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Base-Promoted Direct and Highly Selective Alkynylation of Electron-Deficient Octafluorotoluene

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Cuibo Liu,[a,b] Hui Zhao,[a] Haitao Zhao,*[a] Zhifang Wang,[a,b] Bin Zhang*[a,b]

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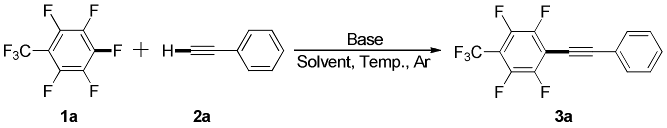
A direct alkynylated strategy of electron-deficient octafluorotoluene via selective C–F bond cleavage is exhibited. The synthesized products are super intermediates for further transformations. Additionally, we give a preliminary explanation on the mechanism of terminal alkynes reacting with octafluorotoluene by density functional theory (DFT).

The C–F bonds activation/cleavage of fluorides is an important and useful tool in organic chemistry. This strategy enables the synthesis of many complex and valuable molecules by the transformations of C–F bonds (intermolecular and intramolecular) into the carbon–carbon and/or carbon–heteroatom bonds.[1] However, compared with the other C–X (Cl, Br, I) bonds, the C–F bonds are much more inert due to the electronegativity of fluorine imparting partial ionic character through partial charges on the carbon and fluorine atoms.[2] Consequently, the activation/cleavage of C–F bonds have become a challenge for the chemists. Although they are generally intrinsic unreactive, in the past few decades, a myriad of technologies have emerged toward C–F bonds cleavage and the following conversions. Among the various available methods, the transition-metal catalyzed strategies and the nucleophilic aromatic substitution reactions (S_NAr) have proved to be the most promising and efficient protocols for such transformations.[3] Although these strategies are effective, the new bonds constructed are mainly focused on the carbon–heteroatom bonds or C_{sp2}–C_{sp3} or C_{sp2}–C_{sp2} bonds of nearly all such studies.[4] In contrast, the reports on the formation of C_{sp2}–C_{sp} bonds through C–F bonds cleavage are rarely reported, and are still challenging.[5] Up to date, only a few examples that can successfully realize the assemble of C_{sp2}–C_{sp} bonds involving the C–F bonds activation/cleavage. For instance, the Yoakim group reported an efficient nucleophilic aromatic substitution of electron-deficient 2-fluoronitrobenzene derivatives with terminal alkynes to deliver a series of internal aryl alkynes by using sodium bis(trimethylsilyl)-amide (NaHMDS) as a base in THF at 60 °C. The existence of nitro group in fluoroarenes is essential for activation of the C–F bond.[6] Prajapati and co-workers developed a novel indium-catalyzed Sonogashira coupling reaction between aryl fluoride and terminal alkynes and avoided the employment of a copper salt, phosphine ligand and palladium.[7] In spite of these achievements, the selected reactants are always limited to the mono-fluorinated substrates.

Recently, the polyfluoroarenes have gradually been regarded as a class of key synthons for synthesizing new polyfluoroarylated compounds, especially the polyfluoroarylated alkynes. Such species exhibit exceptional applications in modern pharmaceuticals and agrochemicals.[8] Because there are more than one fluorine atoms on the aryl ring, it is important to develop facile methods for controlling selective C–F bonds cleavage of polyfluoroarenes to the sole product. Sandford reported the first examples of palladium-catalyzed, microwave-promoted cross-coupling sp^2–sp C–C bond forming reactions of polyfluoroaromatic systems in Sonogashira type processes involving C–F cleavage. Utilizing this methodology a series of mono-alkynylation products at the *orth*-position of the NO_2 group were obtained.[9] More recently, the Cao group has made an important advance on finding a Grignard reagent-assisted, sodium, sodium methoxide and calcium hydroxide participated unasymmetric aryl acetylene synthetic reaction of alkynes with the various aryl fluorides via the C–F bond cleavage. Mechanism investigation revealed that the C–F bond cleavage was attributed to the fact that the electron transferred from an electron-donor species, sodium, to aryl fluoride.[10] Although these elegant advances have been achieved, the development of an efficient and simple method for the construction of polyfluoroarylated alkynes from polyfluoroarenes is highly desirable.

