

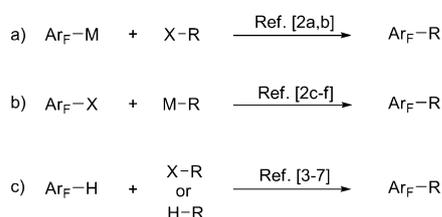
Copper(I)-Catalyzed Alkylation of Polyfluoroarenes through Direct C–H Bond Functionalization**

Shuai Xu, Guojiao Wu, Fei Ye, Xi Wang, Huan Li, Xia Zhao, Yan Zhang, and Jianbo Wang*

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(sp²)–C(sp³) 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]

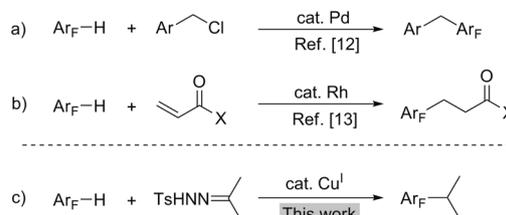
Apparently, the methods based on direct C–H functionalization of polyfluoroarenes are favored in terms of atom and step economy. However, there are at least two factors that



Scheme 1. General methods for introducing polyfluoroarene groups.

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(sp²)–C(sp²) 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] How-



Scheme 2. C(sp²)–C(sp³) bond-forming reactions of polyfluoroarenes.

ever, 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.

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-

[*] S. Xu, G. Wu, F. Ye, X. Wang, H. Li, X. Zhao, Dr. Y. Zhang, Prof. Dr. J. Wang
 Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry
 Peking University, Beijing 100871 (China)
 E-mail: wangjb@pku.edu.cn

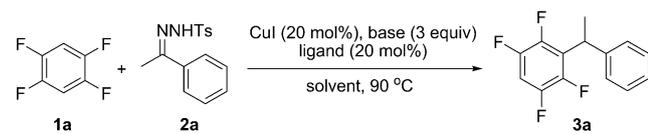
Prof. Dr. J. Wang
 The State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
 354 Fenglin Lu, Shanghai 200032 (China)

[**] The project is supported by the National Basic Research Program of China (973 Program, No. 2015CB856600) and NSFC (Grant No. 21272010 and 21332002)

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201412450>.

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]

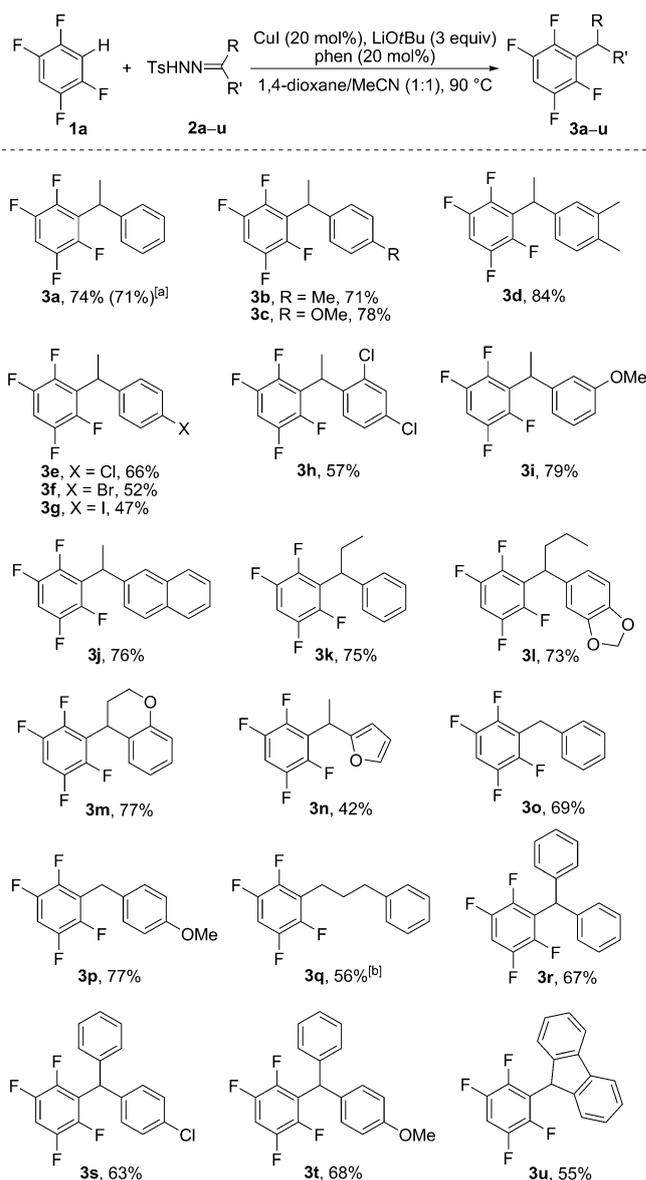


Entry	Solvent	Ligand	Base	Yield [%] ^[b]
1	1,4-dioxane	–	LiOtBu	26
2	1,4-dioxane	bpy	LiOtBu	60
3	1,4-dioxane	phen	LiOtBu	70 (69)
4	1,4-dioxane	PPh ₃	LiOtBu	50
5	1,4-dioxane	dppe	LiOtBu	27
6	1,4-dioxane	phen	Cs ₂ CO ₃	24
7	1,4-dioxane	phen	NaOtBu	16
8	1,4-dioxane	phen	KOtBu	5
9	MeCN	phen	LiOtBu	70
10	1,4-dioxane/MeCN (1:1)	phen	LiOtBu	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 CH₃NO₂ 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 LiOtBu 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 PPh₃ 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 LiOtBu 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



