Synthetic Methods

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Copper(I)-Catalyzed Alkylation of Polyfluoroarenes through Direct C–H Bond Functionalization**

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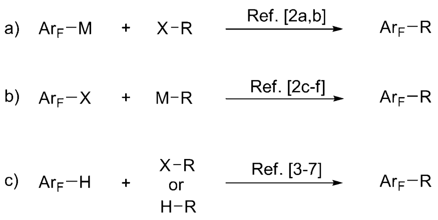
Abstract: *The copper(I)-catalyzed alkylation of electron-deficient polyfluoroarenes with N-tosylhydrazones and diazo compounds has been developed. This reaction uses readily available starting materials and is operationally simple, thus representing a practical method for the construction of C(sp^2)–C(sp^3) bonds with polyfluoroarenes through direct C–H bond functionalization. Mechanistically, copper(I) carbene formation and subsequent migratory insertion are proposed as the key steps in the reaction pathway.*

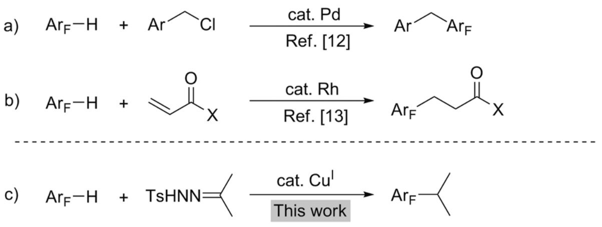
Compounds bearing F-containing groups are useful in materials and life sciences because of the unique effects of F substituents.[1] Polyfluoroarenes are a representative class of such F-containing molecules and have found wide applications. As a result, the development of efficient methods to introduce a polyfluoroaryl group has become an important undertaking for synthetic organic chemists and significant progress has been made in the past years. Most of the methods so far developed are based on polyfluoroaryl metals, halides, or carboxylic acids (Scheme 1 a,b).[2]

Apparently, the methods based on direct C–H functionalization of polyfluoroarenes are favored in terms of atom and step economy. However, there are at least two factors that limit the direct C–H bond functionalization of polyfluoroarenes. First, compared with electron-rich arenes, polyfluoroarenes have poor coordination ability with the catalysts. Second, the strong σ-bonds between transition metals and polyfluoroaryl groups result in difficulties for subsequent transformations. In 2006, Fagnou and co-workers reported the first direct arylation of polyfluoroarenes with a palladium catalyst.[3] In this transformation, polyfluoroarenes are deprotonated and then coordinate with the catalyst. Daugulis and co-workers later developed the transformation with a copper catalyst.[4] Moreover, the direct arylation through oxidative coupling,[5] allylation,[6] alkynylation,[7] and Heck-type reactions[8] of polyfluoroarenes were reported. In addition to palladium catalysts, nickel,[9] and copper[10] have also been used to catalyze some reactions involving polyfluoroarenes.

The studies mentioned above are focused on the construction of a C(sp^2)–C(sp^2) bond. It is worth mentioning that Friedel–Crafts alkylation reactions cannot be applied to polyfluoroarenes because of their electron-deficient nature. As a result, the reports on alkylation of perfluoroarenes are rare.[4a] In 2009, Nakamura and co-workers reported the alkylation with a polyfluoroaryl zinc agent.[11] The group of Zhang subsequently reported the palladium-catalyzed primary benzylation of polyfluoroarenes (Scheme 2 a).[12] However, the reaction is only limited to primary benzylation. Secondary benzyl halides are not used as the substrates, presumably because of the competing β-hydride elimination. In 2010, Zhao and co-workers reported rhodium-catalyzed olefin hydroarylation with polyfluoroarenes, which can be considered as an alternative approach toward alkylation of polyfluoroarenes (Scheme 2 b).[13] However, the secondary benzylation and general alkylation of polyfluoroarenes are still difficult to achieve.



Scheme 1. General methods for introducing polyfluoroarene groups.



Scheme 2. C(sp^2)–C(sp^3) bond-forming reactions of polyfluoroarenes.