Herein, we report a base-promoted direct alkynylation of electron-deficient octafluorotoluene with terminal alkynes via highly selective C–F bonds cleavage. This strategy enables us to obtain a variety of corresponding polyfluoroarylated alkynes in mild to good yields. Most importantly, we give, for the first time, a primary investigation on the high selectivity of the C–F bonds cleavage of polyfluoroarenes reacting with terminal alkynes by density functional theory (DFT).

Table 1 Screening results of octafluorotoluene **1a** reacting with phenylacetylene **2a**



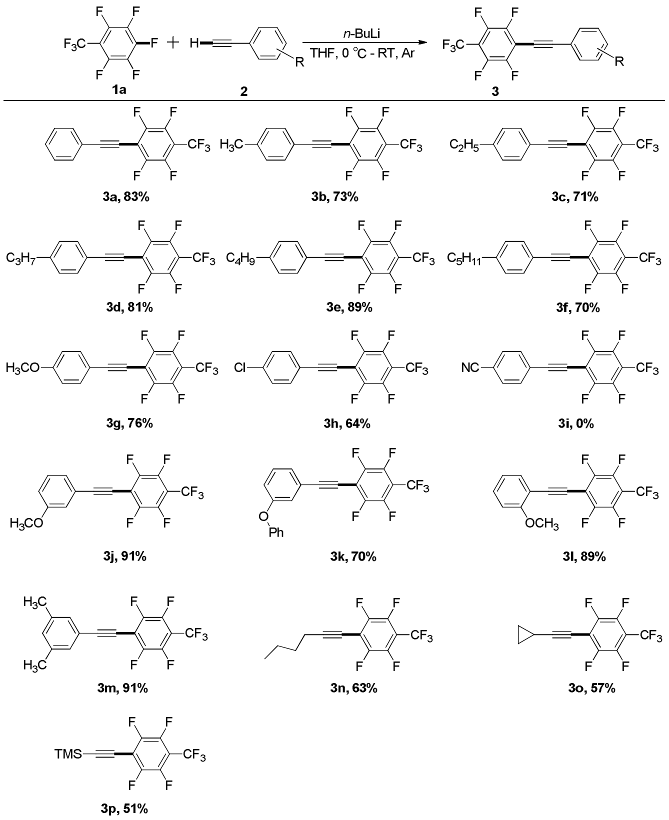
1a **2a** **3a**

Entry[a]	Base	Solvent[b]	Temp. (°C)	Yield (%)[c]
1[d]	K_2CO_3	DMF	RT	-
2[d]	K_2CO_3	DMF	90	-
3[e]	K_2CO_3	DMF	RT	-
4[e]	K_2CO_3	DMF	90	-
5[f]	K_2CO_3	DMF	90	-
6	NaOH	THF	RT	-
7	NaH	THF	RT	-
8	$Zn(Me)_2$	THF	0-RT	-
9	$Zn(Et)_2$	THF	0-RT	-
10	*n*-BuLi	THF	0-RT	83
11[g]	*n*-BuLi	THF	0-RT	71
12	*n*-BuLi	Et_2O	0-RT	46
13	*n*-BuLi	CH_2Cl_2	0-RT	-
14	*n*-BuLi	Toluene	0-RT	-

[a] The reaction employs a molar ratio of **1a** : **2a** : base : = 1.5 : 1 : 1.5. [b] Solvent (2.0 mL). [c] Isolated yield. [d] CuI (1.0 equiv.) is added. [e] $AgNO_3$ (1.0 equiv.) is added. [f] (phenylethynyl)silver (1.0 equiv.) is used instead of **2a**. [g] *n*-BuLi (2.5 equiv.) is used.

