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Catalytic alkynylation of polyfluoroarenes by amide base generated *in situ*

Masanori Shigeno,*[a] Takuya Okawa,[a] Masaya Imamatsu,[a] Kanako Nozawa-Kumada,[a] and Yoshinori Kondo*[a]

Abstract: We herein demonstrate that the amide base generated *in situ* from CsF and $N(TMS)_3$ catalyzes the deprotonative coupling reactions of terminal alkynes with polyfluoroarenes, wherein mono- and dialkynylations occur efficiently for penta- and hexafluorobenzenes, respectively. Tetraalkynylated products could also be synthesized from dialkynylated compounds.

The development of efficient methodologies for synthesizing fluorine-atom-containing aromatic compounds has garnered much attention as such scaffolds are found in a wide range of functional materials, such as biologically active compounds, electronic materials, and liquid crystals.[1] The regioselective substitution of a fluorine atom in polyfluoroarenes by nucleophiles is a simple and direct protocol, given that various polyfluoroarenes are readily available nowadays. Transition metal catalysis drives the transformations to form C-C, C-H, C-O, C-S, C-B, and C-Si bonds.[2] Given the stringent restriction of residual transition metals in pharmaceuticals and electronic materials, establishing transition metal-free synthetic protocols is an important issue. Nucleophilic aromatic substitutions (S_NAr) fulfill these requirements, wherein pronucleophiles with a stoichiometric amount of Brønsted base or pre-prepared nucleophilic reagents can couple with polyfluoroarenes to form C-C, C-H, C-O, C-S, C-N, and C-B bonds.[3,4] Alkynylated fluoroarenes, also obtained via S_NAr reactions, are potentially applicable in electronic materials and can be used for further transformations based on their alkynyl moieties.[5-8] For example, Zhao, Zhang, and coworkers reported the alkynylation of polyfluoroarenes with terminal alkynes using a stoichiometric amount of *n*-BuLi (Figure 1, i).[5] Cao and coworkers also noted that the reaction using terminal alkynes is mediated by Na and *n*-BuMgCl via a $S_{RN}1$ mechanism involving one-electron transfer, in which poorly reactive mono- or difluoroarenes are also transformed by further adding NaOMe and $Ca(OH)_2$ (Figure 1, ii).[6] Alternatively, Watson and coworkers showed that alkynylated products of hexafluoroarene are formed by using aryl alkynyl silanes as nucleophiles in the presence of a catalytic amount of tetrabutyl ammonium fluoride (TBAF) (Figure 1, iii).[7] They also applied the protocol to the preparation of poly(phenylene ethynylene)s bearing alternating aryl-polyfluoroaryl units. Sanji and coworkers reported that monosubstituted polyfluoroarenes undergo substitution reactions with alkynyl silanes in the presence of CsF and 18-crown-6 (Figure 1, iv).[8] In the former

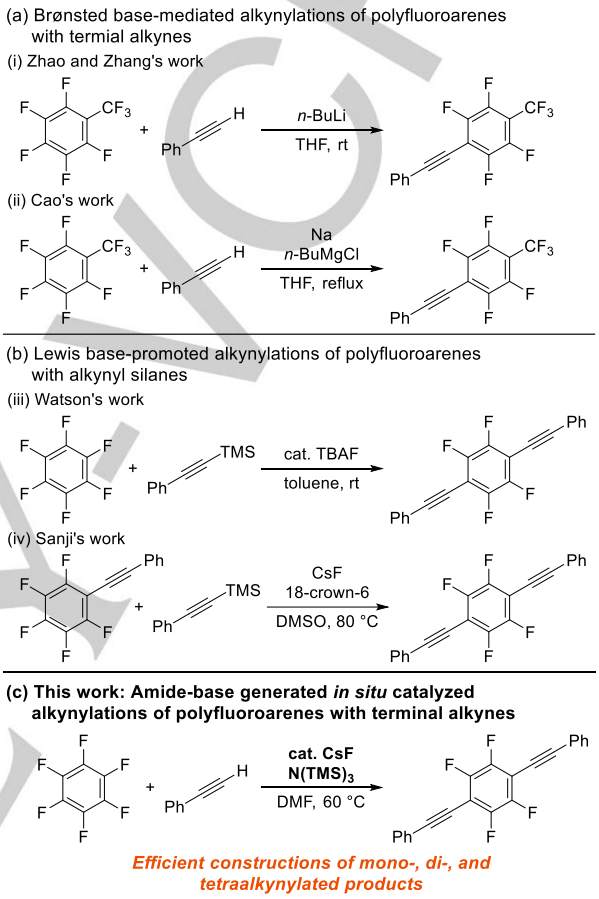

Figure 1. Alkynylation of polyfluoroarenes.