Recently, we developed copper(I)-catalyzed C–H bond functionalization of terminal alkynes,[14] 1,3-azoles[15] and *N*-iminopyridinium ylides[16] with *N*-tosylhydrazones. In these transformations, the reactions are proposed to involve the following general sequence: deprotonation of the rela-

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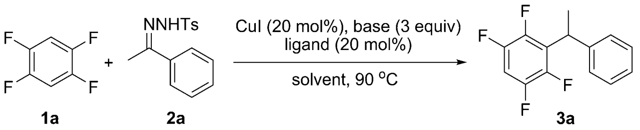
tively acidic C$-$H bond of the substrates followed by transmetalation to a copper(I) catalyst, formation of a copper(I) carbene species with the in situ generated diazo substrate, migratory insertion of the carbene, and finally protonation of the copper(I) species to complete the catalytic cycle. Since the polyfluoroarenes contain C$-$H bonds of similar acidity as that of terminal alkynes and 1,3-zaoles, it is thus expected that polyfluoroarenes could be alkylated in the similar reaction system. In our previous study we have noticed that 1,2,4,5-tetrafluorobenzene could be benzylated, albeit with low efficiency.[15] Herein we report an efficient and general copper(I)-catalyzed alkylation of polyfluoroarenes (Scheme 2c).

Table 1: Optimization of reaction conditions.[a]

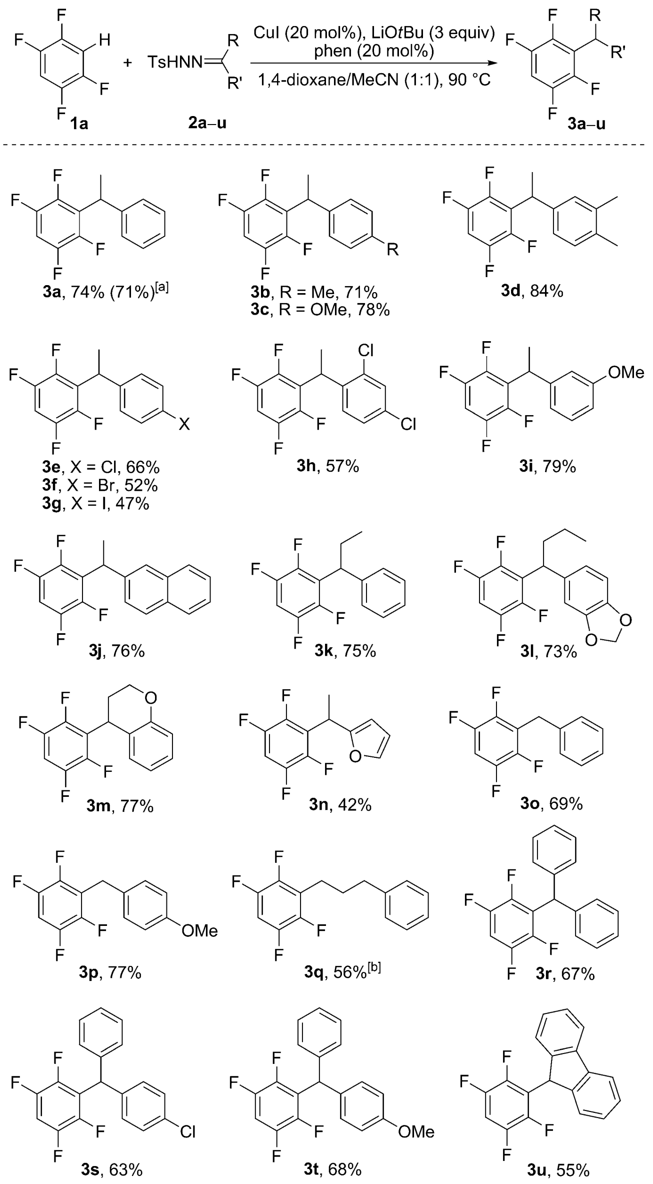


Entry	Solvent	Ligand	Base	Yield [%][b]
1	1,4-dioxane	–	LiO*t*Bu	26
2	1,4-dioxane	bpy	LiO*t*Bu	60
3	1,4-dioxane	phen	LiO*t*Bu	70 (69)
4	1,4-dioxane	PPh_3	LiO*t*Bu	50
5	1,4-dioxane	dppe	LiO*t*Bu	27
6	1,4-dioxane	phen	Cs_2CO_3	24
7	1,4-dioxane	phen	NaO*t*Bu	16
8	1,4-dioxane	phen	KO*t*Bu	5
9	MeCN	phen	LiO*t*Bu	70
10	1,4-dioxane/MeCN (1:1)	phen	LiO*t*Bu	75 (74)

[a] Reaction conditions: the solution of **2a** (0.1 mmol) and **1a** (2.0 equiv) in solvent (0.5 mL) was heated at 90°C for 1 h. [b] Yield determined by ^1H NMR spectroscopy using CH_3NO_2 as the internal standard. [c] The yield given within parentheses refers to that of the isolated product. bpy = bipyridine, Ts = 4-toluenesulfonyl.

