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Fluorine Chemistry **Hot Paper**

Copper-Catalyzed Enantioselective Difluoromethylation-Alkynylation of Olefins by Solving the Dilemma between Acidities and Reduction Potentials of Difluoromethylating Agents

*Zhiqiang Wei, Weiqin Zheng, Xiaolong Wan, and Jinbo Hu**

Abstract: Molecules containing a difluoromethyl group or a propargylic stereocenter are widely used in pharmaceuticals and agrochemicals, and 1,2-functionalization of olefins is an important method for introducing the two groups into molecules simultaneously. The construction of the propargylic stereocenter with terminal alkynes usually requires bases. However, difluoromethylating agents with high reduction potentials often decompose in the presence of bases because of their acidities, and those with low reduction potentials are stable but difficult to undergo the desired single electron transfer (SET) reduction. Using the linear relationship between reduction potential differences (ΔE) and Hammett substituent constants (σ) of difluoromethyl aryl sulfones, we solved the dilemma between acidities and reduction potentials of difluoromethylating agents. Herein, we report the first enantioselective difluoromethylation-alkynylation of olefins with difluoromethyl 4-chlorophenyl sulfone with high enantioselectivity (>90 % ee). We also extended this asymmetric fluoroalkylation-alkynylation reaction with other fluoroalkyl sulfones, which enabled efficient installation of trifluoromethyl, difluoroalkyl, difluorobenzyl, (benzenesulfonyl)-difluoromethyl and monofluoromethyl groups into products.

As a powerful approach to generate organic radical intermediates from various substrates, single electron transfer (SET) reaction has been widely used in modern organic synthesis,[1] and the reduction potential (E) is an important indicator to measure the difficulty of SET reaction. On the other hand, the Hammett plot [$\log(K_R/K_H)$ or $\log(k_R/k_H)$ versus Hammett substituent constants σ; K = equilibrium constant, and k = rate constant) has been one of the most widely used methods for the interpretation of organic reactions and their mechanisms.[2] In 1997, Moe and co-workers deduced that there is a new type of linear correlation between reduction potential differences ($\Delta E = E_R - E_H$) and Hammett substituent constants (σ) of organic compounds in electrochemical reactions, and they experimentally confirmed such linear relationship with substituted quinones.[3] However, unlike the traditional Hammett plot,[2] this new type of Hammett plot (ΔE versus σ)[3] has never been applied in tackling organic reaction problems.[4]

Organic molecules bearing a propargylic stereocenter are frequently found in a myriad of drugs and natural products such as *Efavirenz*, *Alfaprostol* and *Chameacynone*.[5] Liu and co-workers have elegantly developed the copper-catalyzed enantioselective synthesis of such products using terminal alkynes and in situ-generated substituted benzyl radicals (Scheme 1a).[6] It must be noted that Cs_2CO_3 plays an important role in generating tridentate anionic chiral ligands in these reactions.[7] Considering the difluoromethyl group (CF_2H) is isosteric and isopolar to the hydroxyl (OH) and mercapto (SH) groups and can often impart unique biological properties to target molecules,[8] we attempted the enantioselective difluoromethylation-alkynylation of olefins (Scheme 1b). Difluoromethyl benzothiazolyl sulfone (**3a**) with high reduction potential (−1.14 V), which was often used for radical difluoromethylation of olefins,[9] failed in this transformation with **3a** being completely consumed. Surprisingly, when the difluoromethyl sulfone **3a** was replaced with the 1,1-difluoroethyl sulfone **3b** (−1.22 V), the desired product was isolated in 83 % yield. We also screened other difluoromethyl radical precursors **3c**–**3h**[10] in this reaction, and found that no difluoromethylated products were formed (determined by ^{19}F NMR). We quickly realized that all these difluoromethylating agents **3a** and **3c**–**3h** decomposed rapidly to give difluorocarbene,[11] which could be evidenced by the formation of $PhOCF_2H$ from PhONa and **3a** (or **3c**–**3h**) in the presence of Cs_2CO_3 (for details, see SI). Therefore, we realized that less acidic precursors of difluoromethyl radicals are required.

Next, we investigated the relationship between the acidities (represented by the decomposition rates in the presence of Cs_2CO_3) and the substituent constants of R groups on difluoromethyl aryl sulfones **3** (Table 1). We found that as the substituent constants decrease, the acidities of difluoromethyl aryl sulfones **3** become weaker. So we used the difluoromethyl 4-methoxyphenyl sulfone (**3i**) as the difluoromethyl radical precursor. However, although the

