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Cu(I)-Catalyzed Cross-Coupling of Terminal Alkynes with Trifluoromethyl Ketone *N*-Tosylhydrazones: Access to 1,1-Difluoro-1,3-enynes

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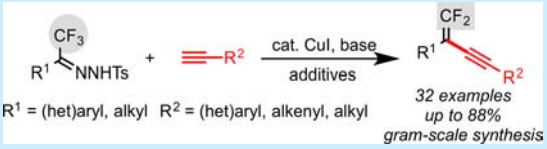
Supporting Information

ABSTRACT: C−C Bond formation and β-F elimination have been achieved in a Cu(I)-catalyzed cross-coupling reaction of terminal alkynes and trifluoromethyl ketone *N*-tosylhydrazones. The reaction represents an efficient synthesis of 1,1-difluoro-1,3-enyne derivatives. Mechanistically, the migratory insertion of the copper carbene intermediate leads to the C−C bond formation, which is followed by C−F bond cleavage.

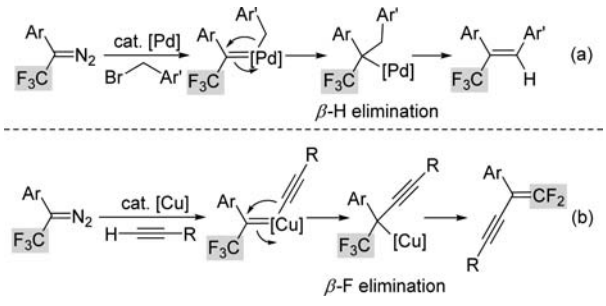


1,3-Enynes are valuable building blocks, which have found wide applications in organic synthesis, medicinal chemistry, and material sciences.[1] On the other hand, the replacement of hydrogen with fluorine has been known to change the organic molecules' physical, chemical and biological properties significantly. Consequently, organofluorine compounds have attracted widespread attention in various fields.[2] In this context, fluorinated 1,3-enynes are expected to be versatile fluorine-bearing building blocks in the synthesis of organofluorine compounds,[3] and the development of efficient methods for their synthesis is of great importance.

Although the methods to access nonfluorinated 1,3-enynes have been well established,[4] the corresponding synthesis of fluorinated 1,3-enynes has been quite limited,[5] especially for the 1,1-difluoro-1,3-enynes. In 1976, Burton reported the reaction of fluoroolefins with phosphonium ylides to afford fluorinated 1,3-enynes.[6] Along with the development of transition-metal-catalyzed cross-coupling reactions, various 1,1-difluorovinyl building blocks have been utilized to react with alkynyl coupling partners. For example, fluorinated iodoethenes and chloroethenes have been coupled with alkynylzinc reagents (Negishi-type coupling)[7] or terminal alkynes (Sonogashira-type coupling).[8] Ichikawa et al. developed a 1,1-difluorovinyl building block from 2,2,2-trifluoroethyl *p*-toluenesulfonate, which was applied in the cross-coupling with alkynyl iodides.[9] Hammond et al. reported an alternative method, in which *gem*-difluorohomoallenyl bromides were used as the source of a 1,1-difluorovinyl moiety.[10] More recently, Jeong et al. reported studies on the synthesis of 1,1-difluoro-1,3-enynes based on Pd-catalyzed coupling reactions.[11] However, the coupling substrates are not easy to prepare and handle. In addition, the synthesis of 1,1-difluoro-1,3-enynes based on Wittig-type reaction was reported in 2000, but only one example was included.[12]

On the other hand, cross-coupling reactions involving carbene migratory insertion have recently emerged as a new type of transition-metal-catalyzed C−C bond-forming reaction. The diazo compounds, either applied directly or generated in situ from the corresponding *N*-tosylhydrazones, have been utilized as the coupling partners.[13] As an application of this type of coupling reactions in the synthesis of CF_3-bearing compounds, it has been recently reported that the Pd-catalyzed cross-coupling of CF_3-bearing *N*-tosylhydrazones with benzyl bromides for the synthesis of trifluoromethylated trisubstituted olefins (Scheme 1a).[14,15] Notably, CF_3-bearing *N*-tosylhydrazones are easy to prepare and bench stable. Besides, Hu et al. have recently disclosed a Cu(I)-catalyzed *gem*-difluoroolefination of diazo compounds with $TMSCF_3$.[16] The reaction is proposed to follow a mechanism involving Cu(I) carbene migratory insertion and β-fluoride elimination. As a continuation of our interest in both carbene-based coupling and organofluorine chemistry, herein we report a 1,1-difluoro-1,3-enyne synthesis through Cu(I)-catalyzed coupling of CF_3-bearing *N*-tosylhydrazones with terminal alkynes (Scheme 1b). The reaction is simple and

Scheme 1. *gem*-Difluoroolefination through Cu(I) Carbene Migratory Insertion/β-Fluoride Elimination



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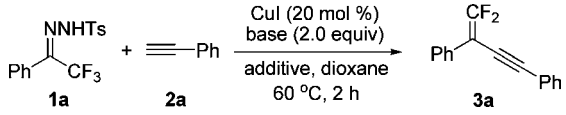
shows wide substrate scope, thus constituting a practical method for the synthesis of 1,1-difluoro-1,3-enynes.

