Copper-catalyzed [3 + 2] Annulation of Azides with a (Difluorovinyl)zinc Complex, Fluoroacetylene Equivalent

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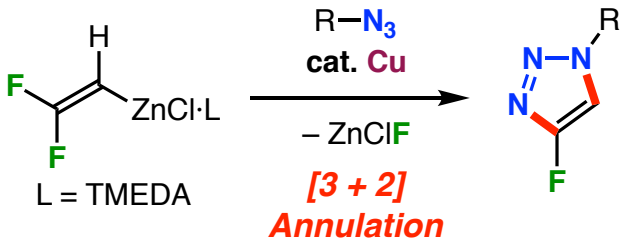
Supporting Information Placeholder

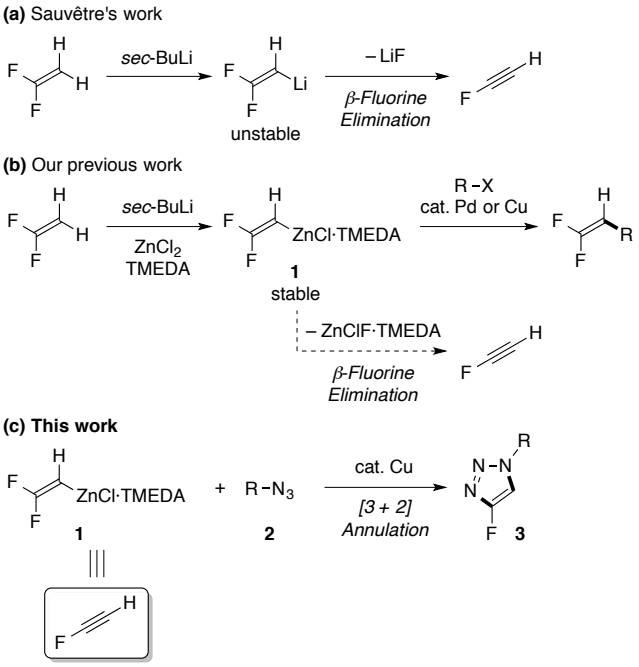


ABSTRACT: The copper-catalyzed [3 + 2] annulation of organic azides with (2,2-difluorovinyl)zinc chloride–TMEDA was achieved via C–F bond cleavage. Thus, a series of 1-substituted 4-fluorotriazoles were synthesized in high yields. In this reaction, the difluorovinylzinc complex functions as an easy-to-handle equivalent of fluoroacetylene (FC≡CH) to undergo cycloaddition with azides. This work offers a facile and practical method for the use of fluoroacetylene, which has been considered to be highly reactive and difficult to handle and control for synthetic applications.

The methods for chemical transformation of various types of fluorine-containing compounds have been developed to achieve considerable progress in pharmaceutical, agrochemical, and materials sciences.[1,2] However, despite the synthetic utility of alkynes, the reactivities of fluoroalkynes that bear a fluorine substituent on the sp carbon remain unclear owing to their instability, difficult preparation, and difficult isolation. Among them, fluoroacetylene (FC≡CH), the second smallest alkyne, was first synthesized in 1959 via the pyrolysis of fluoromaleic anhydride at high temperature (650 °C) under vacuum (5–7 mmHg).[3] However, the required harsh reaction conditions hampered the synthetic versatility of this method. Thereafter, a metalation–elimination protocol using fluorinated haloalkenes has been adopted for the synthesis of fluoroacetylene.[4] Although this method enabled the in situ generation of gaseous fluoroacetylene in solution and its application to synthetic use, its reactions are difficult to control because the metalated intermediates and produced fluoroacetylene are unstable. For example, Sauvêtre have reported the generation of fluoroacetylene via lithiation of 1,1-difluoroethylene (Scheme 1a).[5] In this case, β-fluorine elimination from the intermediary 2,2-difluorovinyllithium proceeded at temperature above −80°C to afford fluoroacetylene.[6]

Recently, we have developed 2,2-(difluorovinyl)zinc chloride–TMEDA (**1**) stabilized by the coordination of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), which serves as a difluorovinyl nucleophile in palladium- and copper-catalyzed couplings (Scheme 1b).[7] We envisaged that the difluorovinylzinc complex could also serve as an easy-to-handle equivalent of fluoroacetylene, which would be of considerable synthetic utility. Thus, we revisited fluoroacetylene chemistry[8] and succeeded in constructing 4-fluorinated triazole rings by treating aryl, benzylic, allylic, and alkyl azides with difluorovinylzinc complex **1**, where Huisgen-type [3 + 2] annulation[9,10] occurred (Scheme 1c).

