than that under stoichiometric conditions. Exemplified by **2j**, the increasing steric bulkiness at the  $\gamma$ -position in the propargyl phosphate would hamper the addition/elimination process to allow the ate-type-copper-mediated oxidative addition pathway to be predominant under catalytic conditions.

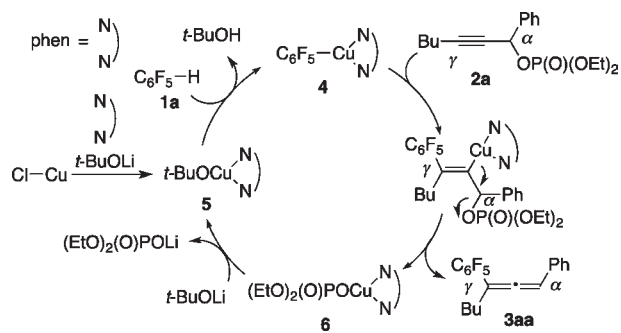
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**Scheme 2.** Plausible Mechanism for the Formation of  $\gamma$ -Substituted Allene **3aa**



In conclusion, we have developed an efficient copper catalyst for the reaction of polyfluoroarenes with propargyl

phosphates, providing the (polyfluoroaryl)allenes directly. To the best of our knowledge, this is the first example of the direct introduction of allenyl moieties to electron-deficient arenes, although the regioselectivity is still dependent on the substitution pattern of the phosphates. Further efforts seek to improve the  $\gamma/\alpha$  selectivity by catalyst control and to expand the arene substrate scope.

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**Supporting Information Available.** Detailed experimental procedures and characterization data of compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.