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Copper-Catalyzed Direct Alkynylation of Electron-Deficient Polyfluoroarenes with Terminal Alkynes Using O_2 as an Oxidant

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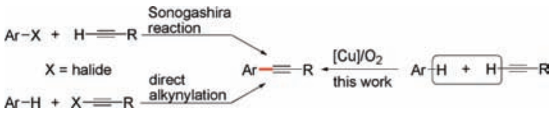
Metal-catalyzed cross-coupling of aryl halides with terminal alkynes, namely the Sonogashira reaction, represents one of the most commonly used methods for the synthesis of aryl alkynes.[1] We can envision that the development of metal-catalyzed direct alkynylation of the C−H bond as an alternative to the Sonogashira reaction would provide more efficient and straightforward routes to the same products. However, in spite of significant advances made in the development of metal-catalyzed direct C−H functionalization,[2,3] to date, the direct catalytic C−H alkynylation with terminal alkynes as coupling partners remains a great challenge, largely because of the lack of solutions to the problem associated with the undesired homocoupling of terminal alkynes under oxidative conditions.[4] Recently, Yamaguchi, Gevorgyan, and others, in their pioneering work, demonstrated that the direct alkynylation of phenols,[5] anilines,[6] and heterocycles[7] were achieved by using the alkynyl source derived from terminal alkynes, for example, alkynyl halides and benziodoxolone-based hypervalent iodine reagents.

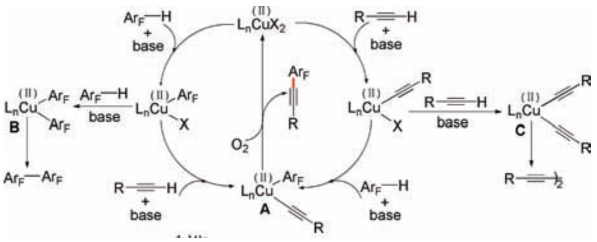
Scheme 1. Different Routes to Synthesize Aryl Alkynes



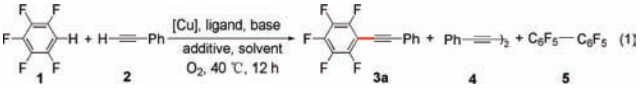
Herein, we describe a Cu-catalyzed method for the construction of $C(sp^2)-C(sp)$ bond via direct alkynylation of aromatic C−H bond with a broad range of terminal alkynes as coupling partners (Scheme 1). This protocol uses O_2 as an oxidant and enables the direct alkynylation of electron-deficient polyfluoroarenes to occur under mild conditions (40 °C), furnishing the products, fluorinated aryl alkynes that demonstrate importance in organic synthesis[8] and material science.[9] To the best of our knowledge, the reaction presented here represents the first example of direct alkynylation of an aromatic C−H bond with terminal alkynes.

On the basis of recent advances in metal-catalyzed oxidative cross-coupling reactions involving terminal alkynes,[10] we have recently achieved Cu-catalyzed intermolecular aerobic oxidative amination of acidic C−H bonds in polyfluoroarenes,[11] which inspired us to further investigate Cu-catalyzed direct alkynylation of polyfluoroarenes with terminal alkynes. We reasoned that this direct alkynylation reaction could occur through the catalytic pathway shown in Scheme 2. If this process is operative, the formation of Cu(alkynyl)(fluoroaryl) complex **A**, which delivers the desired cross-coupling products by way of reductive elimination, is expected to compete with the formations of the symmetrically substituted $Cu(fluoroaryl)_2$ complex **B** and $Cu(alkynyl)_2$ complex **C**. The latter intermediates were proposed to give rise to homocoupling products of polyfluoroarenes[12] and terminal alkynes.[4,10a] Based on these hypotheses, our strategy to overcome the undesired homocoupling is the identification of factors that favor the formation of the Cu(alkynyl)(fluoroaryl) complex rather than the formations of the $Cu(fluoroaryl)_2$ complex and the $Cu(alkynyl)_2$ complex.

Scheme 2. Proposed Mechanistic Hypothesis for Cu-Catalyzed Direct Alkynylation of Polyfluoroarenes with Terminal Alkynes



Initially, we examined the reaction of pentafluorobenzene (**1**) with phenylacetylene (**2**) under the conditions similar to those for the alkyne amidation[10a] (eq 1; the detailed results of optimization studies are provided in the Supporting Information).



However, the reaction of **1** with **2** conducted in DMSO at 70 °C under 1 atm of O_2 in the presence of $CuCl_2$ (20 mol %) as catalyst and weak bases (2 equiv) such as $NaHCO_3$ and K_3PO_4 did not form the cross-coupling product **3a** in the detectable amount. Instead, a large amount of diyne byproduct **4** was produced. Because no **5** was detected in these reactions, we speculated that stronger bases such as *t*BuOLi might be required for the deprotonation of **1**. Under otherwise identical conditions, replacing weaker bases with *t*BuOLi led to the formation of **3a** and allowed this reaction to proceed at 40 °C with 11% yield obtained. The introduction of 1,10-phenanthroline ligand (20 mol %) improved the yield (49%). CuBr was proved to be more active than other Cu sources, furnishing **3a** in 61% yield. Since two electron-deficient coupling components may be reluctant to undergo reductive elimination from the metal center,[13] a variety of π-acceptor ligands that were previously reported to promote reductive elimination[14] were used as additives to accelerate the formation of **3a**. We were pleased to find that 15 mol % of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in combination with $CuCl_2$ significantly improved the yield to 72% as a consequence of suppressing formation of **4**, while the combination of CuBr with DDQ slightly improved this reaction (64% yield). Surprisingly, analogues of DDQ such as BQ had negative effects on this reaction. The beneficial effect of DDQ remains to be elucidated since it is also possible that DDQ serves as an electron-transfer mediator to facilitate aerobic reoxidation of the catalyst.[15] Further screening of solvents revealed that DMSO is the optimal solvent. Compared to 1,10-phenanthroline, other nitrogen-containing ligands were less effective, pointing to the effect of ligands on the reaction selectivity. Gratifyingly, 85% yield was obtained when utilizing *t*BuOLi (3 equiv), $CuCl_2$ (30 mol %), 1,10-phenanthroline (30 mol %) and DDQ (15 mol %).