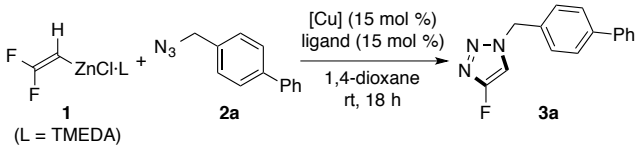
Scheme 1. Fluoroacetylene and Its Equivalent



First, we selected 4-(azidomethyl)biphenyl (**2a**) as a model compound for the examination of annulation with (difluorovi-

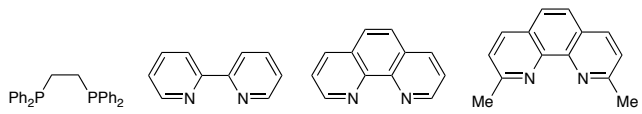
nyl)zinc complex **1**, which was prepared according to the reported procedure[7] via the deprotonation of 1,1-difluoroethylene and subsequent transmetalation and ligation (Table 1). Although only a trace amount of annulated product was provided upon the reaction of **2a** and **1** without a catalyst (Entry 1), the use of copper catalysts in 1,4-dioxane at room temperature efficiently afforded the corresponding [3 + 2] annulation product, 4-fluorotriazole **3a** (Entries 2–7). Among copper catalysts screened, CuCl was determined to be a prospective catalyst, which afforded **3a** in 81% yield (Entry 7). To improve the yield of **3a**, we screened ligands on CuCl. While phosphine ligands suppressed annulation (Entries 8 and 9), nitrogen ligands were effective (Entries 10–13). Specifically, 1,10-phenanthroline improved the yield of **3a** up to 86% (Entry 12).

Table 1. Screening of Conditions for [3 + 2] Annulation of **2a** with **1**.



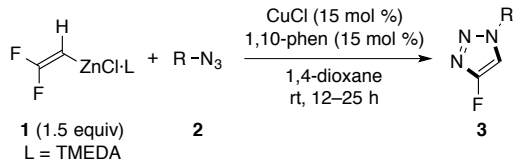
entry	[Cu]	ligand	**3a** (yield %)[a]
1	None	–	trace
2	Cu_2O	–	trace
3	$CuSO_4$	–	2
4	CuOAc	–	80
5	CuI	–	70
6	CuBr	–	78
7	CuCl	–	81
8	CuCl	PPh_3[b]	2
9	CuCl	dppe	14
10	CuCl	pyridine[b]	80
11	CuCl	2,2'-bpy	83
12	CuCl	1,10-phen	86 (83)
13	CuCl	2,9-diMe-1,10-phen	84

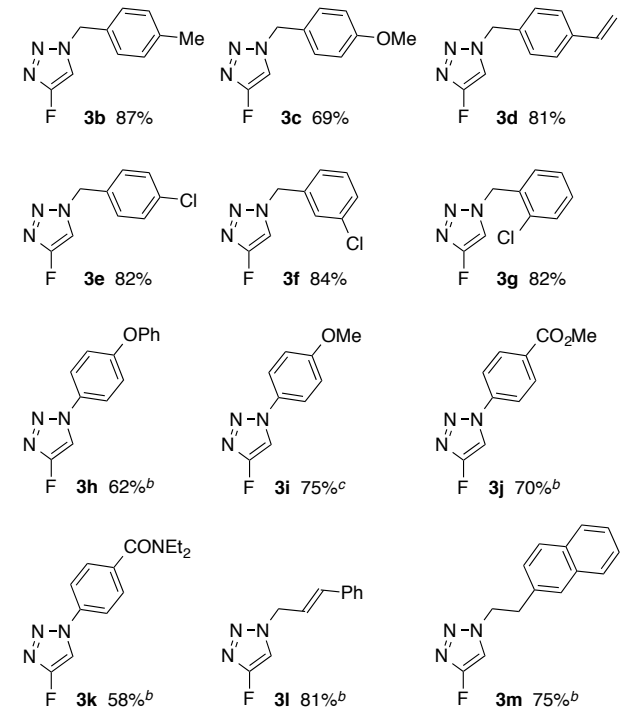
[a]Yield was determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard. Isolated yield was shown in parentheses. [b]30 mol %.