As shown in Table 1, 1,2,4,5-tetrafluorobenzene (**1a**) and the *N*-tosylhydrazone **2a** were used for the optimization of the reaction conditions. The reaction with 20 mol% CuI and LiO*t*Bu in 1,4-dioxane without a ligand gave the expected alkylation product **3a** in 26% yield (Table 1, entry 1). We then examined the effect of ligands and found that the addition of either bipyridine (bpy), 1,10-phenanthroline (phen), or PPh_3 could significantly improve the yields (entries 2–4), presumably as a result of the improvement of the solubility of the catalyst. The *trans*-effect of the appropriate ligand may also accelerate the transmetalation process.[17] The reaction is sensitive to the base and it was identified that LiO*t*Bu could give best results (entries 6–8). Also, an excess amount of **1a** is necessary for obtaining the optimal yield. Finally, the examination of the solvent used showed that the mixed solvent of 1,4-dioxane and acetonitrile in a 1:1 ratio could slightly improve the yield.

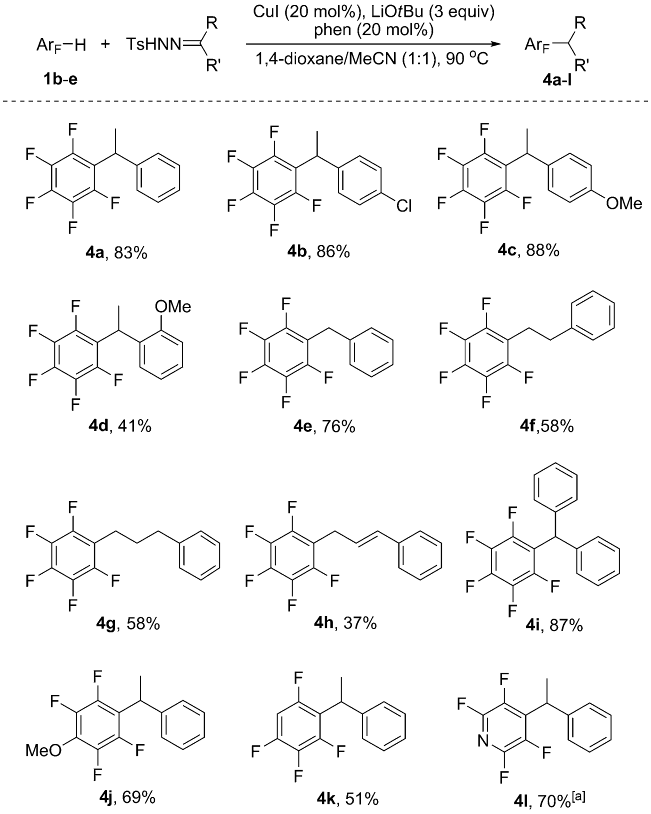
With the optimized reaction conditions in hand, we proceeded to investigate the scope of the reaction. First, with **1a** as the substrate, we studied the scope of *N*-tosylhydrazones. As shown in Scheme 3, the reaction worked well with a series of *N*-tosylhydrazones (**2a–u**), thus affording the corresponding products **3a–u** in moderate to good yields. In general, the substrates with electron-donating groups on the aromatic ring gave slightly higher yields (**3b–d**). The reaction proceeded well with the substrates bearing halogen substituents, thus giving the products in moderate yields (**3e–g**). For the substrate with an iodo substituent, the addition of one equivalent of LiI could suppress the by-product resulting from iodo substitution.[4a]