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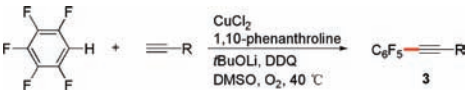
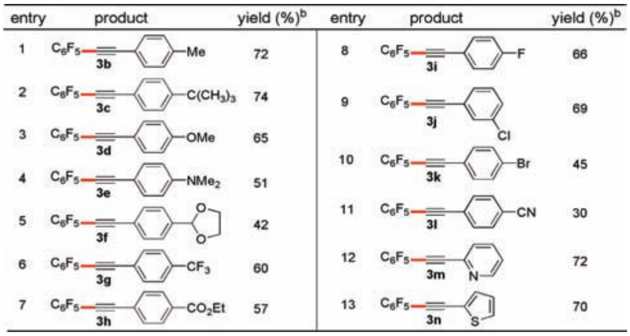
Table 1. Cu-Catalyzed Direct Alkynylation of Pentafluorobenzene with Terminal Alkynes[a]



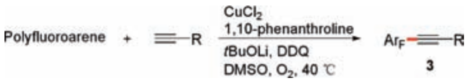


entry	product	yield (%)[b]	entry	product	yield (%)[b]
1	3b (–Me)	72	8	3i (–F)	66
2	3c (–C(CH$_3$)$_3$)	74	9	3j (Cl)	69
3	3d (–OMe)	65	10	3k (–Br)	45
4	3e (–NMe$_2$)	51	11	3l (–CN)	30
5	3f	42	12	3m (N)	72
6	3g (–CF$_3$)	60	13	3n (S)	70
7	3h (–CO$_2$Et)	57			

[a] Reaction conditions: alkyne (0.2 mmol), pentafluorobenzene (5 equiv), CuCl$_2$ (30 mol %), 1,10-phenanthroline (30 mol %), *t*BuOLi (3 equiv), DDQ (15 mol %), DMSO (1.5 mL, 0.13 M), 1 atm of O$_2$, 40 °C, 12 h. [b] Isolated yields.

This reaction exhibited the broad substrate scope with respect to terminal alkynes (Table 1).[16] Both electron-donating (entries 1−5) and -withdrawing substituents (entries 6−11) were compatible on the aryl alkynes, leading to highly functionalized products in reasonable to good yields. The heterocyclic alkynes also served as suitable coupling partners (entries 12 and 13). In addition, the tolerance of chloro and bromo substituents (entries 9 and 10) provided a complementary platform for further functional group manipulations via conventional Pd(0)-catalyzed cross-coupling reactions. Because of the decomposition of 4-ethynylbenzonitrile under the standard conditions, the moderate yield was obtained.

Table 2. Cu-Catalyzed Direct Alkynylation of Polyfluoroarenes with Terminal Alkynes[a]



3o (R = H) 84%
3p (R = Me) 76%
3q (R = F) 85%
3r 70%
3s 61%
3t (R = H) 42%
3u (R = F) 41%
3v (R = H) 58%
3w (R = OMe) 57%
3x (R = CF$_3$) 58%
3y (R = NO$_2$) 57%
3z 41%[b]

[a] See Table 1. [b] 2,3,5,6-Tetrachloropyridine (3 equiv), *t*BuOLi (2 equiv).

This reaction was also amenable to a range of tetrafluoroarenes containing additional substituents (Table 2). For example, 2,3,5,6-tetrafluorobenzotrifluoride smoothly underwent direct alkynylation in good yields (**3o**−**3s**). Other tetrafluoroarenes afforded the corresponding coupled products in synthetically useful yields (**3t**−**3y**). Interestingly, 2,3,5,6-tetrachloropyridine also reacted with phenylacetylene, albeit in a moderate yield (**3z**). However, both tri- and difluoroarenes were unreactive, presumably due to the significant difference in acidity between the tri- and difluoroarenes and phenylacetylene. In this case, the deprotonation of the latter dominates over the former, which would lead to the formation of diyne as the almost sole product.

In summary, we have developed a Cu-catalyzed method to construct C(sp^2)−C(sp) bonds through direct alkynylation of electron-deficient polyfluoroarenes with terminal alkynes. This reaction proceeds under mild conditions and tolerates a number of functional groups. Further studies are underway to expand the substrate scope of this method to other electron-deficient arenes.

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

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(16) For the results of reactions with alkyl-and silyl-substituted alkynes, see: Table S2 in Supporting Information.

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