At the outset, the study was carried out with trifluoromethylated *N*-tosylhydrazone **1a** and phenylacetylene **2a** as the substrates in the ratio of 1:1. They were treated with CuI (20 mol %), LiO*t*Bu (2.0 equiv) in dioxane (0.67 M) at 60 °C for 2 h. The product **3a** was isolated in 56% yield (Table 1, entry 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	base	ligand (mol %)	additive (mol %)	yield[b] (%)
1	LiO-*t*-Bu	none	none	56
2	KO-*t*-Bu	none	none	25
3	K_2CO_3	none	none	29
4	LiO-*t*-Bu	none	TBAC (20)	62
5[c]	LiO-*t*-Bu	none	TBAC (20)	71
6[c]	LiO-*t*-Bu[d]	none	TBAC (20)	73
7	LiO-*t*-Bu	none	TBAC (20), LiOTf (100)	71
8	LiO-*t*-Bu	pyridine (20)	TBAC (20), LiOTf (100)	35[e]
9	LiO-*t*-Bu	1,10-phen (20)	TBAC (20), LiOTf (100)	10[e]

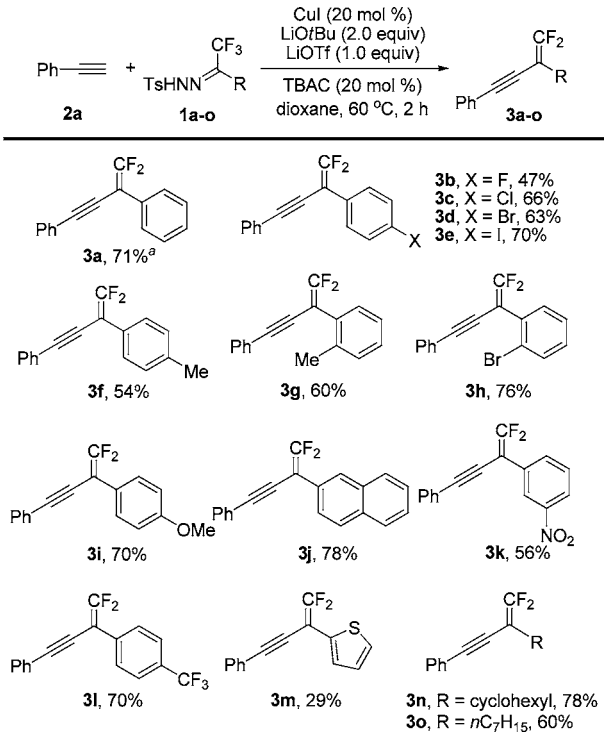
[a]Unless otherwise noted, the reactions were carried out on a 0.2 mmol scale with a **1a**/**2a** ratio of 1:1, base (200 mol %). [b]Unless otherwise noted, the yields refer to isolated products. [c]The ratio of **1a** and **2a** is 1:1.5. [d]300 mol % LiO-*t*-Bu. [e]^{19}F NMR yields with trifluorotoluene as the internal standard by 400 MHz NMR. TBAC = tetrabutylammonium chloride; LiOTf = lithium triflate. 1,10-phen =1,10-phenanthroline.

Encouraged by the initial results, we proceeded to optimize the reaction by first screening the bases and found that LiO-*t*-Bu gave the best results (entries 1−3). Subsequently, we observed that the yield could be slightly improved by adding phase transfer catalyst (entry 4). Changing the substrates ratio from 1:1 to 1:1.5 could further improve the yield (entry 5), while increasing the amount of base gave a similar result (entry 6). Since C−F bond cleavage is involved in the reaction, it is thus considered that additives that can effectively combine fluoride anion may enhance the reaction. As expected, adding LiOTf (1.0 equiv) slightly improved the yield under the condition that the substrates ratio remains 1:1 (entry 7). Finally, it was found that adding pyridine or 1,10-phenanthroline ligand had negative effects on the reaction (entries 8 and 9).

With the optimized reaction conditions in hand, the substrate scope of this reaction was then investigated with a series of *N*-tosylhydrazones and alkynes. As illustrated in Scheme 2, various trifluoromethylated *N*-tosylhydrazones **1a**−**o**, including aryl and alkyl *N*-tosylhydrazones, could react smoothly with phenylacetylene **2a** to afford the corresponding 1,1-difluoro-1,3-enynes **3a**−**o** in moderate to good yields. The reaction is not significantly affected by the electronic nature of the substituents. Thiophenyl-substituted *N*-tosylhydrazone **1m** is also compatible in this transformation, albeit giving the product **3m** in low yield. Notably, the reaction is also applied to alkyl *N*-tosylhydrazones, affording the corresponding products in good yields (**3n**,**o**).