Using the determined optimal conditions, the scope of reaction with respect to azides **2** was investigated (Table 2). Benzylic azides **2b** and **2c** bearing methyl and methoxy groups on 4-positions successfully underwent copper-catalyzed [3 + 2] annulation with **1** to afford corresponding 1-benzylic 4-fluorotriazoles **3b** and **3c** in 87% and 69% yields, respectively. Because the vinyl group was tolerated under the conditions used, benzylic triazole **3d** bearing a vinyl group was synthesized in 81% yield. The annulation of benzylic azides **2e**–**2g** bearing a chlorine substituent at para, meta, or ortho positions proceeded effectively regardless of the position of the substituent, which led to corresponding triazoles **3h**–**3k** in 82%, 84%, and 82% yields, respectively. Although the reactions of aryl azides **2h**–**2k** required 2.5 equiv of (difluorovinyl)zinc complex **1**, triazoles **3h**–**3k** bearing aryl ether, alkyl ether, ester, and amide moieties were obtained in good to high yields. Not only allylic azide **2l** but also alkyl azide **2m** participated in [3 + 2] annulation, which led to the synthesis of 1-allylated and 1-alkylated 4-fluorotriazoles **3l** and **3m** in 81% and 75% yields, respectively.

Table 2. Synthesis of 1-Substituted 4-Fluorotriazoles **3**.[a]

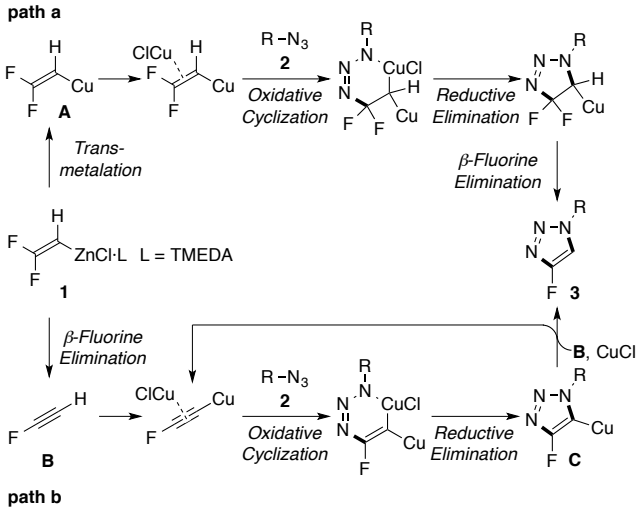




[a]Isolated yield. [b]**1** (2.5 equiv) was used. [c]**1** (2.5 equiv), CuCl (30 mol %), and 1,10-phen (30 mol %) were used.

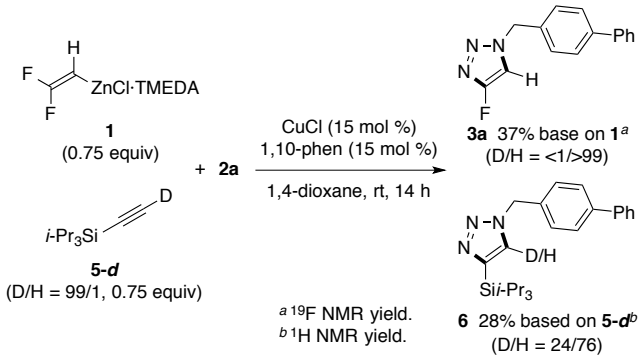
We assumed that the [3 + 2] annulation began with transmetalation between (difluorovinyl)zinc complex **1** and the copper(I) salt, which probably generated (difluorovinyl)copper **A** (Scheme 2, path a). Fokin advocated a mechanism involving two copper components for the Huisgen reaction of azides with terminal alkynes.[10] In his mechanism, the two copper components initially activate the alkyne moiety and then promote the formation of intermediary metalacycles in an oxidative cyclization-like manner. Thus, the in situ-generated (difluorovinyl)copper **A** would undergo the oxidative cyclization–reductive elimination sequence with the aid of another copper, followed by β-fluorine elimination to afford **3**. There remains another possible pathway involving fluoroacetylene **B** generated via β-fluorine elimination at an early stage. The protonation of triazolyl copper **C** probably proceeds with **B** as the final step (Scheme 2, path b).

Scheme 2. Plausible Reaction Mechanisms



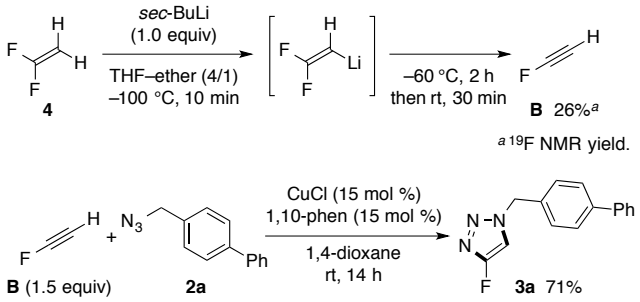
To gain mechanistic insight, a competition experiment was conducted using deuterated (triisopropylsilyl)acetylene **5-*d*** (D/H = 99/1). The treatment of azide **2a** with (difluorovinyl)zinc complex **1** in the presence of the copper catalyst and **5-*d*** afforded fluorinated triazole **3a** (D/H = <1/>99) derived from **1**, and nonfluorinated triazole **6** (D/H = 24/76) derived from **5-*d***; 5-deuterated **3a** was not observed (Scheme 3). If the annulation of **2a** with **1** involves the protonation step (from **C** to **3**), a substantial H/D scrambling would be observed via deuteration with **5-*d***. Thus, this result suggests that the [3 + 2] annulation of azides **2** with (difluorovinyl)zinc complex **1** probably does not proceed via the generation of fluoroacetylene **B**.