Brønsted base system, the highly reactive reagents *n*-BuLi, Na, and *n*-BuMgCl were required, where these reagents potentially limit the functional group tolerance. The latter Lewis base system requires the use of alkynyl silanes as nucleophiles instead of terminal alkynes, although terminal alkynes are generally more available than alkynyl silanes. Thus, the establishment of practical and efficient alkynylations using terminal alkynes is highly desired.

We previously found that the amide base generated *in situ* from a catalytic amount of fluoride salt with a stoichiometric amount of aminosilane promotes the deprotonative functionalization of C-H bonds in pronucleophiles, such as heteroarenes, acetates, and methyl(hetero)arenes, with carbonyl compounds.[9] In this study, the system is demonstrated to be applicable to the coupling reaction of terminal alkynes with polyfluoroarenes. The amide base generated from CsF and $N(TMS)_3$ efficiently catalyzes the dialkynylations of hexafluorobenzene **1a**, as well as monoalkynylations of pentafluorobenzenes (Figure 1, c).[10] The current system also

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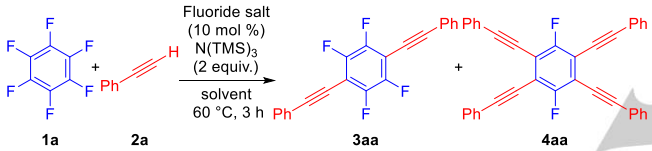
enables the construction of tetraalkynylated products from the dialkynylated compounds. The details are presented herein.

Initially, the effect of fluoride salts was examined in the reaction of hexafluorobenzene **1a** and phenylacetylene **2a** (Table 1). Among the alkali-metal fluoride salts, CsF was the most effective for maximizing the reaction yield of the dialkynylated product **3aa** (isolated yield: 88%; entries 1−5).[11-13] Tetramethylammonium fluoride (TMAF) and tetrabutylammonium difluorotriphenylsilicate (TBAT) also gave **3aa** in 55% and 63% yields, respectively (entries 6 and 7). Solvents other than *N*,*N*-dimethylformamide (DMF) were also employed, where the reaction proceeded in dimethyl sulfoxide (DMSO) and *N*,*N*-dimethylacetamide (DMA) with yields of 78% and 84%, respectively. However, THF and toluene did not promote the reaction (entries 8−11). When the reaction was performed with a reduced amount of CsF (5 mol%) or **2a** (3.0 equiv.), the product yield decreased (entries 12 and 13). The effects of the amount of $N(TMS)_3$ were then examined (entries 14 and 15). When 4 equiv. of $N(TMS)_3$ was employed, **3aa** was formed in 59% yield, along with a significant amount of the tetrasubstituted product **4aa** (30% yield), the synthesis of which is discussed later.

Table 1. Optimization of the dialkynylation reaction of **1a** with **2a**



Entry	Fluoride salt	Solvent	**3aa** (%)[a]	**4aa** (%)[a]
1	LiF	DMF	0	0
2	NaF	DMF	0	0
3	KF	DMF	0	0
4	RbF	DMF	61	0
5	CsF	DMF	91 (88)[b]	0
6	TMAF	DMF	55	13
7	TBAT	DMF	63	1
8	CsF	DMSO	78	0
9	CsF	DMA	84	0
10	CsF	THF	0	0
11	CsF	Toluene	0	0
12	CsF (5 mol %)	DMF	56	0
13[c]	CsF	DMF	82	1
14[d]	CsF	DMF	58	0
15[e]	CsF	DMF	59	30

[a]Yields were determined by ^{19}F-NMR spectroscopy using 4-fluorotoluene as an internal standard. [b]Isolated yield. [c]**2a** (3 equiv.) was used. [d]$N(TMS)_3$ (1.5 equiv.) was used. [e]$N(TMS)_3$ (4 equiv.) was used.