Compared with typical transition-metal-mediated processes for the C–F bonds cleavage of polyfluoroarenes, the metal-free S_NAr reactions are often found to be simpler, milder, and environmentally more benign. Our previous studies on the preparation of polyfluoroarylated compounds are exactly based on this strategy and investigations reveal that the nucleophilic anions are the key for the S_NAr reaction of polyfluoroaneres.[11] We want to apply the S_NAr approach to the synthesis of polyfluoroarylated alkynes. Hence, seeking proper routes to generate phenyl acetylide anion is essential for the success. Literatures show that metal acetylides can be formed in suit in some nucleophilic addition reactions or coupling reactions.[12] So, at the beginning, we examine the reaction of octafluorotoluene **1a** with phenylacetylene **2a** in DMF under Ar. To our disappointment, the ^{19}F NMR analysis of the crude reaction mixture demonstrates that no detectable amount of the product is obtained when we employ copper acetylides and silver acetylides as the nucleophile, no matter the temperature is at 0 °C, at R.T., or even at 90 °C (Table 1, entries 1-4). Even if the silver acetylide is prepared beforehand, it is still useless (Table 1, entry 5). It is known that the deprotonation of a terminal alkyne is more favourable under a strong base condition.[13] We turn our attention to the strong bases. Examinations of NaOH, NaH, $Zn(Me)_2$, $Zn(Et)_2$ for this reaction in THF to deliver an information that they are all ineffective (Table 1, entries 6-9). However, the introduction of 1.5 equiv *n*-BuLi can facilitate the reaction, and 83% yield of the polyfluoroarylated product is furnished (Table 1, entry 10). Deep analyses of the product by ^{1}HNMR, ^{19}FNMR, and ^{13}CNMR technologies show that this alkynylation reaction of octafluorotoluene **1a** occurs at the *para*-C atom of the CF_3 group. The reactions at the *meta*- and *orth*-position of the CF_3 group do not occur. This interesting result indicates that our reaction is of high selectivity. But, the increasing the loading of *n*-BuLi exerts a negative influence on the reaction efficiency (Table 1, entry 11). The lower yield may be due to the side reaction caused by the large excess of *n*-Butyl anion reacting with polyfluoroarenes. A simple investigation of solvents implies that only THF gives the best result, and the others are less effective or even unreactive (Table 1, entries 12-14). Noteworthy, the dimerized byproduct of phenylacetylene is not observed in our reaction system, which is distinct from the transition-metal-mediated processes of alkynes.[14]

Table 2 Direct alkynylation of octafluorotoluene **1a** with various terminal alkynes[a]

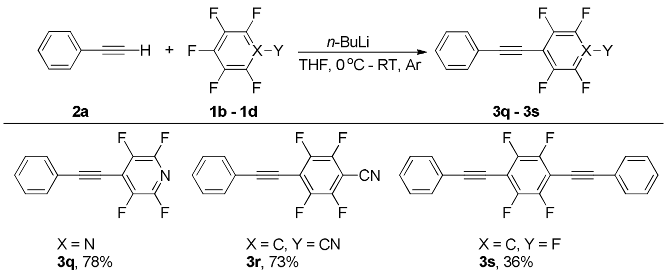


3a, 83% **3b, 73%** **3c, 71%**
3d, 81% **3e, 89%** **3f, 70%**
3g, 76% **3h, 64%** **3i, 0%**
3j, 91% **3k, 70%** **3l, 89%**
3m, 91% **3n, 63%** **3o, 57%**
3p, 51%

[a] Reaction Conditions: **1a** (0.3 mmol), **2** (0.2 mmol), *n*-BuLi (0.3 mmol) are added in anhydrous THF (2.0 mL) stirring at 0 °C to RT for 36 h. Yield: isolated yield.