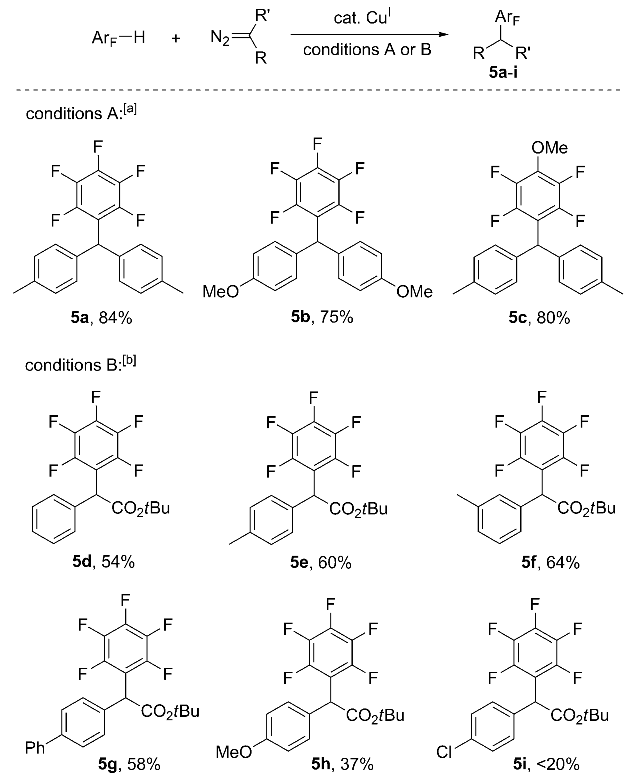
Scheme 3. Scope of *N*-tosylhydrazones. Reaction conditions: fluoroarene **1a** (0.60 mmol, 2.0 equiv), *N*-tosylhydrazone **2a–u** (0.30 mmol, 1.0 equiv), CuI (20 mol%), 1, 10-phenanthroline (20 mol%), LiO*t*Bu (3.0 equiv), 1,4-dioxane (0.75 mL), and MeCN (0.75 mL), 90°C, 2 h. [a] The reaction was scaled up to 10.0 mmol of *N*-tosylhydrazone. [b] The reaction was carried out at 110°C.

In addition to the *N*-tosylhydrazones derived from acetophenones, those derived from acetonaphthone (**3j**) and propiophenone (**3k**) are also suitable substrates (Scheme 3). *N*-Tosylhydrazones derived from cyclic ketone and 2-acetylfuran also worked well in this reaction to give **3m** and **3n**, respectively. Next, *N*-tosylhydrazones derived from benzaldehydes were examined and the reaction proceeded smoothly (**3o,p**). Notably, the reaction with *N*-tosylhydrazone derived from alkyl aldehyde was found to give the desired product, although it was necessary to carry out the reaction at an elevated temperature (**3q**). In addition, the reaction with *N*-tosylhydrazones derived from benzophenones gave the corresponding triarylmethane derivatives **3r–t**, which have various applications in materials science[18] and biological studies.[19]

Next, we investigated the scope of other polyfluoroarenes. As summarized in Scheme 4, polyfluoroarenes **1b–e** were submitted to this transformation and the corresponding alkylation products could be obtained in moderate to good yields. Pentafluorobenzene (**1b**) reacted with various *N*-tosylhydrazones, including that derived from cinnamaldehyde which afforded the allylation product **4h**. Other polyfluoroarenes, such as 1,2,4,5-tetrafluoro-3-methoxybenzene (**1c**) or 1,2,3,5-tetrafluorobenzene (**1d**) also worked, thus giving the corresponding products **4j** and **4k**. As for 2,3,5,6-tetrafluoropyridine (**1e**), the reaction time needed to be shortened to 30 minutes to prevent fluoro substitution by *t*BuO⁻. In this case the desired alkylation product **4l** could be obtained in 70 % yield.



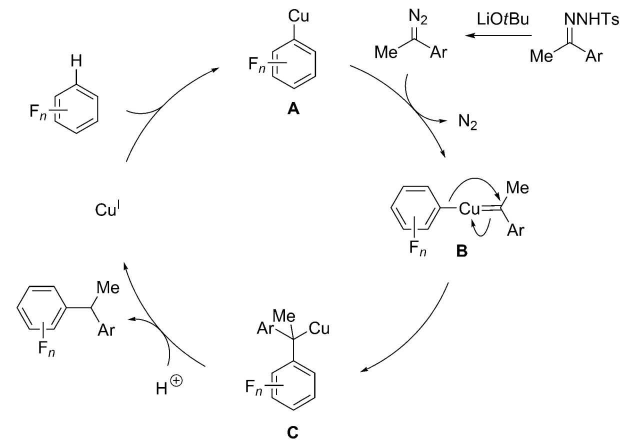
Scheme 4. Scope of polyfluoroarenes and *N*-tosylhydrazones. Reaction conditions: fluoroarene **1b–e** (0.60 mmol, 2.0 equiv), *N*-tosylhydrazone (0.30 mmol, 1.0 equiv), CuI (20 mol%), 1,10-phenanthroline (20 mol%), LiO*t*Bu (3.0 equiv), 1,4-dioxane (0.75 mL), and MeCN (0.75 mL), 90 °C, 2 h. [a] The reaction time was 30 min.