The scope of alkynes was investigated under the optimized conditions (Figure 2). Tolylacetylenes **2b**−**2d** provided the dialkynylated products **3ab**−**3ad,** irrespective of the position of the methyl substituent, with yields of 89%, 91%, and 75%, respectively. Similarly, the reactions of methoxyphenylacetylenes **2e**−**2g** proceeded smoothly to furnish the corresponding products in good to high yields. 4-Biphenylacetylene **2h** was converted to the product in 85% yield.

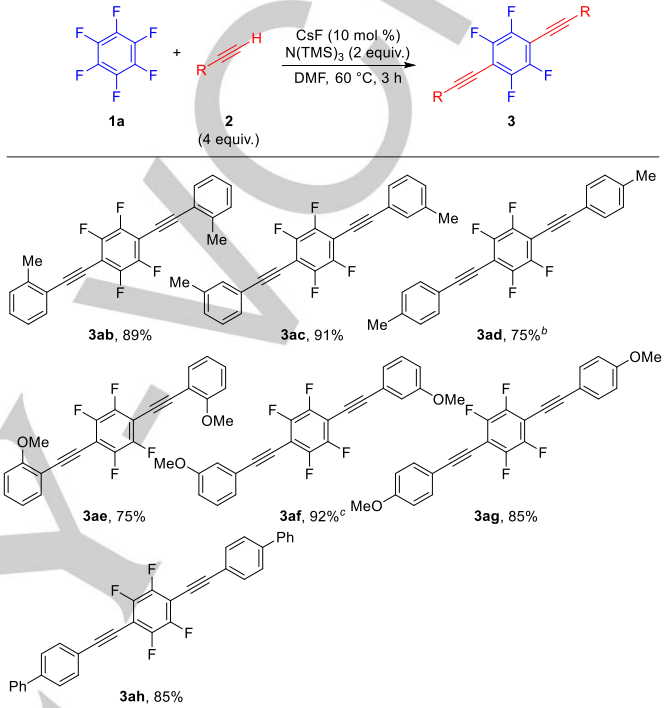


Figure 2. Scope of alkynes **2** in the dialkynylation of **1a**.[a] [a]Isolated yields. [b]CsF (20 mol %) was used. [c]Reaction was conducted for 24 h.

The present system was also applied to the alkynylation of monosubstituted pentafluorobenzenes **5** (Figure 3). Pentafluorobenzene **5a** bearing a phenyl group coupled with **2a** to form the product **6aa** in 82% yield.[14] The highly electron deficient perfluorotoluene **5b** also smoothly underwent the substitution reaction at room temperature to produce **6ba** in 79% yield.[15] Phenylethynyl-substituted pentafluorobenzene **5c** was used for the alkynylation reaction with various acetylenes, which resulted in the formation of asymmetric products. Tolylacetylenes **2b** and **2c** reacted with **5c** to afford **6cb** and **6cc** in 77% and 66% yields, respectively. The reactions of arylacetylenes **2i** and **2j** bearing bromo and iodo atoms, respectively, also provided the corresponding products. Ester and cyano moieties were tolerated in the reaction to give the products in yields of 89% and 72%, respectively. (2-Pyridyl)acetylene **2m** also underwent alkynylation with **5c** to form **6cm** in 60% yield.