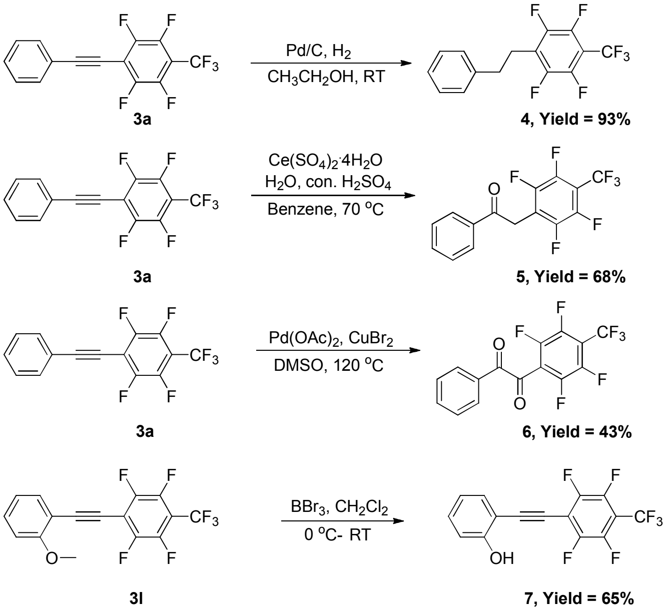
Having identified the optimized reaction conditions, we seek to evaluate the substrate scope of this transformation. As listed in Table 2, this C–F bond cleavage and C_{sp2}–C_{sp} bond formation reaction proceeds smoothly over a wide range of terminal alkynes. For the aromatic alkynes, most of them give the corresponding products in middle to excellent yields (64-91%). Compared with the electron donating groups, the substrates bearing the electron withdrawing groups give rise to the products in slightly lower yields (Table 2, entries **3b-3h**, **3j-3m**). Especially, when there is a cyano group on the aromatic ring, this S_NAr reaction does not occur (Table 2, entry **3i**). The negative result may be ascribed to its strong electron-withdrawing property that largely weakens the ability of acetylide anion to nucleophilic attack to **1a**. The same substituents can lie at different positions of aromatic ring to generate the desired products in good yields (Table 2, entries **3g**, **3j**, **3l**). Additionally, the di-substituted alkyne does not hamper the reaction and affords the polyfluoroarylated alkyne in high yields (Table 2, entry **3m**). With regard to the aliphatic alkynes, such as hex-1-yne, ethynylcyclopropane and ethynyltrimethylsilane, they are all amenable to the standard conditions to furnish the corresponding products in acceptable yields (Table 2, entries **3n-3p**).

Table 3 Direct alkynylation of **2a** with the other polyfluoroarenes[a]



[a] Reaction Conditions: the other polyfluoroarenes **1b** – **1d** (0.3 mmol), **2a** (0.2 mmol), *n*-butyl lithium (0.3 mmol) are added in anhydrous THF (2.0 mL) stirring at 0 °C to RT for 36 h. Yield: isolated yield.

Next, the other polyfluoroarenes are also investigated under the standard conditions. For example, when pentafluoropyridine **1b** and pentafluorobenzonitrile **1c** react with phenylacetylene **2a**, the yields of the polyfluoroarylated alkynes are 78% and 73% respectively (Table 3, entries **3q** and **3r**). However, when hexafluorobenzene **1c** is selected as the substrate, the di-alkynylated product of octafluorotoluene is accomplished (Table 3, **3s**).



Scheme 1 Further synthetic transformations of the products.

The synthesized polyfluoroarylated alkynes are also versatile synthetic intermediates, and can be readily transformed into other functionalized organofluorine molecules (Scheme 1). For example, direct hydrogenation of **3a** using a Pd/C/H$_2$ catalytic system at ambient conditions gives the corresponding polyfluoroaryl-containing alkane **4** in high yield. Oxidation of **3a** with Ce(SO$_4$)$_2$.4H$_2$O as the oxidant affords the 2-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)-1-phenylethanone **5** in a middle yield. Reaction of **3a** in the presence of Pd(OAc)$_2$ and CuBr$_2$ can deliver the *orth*-dicarbonyl compound **6**. Employing BBr$_3$ as the demethylation reagent, the product **3l** can be transformed into the 2-hydroxy substituted polyfluoroarylated alkyne **7**, which is difficult to be synthesized by using other methods. All these efficient and versatile transformations of the products illustrate that the obtained polyfluoroarylated alkynes can be used as superior reaction intermediates, and may find wide applications in other fields.

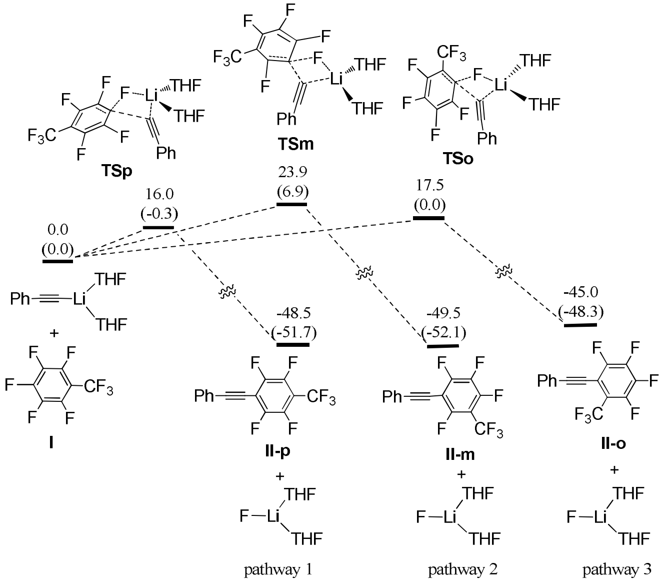


Fig. 1 Energy profiles calculated for the S$_N$Ar reaction. The relative free energies and electronic energies (in parentheses) are given in kcal/mol.