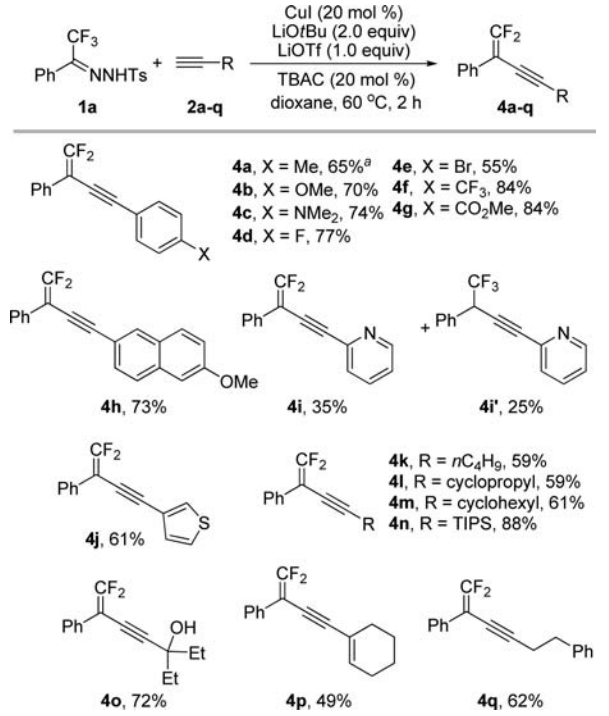
Next, the scope of alkynes was investigated with a series of terminal alkynes **2a**−**q**. As shown in Scheme 3, under the standard conditions the coupling reaction affords the corresponding 1,1-difluoro-1,3-enynes **4a**−**q** in good yields. A series of *para*-substituted aromatic alkynes were examined, and we found that the electronic nature of the substituents did not appreciably affect the reaction (Scheme 3, **4a**−**g**). Interestingly,

Scheme 2. Reaction Scope of *N*-Tosylhydrazones[a]



[a]Reaction conditions: CuI (20 mol %), TBAC (20 mol %), LiOTf (0.2 mmol), **1a**−**o** (0.2 mmol), **2a** (0.2 mmol), dioxane (3.0 mL), 60 °C under N_2 for 2 h, isolated yields.

Scheme 3. Reaction Scope of Alkynes[a]



[a]Reaction conditions: CuI (20 mol %), TBAC (20 mol %), LiOTf (0.2 mmol), **1a** (0.2 mmol), **2a**−**q** (0.2 mmol), dioxane (3.0 mL), 60 °C under N_2 for 2 h, isolated yields.

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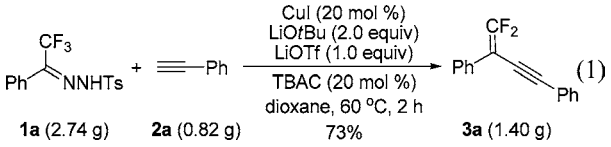
when 2-ethynylpyridine was added to the reaction, in addition to the expected 1,1-difluoro-1,3-enyne product **4i**, trifluoromethylated product **4i′** was also isolated. The formation of **4i′** is attributed to the protonolysis of the organocopper intermediate, which is generated from the migratory insertion of Cu(I) carbene intermediate (vide infra). 3-Ethynylthiophene was also found as suitable substrate, giving product **4j** in 61% yield. Likewise, a series of alkyl substituted alkynes were examined, and in all the cases the corresponding products could be obtained in moderate to good yields. In particular, with TIPS-protected alkyne as the substrate, the corresponding product **4n** could be isolated in 88%. Notably, free hydroxyl group and alkenyl group also tolerate the reaction (**4o** and **4p**).

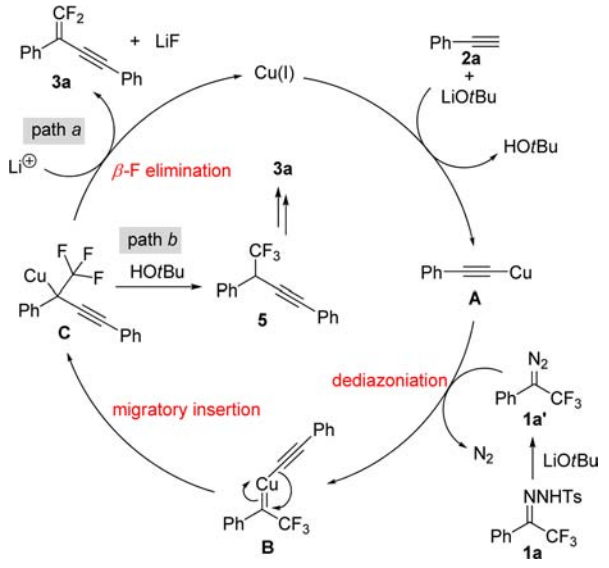
To demonstrate the practical usefulness of this reaction, a gram-scale experiment was carried out with *N*-tosylhydrazone **1a** and ethynylbenzene **2a**. The gram-scale experiment gave comparable result (eq 1).