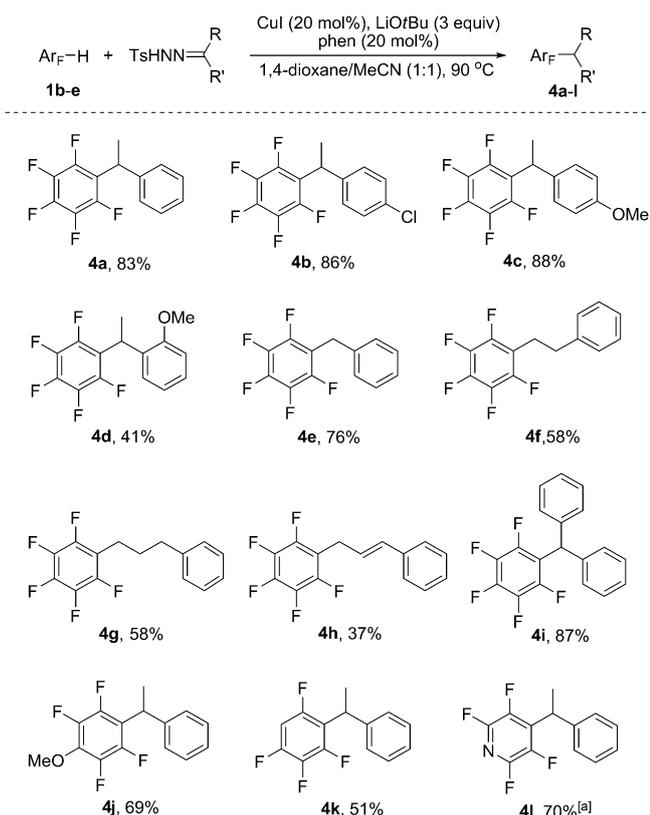
Scheme 3. Scope of *N*-tosylhydrazones. Reaction conditions: fluoroarene **1a** (0.60 mmol, 2.0 equiv), *N*-tosylhydrazone **2a–u** (0.30 mmol, 1.0 equiv), CuI (20 mol%), 1,10-phenanthroline (20 mol%), LiOtBu (3.0 equiv), 1,4-dioxane (0.75 mL), and MeCN (0.75 mL), 90 °C, 2 h. [a] The reaction was scaled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

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]

In addition to the *N*-tosylhydrazones derived from acetophenones, those derived from acetophenone (**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**

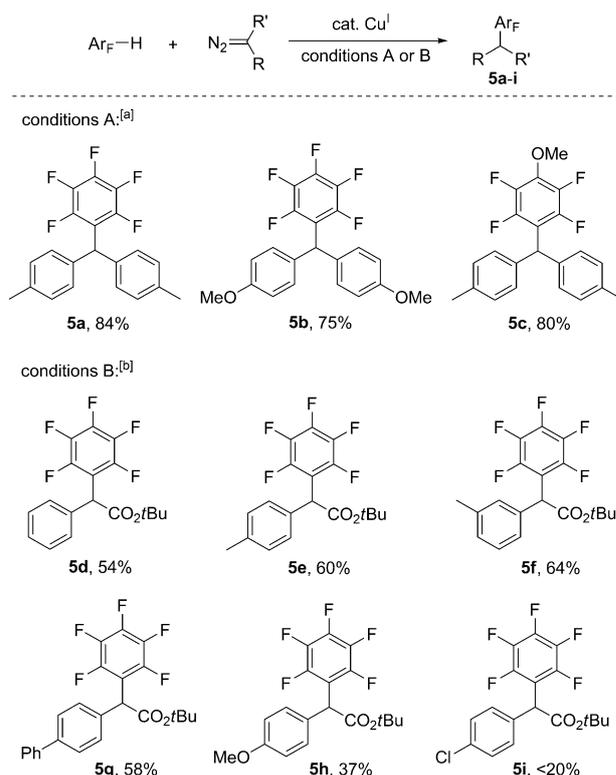
and **3n**, respectively. Next, *N*-tosylhydrazones derived from benzaldehydes were examined and the reaction proceeded smoothly (**3o,p**). Notably, the reaction with *N*-tosylhydrazone derived from alkyl aldehyde was found to give the desired product, although it was necessary to carry out the reaction 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



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%), LiOtBu (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.

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 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%), LiOtBu (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]BF₄ (20 mol%), LiOtBu (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(CH₃CN)₄]BF₄ 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

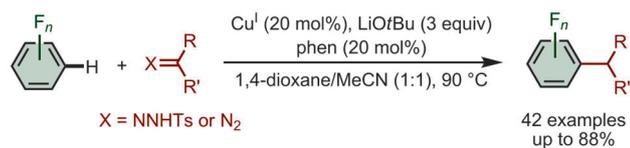
Communications



Synthetic Methods

S. Xu, G. Wu, F. Ye, X. Wang, H. Li,
X. Zhao, Y. Zhang,
J. Wang* ————— ■■■■-■■■■

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



Along came “Poly”: C(sp²)–C(sp³) bond formation through direct C–H functionalization proceeds through a copper(I)-catalyzed alkylation of electron-poor polyfluoroarenes with *N*-tosylhydrazones or

diazo compounds. The transformation represents a highly efficient practical method for the direct alkylation of polyfluoroarenes. phen = 1,10-phenanthroline, Ts = 4-toluenesulfonyl.