The tetrasubstituted products could also be synthesized from the disubstituted compound **3aa** (Figure 4). When **3aa** was subjected to the reaction with **2a**, alkynylation occurred to produce **4aa** in 71% yield.[16,17] Using this protocol, tetrasubstituted arenes having two different alkynyl moieties could also be obtained. The reactions of alkynes **2b**, **2c**, and **2g** furnished the corresponding

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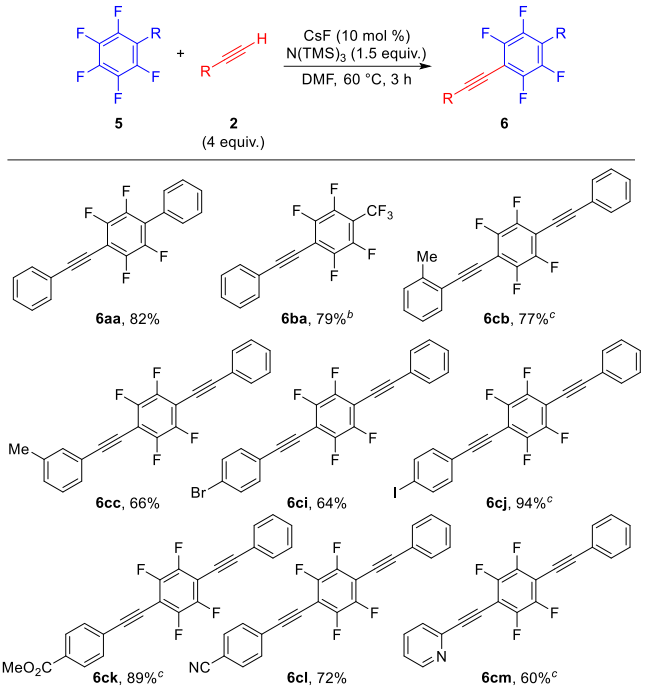

Figure 3. Alkynylation of pentafluorobenzenes **5**.[a] [a]Isolated yields. [b]Reaction was conducted with $N(TMS)_3$ (2 equiv.) at room temperature for 2 h. [c]Reaction was conducted with $N(TMS)_3$ (2 equiv.) and alkyne **2** (1.1 equiv.) for 24 h.

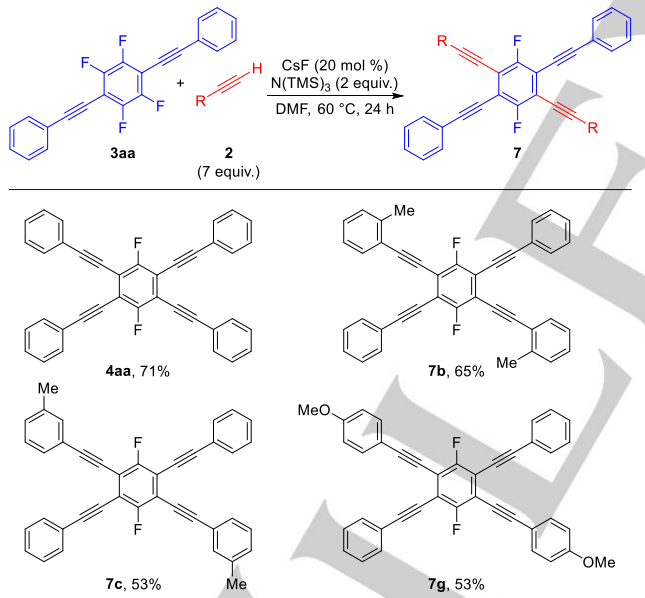

Figure 4. Construction of tetraalkynylated arenes **4aa** and **7**.[a] [a]Isolated yields.

compounds **7b**, **7c**, and **7g** in 65%, 53%, and 53% yields, respectively.

A plausible mechanism was proposed, as illustrated in Figure 5, whereby cesium amide base **A** is initially generated *in situ* from CsF and $N(TMS)_3$, along with formation of the strong Si-F bond in TMS-F (trimethylsilylfluoride),[18] which subsequently deprotonates **2a** to give the acetylide intermediate **B**. Subsequent nucleophilic substitution of **1a** with **B** furnishes the monoalkynylated product