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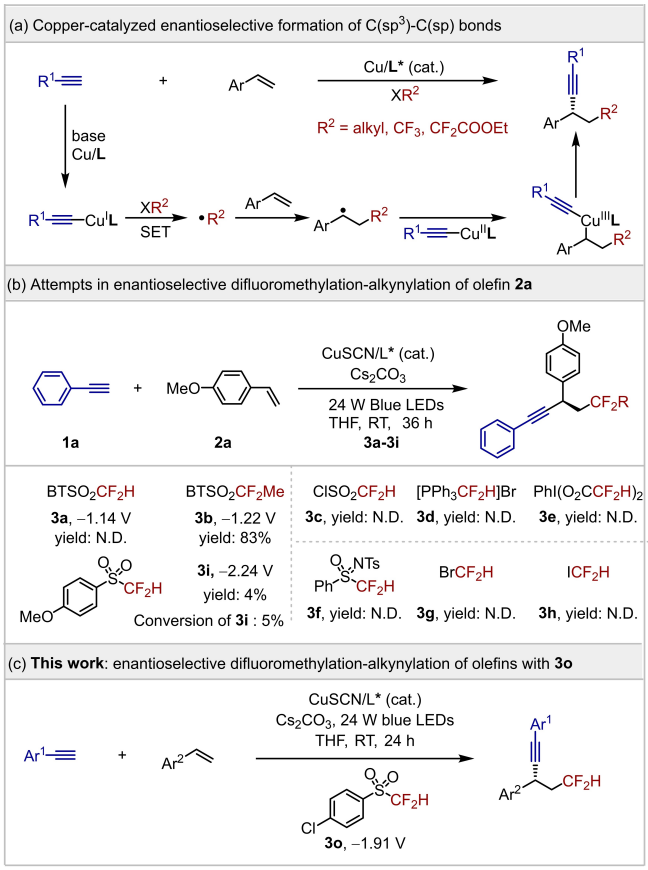
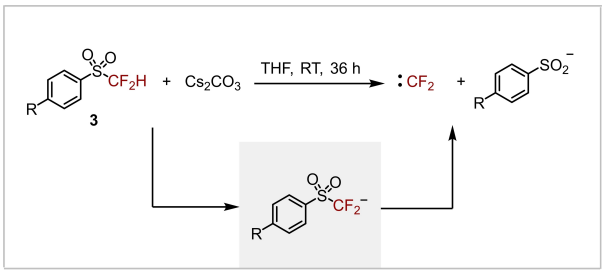


Scheme 1. Enantioselective intermolecular 1,2-functionalization of olefins. N.D. = not detected.

Table 1: Investigation on the acidities of difluoromethyl aryl sulfones.[a]



Entry	R	σ[c]	Recovery of **3** (%)[b]	*E* (V)[d]	Δ*E* (V)
1	OMe, **3i**	−0.27	>**99**	−2.24	−0.19
2	*t*Bu, **3j**	−0.20	>**99**	−2.18	−0.13
3	Me, **3k**	−0.17	>**99**	−2.17	−0.12
4	Ph, **3l**	−0.01	>**99**	−2.07	−0.02
5	H, **3m**	0	>**99**	−2.05	0
6	F, **3n**	0.06	**98**	−2.01	0.04
7	Cl, **3o**	0.23	**93**	−1.91	0.14
8	CF_3, **3p**	0.54	**86**	−1.68	0.37
9	CN, **3q**	0.66	**78**	−1.59	0.46

[a] Reaction conditions: **3** (0.3 mmol), Cs_2CO_3 (0.4 mmol), THF (2.0 mL). [b] Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. [c] Hammett substituent constants are cited from reference [2a]. [d] *E* refers to the reduction potential using Ag/AgCl as reference. $\Delta E = E_R - E_H$.

acidity of **3i** is weak enough to avoid its decomposition to difluorocarbene in the presence of Cs_2CO_3, the reduction potential of **3i** (−2.24 V) is not high enough to enable an efficient SET process to generate difluoromethyl radical species (Scheme 1b). As a result, the introduction of a difluoromethyl group and a propargylic stereocenter into molecules simultaneously seems to be a contradiction owing to the dilemma between acidities and reduction potentials of the difluoromethylating agents. Herein, we report a method to solve this dilemma using the linear relationship between the reduction potentials and substituent constants of difluoromethyl aryl sulfones (Figure 1), which enabled us to achieve the first enantioselective difluoromethylation-alkynylation of olefins with difluoromethyl 4-chlorophenyl sulfone **3o** (Scheme 1c).

The main challenge in enantioselective difluoromethylation-alkynylation of olefins is the lack of an appropriate difluoromethyl radical precursor that is able to tolerate Cs_2CO_3. Our group has been dedicated to the investigation of fluoroalkyl sulfones as robust reagents in organic synthesis.[12] Firstly, we chose $PhSO_2CF_2H$ (**3m**), an easily available sulfone that is stable in the presence of Cs_2CO_3, as a difluoromethylating agent for this reaction (Table 2, entries 1–3). To our delight, the target product **4a** was produced in 13 % yield with 90 % ee under the irradiation of blue LEDs (Table 2, entry 1). And the product yield and ee value of the reaction were found to gradually increase when we used sterically more hindered and electron-rich ligands (Table 2, entries 2–3). However, although **3m** is compatible with Cs_2CO_3, its reduction potential (−2.05 V) is still not high enough to generate the difluoromethyl radical efficiently. Hence, difluoromethyl 4-cyanophenyl sulfone (**3q**) with higher reduction potential (−1.59 V) was subjected to this reaction. However, the difluoromethylation-alkynylation of **2a** with **3q** could not proceed (Table 2, entry 4), suggesting that the high substituent constant (for CN group,