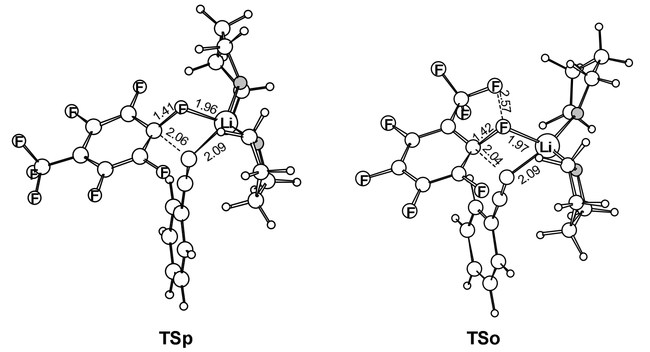


Fig. 2 Optimized structures involved in the pathways related to Fig. 1 and selected structural parameters are given (bond lengths in Å).

In order to gain some insight into the S$_N$Ar reaction, DFT calculations are carried out using octafluorotoluene and (phenylethynyl)lithium as model reactants. As mentioned in the experimental sections, our reactions are carried out in THF. The THF as ligands is always observed for the single-crystal structures of some organic lithiums crystallized in the THF solvent.[15] Thus, we consider the solvent effects by adding two THF ligands to the (phenylethynyl)lithium.

Fig. 1 shows the reaction profiles for octafluorotoluene reacts with (phenylethynyl)lithium at the *para*-, *meta*- and *ortho*-position respectively (pathways 1-3). In pathway 1, the (phenylethynyl)lithium attacks the *para*-C atom of the CF_3 group in octafluorotoluene to give the *para*-substituted product **II-p**. This one-step reaction occurs via a four-membered transition state **TSp** and no σ-complex found in our calculations. Similar processes also occur in pathways 2 and 3. The reaction barrier of the pathway 1 is 16.0 kcal/mol, and that of the pathway 2 and 3 are 17.5 kcal/mol and 23.9 kcal/mol, respectively. It is known that CF_3 group is electron-withdrawing group, the S_NAr reaction more likely occurs at the electron deficiency *para*- and *ortho*-position. From Fig. 1 we can clearly see that the energy barrier for the pathway 2 is rather higher than that of the pathways 1 and 3.

To understand why the S_NAr reaction occurs via pathway 1 rather than pathway 3, we compare the optimized structures **TSp** and **TSo**. As shown in Fig. 2, the F atom of the CF_3 group in **TSo** is 2.57 Å from the *orth* F atom. The distance is shorter than the Van der Waals radius of two F atom (2.70 Å). Hence, there exists steric hindrance between two fluorine atoms in transition state **TSo**. This steric hindrance leads to a higher energy for **TSo** comparing with **TSp**, because there is no such effect in transition state **TSp**.

Due to the fact that the progress is highly exothermic, reversibility of the reactions could be excluded.

Conclusions

In conclusion, we have developed a base-promoted, efficient and straightforward method for the successful formation of C_{sp2}–C_{sp} bond via selective C–F bond cleavage of electron-deficient octafluorotoluene reacting with terminal alkynes. These reactions can be operated under mild conditions without additional metal or ligands. By using this methodology, a series of corresponding polyfluoroarylated alkynes are constructed in moderate to good yields with high regioselectivity and good functional group compatibility. Additionally, the synthesized products can be used as versatile intermediates for further transforming into other organic molecules. Furthermore, a DFT calculation is conducted on the high selectivity of this reaction and reveals that the process is finished in one-step via a four-membered transition state.

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Notes and references

[a] Department of Chemistry, School of Science, Tianjin University, Tianjin 300072, P. R. China. Fax&Tel: +86-22-27403475; E-mail: bzhang@tju.edu.cn (B. Z.). htzhao@tju.edu.cn (H. Z.)

[b] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, P. R. China.

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