Scheme 3. Competition Experiment Using Deuterated Acetylene **5-*d***



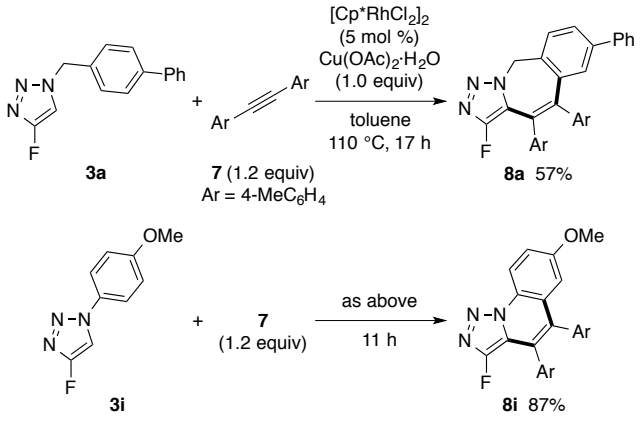
In addition, the reaction of fluoroacetylene **B**, prepared via the lithiation of 1,1-difluoroethylene (**4**) followed by β-fluorine elimination,[5,6] was examined. After the treatment of **4** with *sec*-BuLi at −100 °C, the reaction mixture was kept at −60 °C for 2 h, and then the temperature was increased to room temperature (Scheme 4). After stirring at room temperature for another 30 min, fluoroacetylene **B** was obtained as a THF–ether solution but only in 26% yield, which was characterized by ^{19}F NMR spectroscopy (δ −17.8 ppm relative to C_6F_6, singlet).[11] Additionally, when the obtained fluoroacetylene **B** in solution was treated with azide **2a** in the presence of the copper catalyst, triazole **3a** was obtained but only in 71% isolated yield (Scheme 4). Although this reaction apparently proceeds via the [3 + 2] annulation of azides **2** with **B**, the efficiency of the entire reaction remains quite low (<20% from **4**) and not practical. Moreover, the decrease in yield (71%) compared to 86% (Table 1, Entry 12) supports the fluoroacetylene-free mechanism in the [3 + 2] annulation of **2** with **1** (Scheme 2, path a).

Scheme 4. Generation of Fluoroacetylene **B** and Its Reaction with Azide **2a**



Further chemical transformations of triazoles **3** were examined. Because triazole rings are known to serve as a directing group,[12] the constructed fluorotriazole rings were applied to promote the rhodium-catalyzed C–H bond activation of a benzene ring on triazole nitrogen according to the annulation using pyrazole derivatives reported by Miura and Satoh (Scheme 5).[13] In the presence of $[Cp^*RhCl_2]_2$ as a catalyst and $Cu(OAc)_2·H_2O$ as an oxidant, the [5 + 2] annulation of 1-benzylated 4-fluorotriazole **3a** with diarylacetylene **7** effectively proceeded via domino C–H bond activation to afford azepine derivative **8a** in 57% yield. Similarly, 1-arylated 4-fluorotriazole **3i** underwent [4 + 2] annulation under the same conditions to afford pyridine derivative **8i** in 87% yield. Thus, fluorine-containing tricyclic compounds were readily synthesized by the combination of the copper-catalyzed [3 + 2] annulation and rhodium-catalyzed [5 + 2]/[4 + 2] annulation.

Scheme 5. Annulation of Triazoles **3** with Alkyne **7** via the Rhodium-Catalyzed Domino C–H Bond Activation



In summary, we achieved the copper-catalyzed [3 + 2] annulation of azides with (2,2-difluorovinyl)zinc chloride–TMEDA. We offer a facile and practical method for the use of a fluoroacetylene equivalent, which has been considered to be

highly reactive and difficult to handle and control for synthetic applications. Of note, the protocol provides an efficient method for the synthesis of 4-fluorotriazoles bearing a wide variety of substituents on the 1-position as promising candidates for pharmaceuticals and agrochemicals, which are difficult to prepare by conventional methods.[14,15]

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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