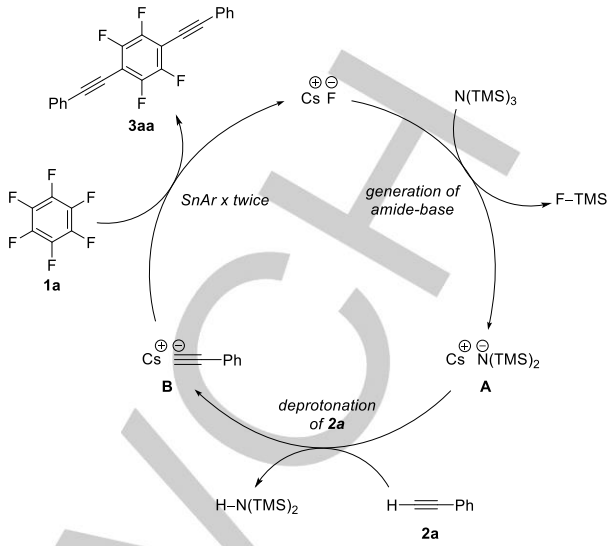

Figure 5. Plausible mechanism.

5c, in which CsF is regenerated. Further substitution occurs on **5c**, resulting in formation of the dialkynylated product **3aa**.

In summary, the catalytic amide base system generated *in situ* facilitated the alkynylation of polyfluorobenzenes. Dialkynylated products were obtained from **1a**, and monoalkynylated products were formed from monosubstituted pentafluorobenzenes **5**. The system was also used for the synthesis of tetraalkynylated products. Application of the system to other types of S_NAr reactions is our next research project.

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Keywords: Alkynes • Polyfluoroarenes • Aromatic substitution • Amide-base • C-C coupling

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[10] In the previously reported Brønsted base system, the dialkynylation of polyfluoroarenes was not well studied compared to the monoalkynylation. See references 5-8.

[11] Such para-selectivity is often observed in the S_NAr reaction of pentafluorobenzenes, see the comprehensive review in reference 3. Also see: R. D. Chambers, P. A. Martin, G. Sandford, D. L. H. Williams, *J. Fluorine Chem.* **2008**, *129*, 998.

[12] In the optimized condition (Table 1, entry 5), neither regioisomers of dialkynylated products (*ortho*- and *meta*-substituted products) nor mono-alkynylated product corresponding to **5c** were detected.

[13] In this study, the reaction was set up in a glove box under an Ar atmosphere. In contrast, when the reaction was set up outside the glove box, **3aa** was obtained in a lower yield of 33% (results not shown).

[14] Paleta and coworkers showed that the S_NAr reactions of **5a** with alcohol, amine, and thiol nucleophiles take place exclusively at the *para*-position to the phenyl group. They also performed density functional theory (DFT) calculations, which supported the *para*-selectivity from the viewpoint of the relative transition state energies. See: J. Kvíčala, M. Beneš, O. Paleta, V. Král, *J. Fluorine Chem.* **2010**, *131*, 1327.

[15] Zhao, Zhan, and coworkers reported that the *para*-selective alkynylations of **5b** with terminal alkynes proceed in the presence of *n*-BuLi. Using DFT calculations, they showed that the energy barrier for the *para*-alkynylation is smaller than those for the *ortho*- and *meta*-alkynylations. See reference 5a. Also see reference 4d for the DFT calculations of the *para*-selective hydrodefluorination of pentafluorobenzene with triphenylsilane.

[16] The reaction conditions for the synthesis of **4aa** were preliminarily examined, see Table S1.

[17] The reactivity of **3aa** in the alkynylation was confirmed to be lower than that of **1a** by the same-condition experiments (Table 1, entry 5; Table S1, entry 1), which is due to the lower electrophilicity of the former. Thus, larger amounts of CsF (20 mol %) and alkynes **2** (7 equiv.) as well as a longer reaction time (24 h) were required to achieve the efficient dialkynylations of **3aa** (Figure 4 and Table S1).

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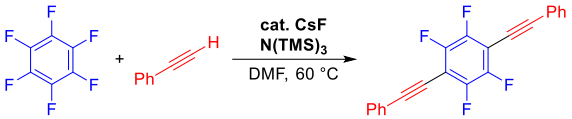

Efficient constructions of mono-, di-, and tetraalkynylated products

Amide base generated *in situ* from CsF and $N(TMS)_3$ catalyzes the deprotonative coupling reactions of terminal alkynes with polyfluoroarenes, wherein mono- and dialkynylations occur efficiently for penta- and hexafluorobenzenes, respectively. Tetraalkynylated products can also be synthesized from dialkynylated compounds.

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