(1)

A plausible mechanism is proposed to account for this Cu(I)-catalyzed reaction (Scheme 4). First, alkynylcopper species **A** is

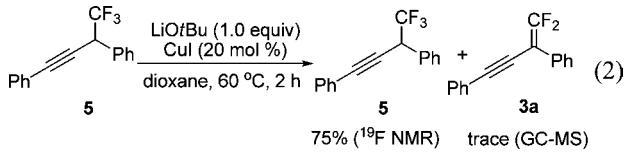
Scheme 4. Proposed Reaction Mechanism



generated from CuI and alkyne **2a** in the presence of LiO-*t*-Bu. Then Cu(I) carbene **B** is generated through dediazoniation of the in situ generated diazo substrate **1a′**. Subsequently, carbene migratory insertion of intermediate **B** occurs to afford intermediate **C**, which is followed by *β*-fluoride elimination to deliver the 1,1-difluoro-1,3-enyne product **3a**. *β*-Fluoride elimination has been extensively explored by Ichikawa and co-workers as a useful strategy in the synthesis of organofluorine compounds.[17] Notably, *β*-fluoride elimination from organocupper species under catalytic conditions is rare. To the best of our knowledge, the report by Hu and co-workers in 2013 on the Cu(I)-catalyzed *gem*-difluoroolefination of diazo compounds seems to be the only previously reported example of *β*-fluoride elimination in a Cu(I)-catalyzed reaction.[16]

An alternative reaction pathway from **C** is the generation of **5** through protonolysis, instead of direct *β*-fluoride elimination from **C**.[18] In the presence of base, deprotonation may subsequently occur from **5** to form a carbanion, which is followed by *β*-fluoride elimination to give **3a**. In the case of **4i** and **4i′** shown in Scheme 3, the trifluoromethylated product could be indeed isolated in certain cases. The electronic effects may play a role in directing the reaction pathway from intermediate **C** to either *β*-fluoride elimination or protonolysis.

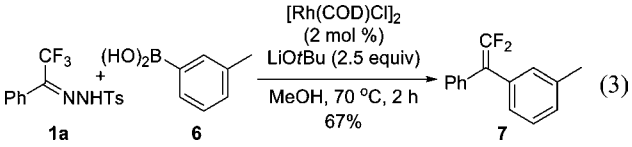
To verify whether this mechanism is operative, a control experiment has been carried out by submitting the independently synthesized trifluoromethylated compound **5** to the standard reaction conditions. Inspection of the crude reaction mixture indicated that compound **5** was mostly recovered, and the 1,1-difluoro-1,3-enyne product **3a** was observed in only trace amounts (eq 2). Therefore, dehydrofluorination from the



(2)

trifluoromethylated product **5** seems unlikely. Therefore, the results do not provide supportive evidence for path ***b***. However, further rigorous studies are needed to establish the reaction mechanism unambiguously.

Finally, to demonstrate that such a *gem*-difluoroolefin synthesis through *β*-fluoride elimination may also be applicable to other related catalytic systems, we have treated *N*-tosylhydrazone **1a** and *m*-tolylboronic acid **6** with a Rh(I) catalyst.[19] As expected, the *gem*-difluoroolefination product **7** could be obtained in 67% yield (eq 3). This reaction should



(3)

follow a similar reaction mechanism as shown in Scheme 4, including Rh(I) carbene migratory insertion and subsequent *β*-fluoride elimination from a Rh(I) species.[20]

In summary, we have developed an efficient method for the synthesis of 1,1-difluoro-1,3-enynes through Cu(I)-catalyzed cross-coupling of trifluoromethyl ketone *N*-tosylhydrazones with terminal alkynes. The reaction uses readily available starting materials and shows good functional group tolerance. In this transformation, the trifluoromethyl group has been used as the source of difluoromethylene group. Mechanistically, the reaction is featured by the combination of Cu carbene migratory insertion and *β*-fluoride elimination in one catalytic cycle. Further application of CF_3-bearing *N*-tosylhydrazones in the synthesis of organofluorine compounds is still ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experiment details, spectral data, and ^1H and ^{13}C NMR spectra for products. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00980.

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Notes

The authors declare no competing financial interest.

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