Scheme 5. Copper(I)-catalyzed reaction of diazo compounds with polyfluoroarenes. [a] Conditions A: fluoroarene (0.40 mmol, 2.0 equiv), diazo compound (0.20 mmol, 1.0 equiv), CuI (20 mol%), 1, 10-phenanthroline (20 mol%), LiO*t*Bu (3.0 equiv), 1,4-dioxane (1.0 mL), 90 °C, 3 h. [b] Conditions B: fluoroarene (0.40 mmol, 2.0 equiv), diazo compounds (0.20 mmol, 1.0 equiv), [Cu(MeCN)$_4$]BF$_4$ (20 mol%), LiO*t*Bu (2.0 equiv), 1,4-dioxane (1.0 mL), 90 °C, 3 h.

After achieving the alkylation of polyfluoroarenes with *N*-tosylhydrazones, we further investigated the direct reaction of diazo compounds under the similar reaction conditions (Scheme 5). The reaction with diaryldiazomethanes proceeded smoothly under the same reaction conditions as shown above, thus affording the corresponding alkylation products **5a–c** in good yields (Scheme 5, conditions A). However, only trace amounts of the alkylation product could be obtained when using diazoesters as the substrates under the same reaction conditions. Upon screening the catalysts, it was found that 20 mol % [Cu(CH$_3$CN)$_4$]BF$_4$ afforded the optimal results (Scheme 5, conditions B). Notably, the reactions with diazoesters are sensitive to the substituents on the aromatic ring of the diazo substrates. The diazoesters bearing an electron-donating group or electron-withdrawing group on the aromatic ring afforded the desired products **5h** and **5i** in diminished yields.

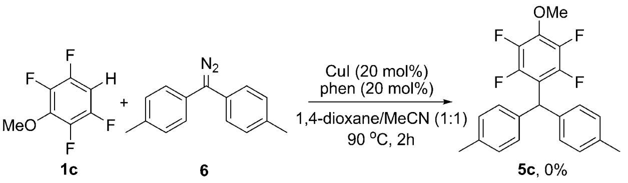
Based on our previous studies,[14–16] we propose the reaction mechanism as shown in Scheme 6. The reaction is initiated by the deprotonation of the relatively acidic C–H bond of the polyfluoroarene substrate. It is then followed by transmetalation to a copper(I) catalyst to generate the polyfluoroaryl copper species **A**. Subsequently, **A** reacts with the in situ-generated diazo substrate to form the copper carbene species **B**, from which migration insertion occurs to



Scheme 6. Proposed reaction mechanism.

generate the intermediate **C**. Finally, protonation of **C** delivers the alkylation product and completes the catalytic cycle.

An alternative mechanism to account for the reaction is copper(I) carbene aromatic substitution. However, such electrophilic substitution reaction normally occurs for relatively electron-rich aromatic rings.[20] To gain further insights into the reaction, we carried out the reaction in the absence of base by using the diaryldiazomethane (**6**) as the substrate [Eq. (1)]. Inspection of the crude reaction mixture by GC-MS and ^{1}H NMR spectroscopy indicated that alkylation product **5c** was not formed. The result is not supportive of an electrophilic substitution mechanism, in which case the base is not necessary.



In conclusion, we have developed an efficient copper(I)-catalyzed alkylation reaction of polyfluoroarenes with *N*-tosylhydrazones through direct C−H functionalization, thus affording the diarylmethane derivatives or triarylmethane derivatives in moderate to good yields. Considering the ease of synthesis for *N*-tosylhydrazones and the benefits of the cheap copper(I) catalyst, this reaction represents an efficient and practical access to introduce an alkyl group (in particular secondary benzyl group) to polyfluoroarenes, a reaction which is difficult to realize through other transition-metal-catalyzed C−H bond functionalization methods.

Keywords: C−H activation · carbenes · copper · diazo compounds · synthetic methods

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