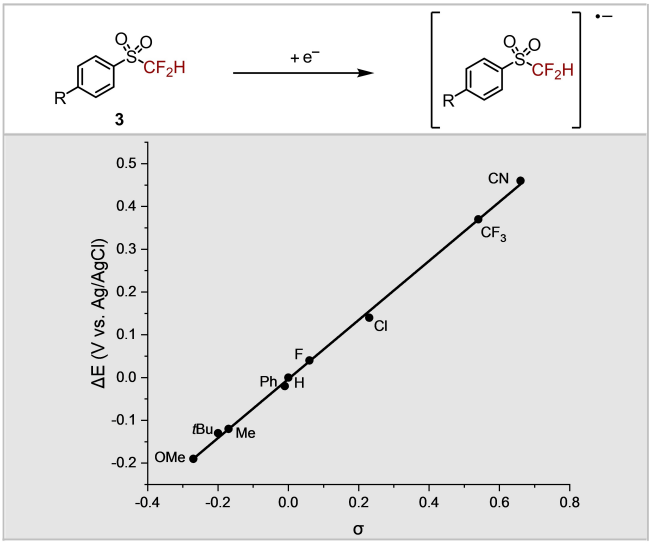
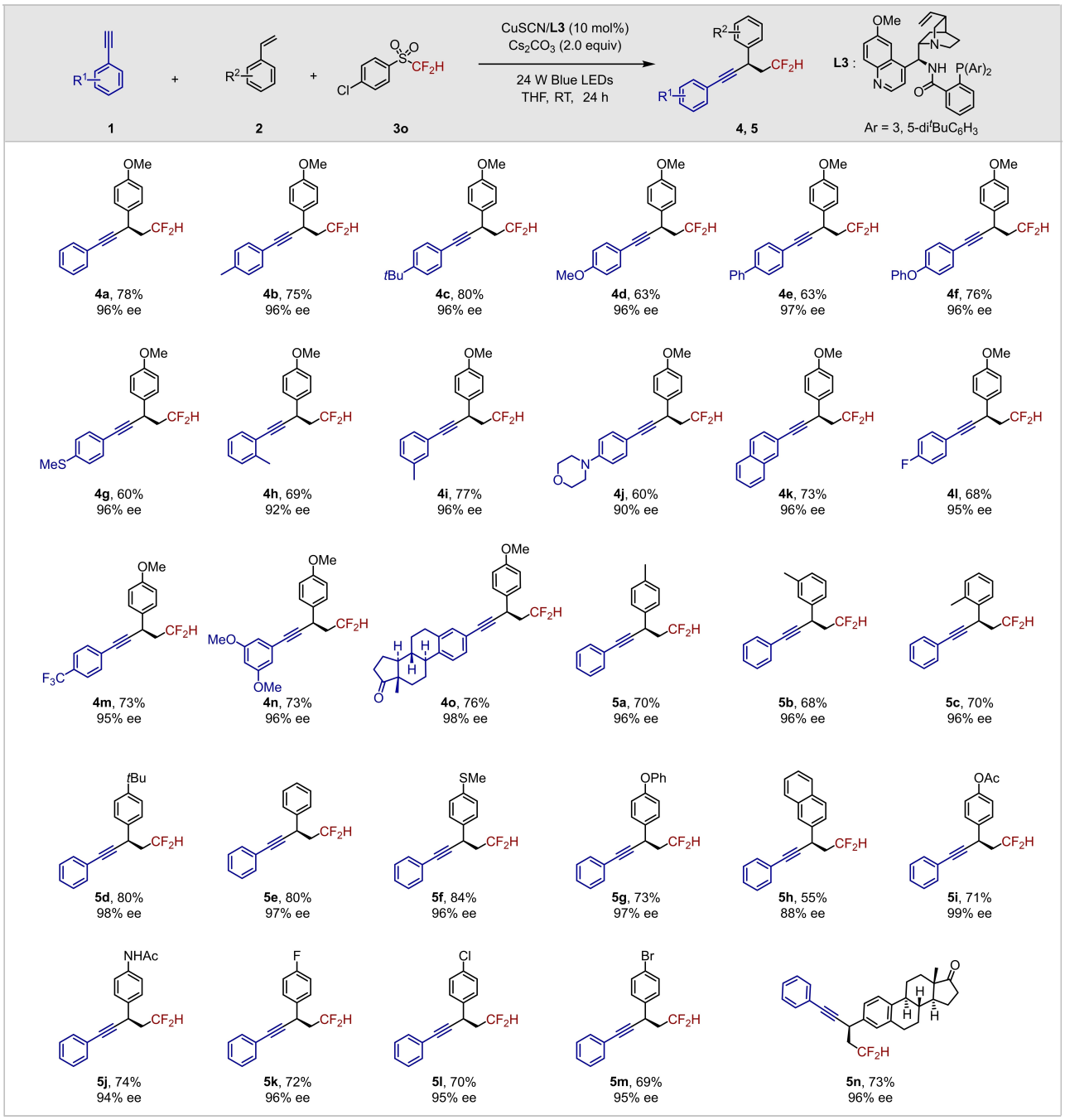


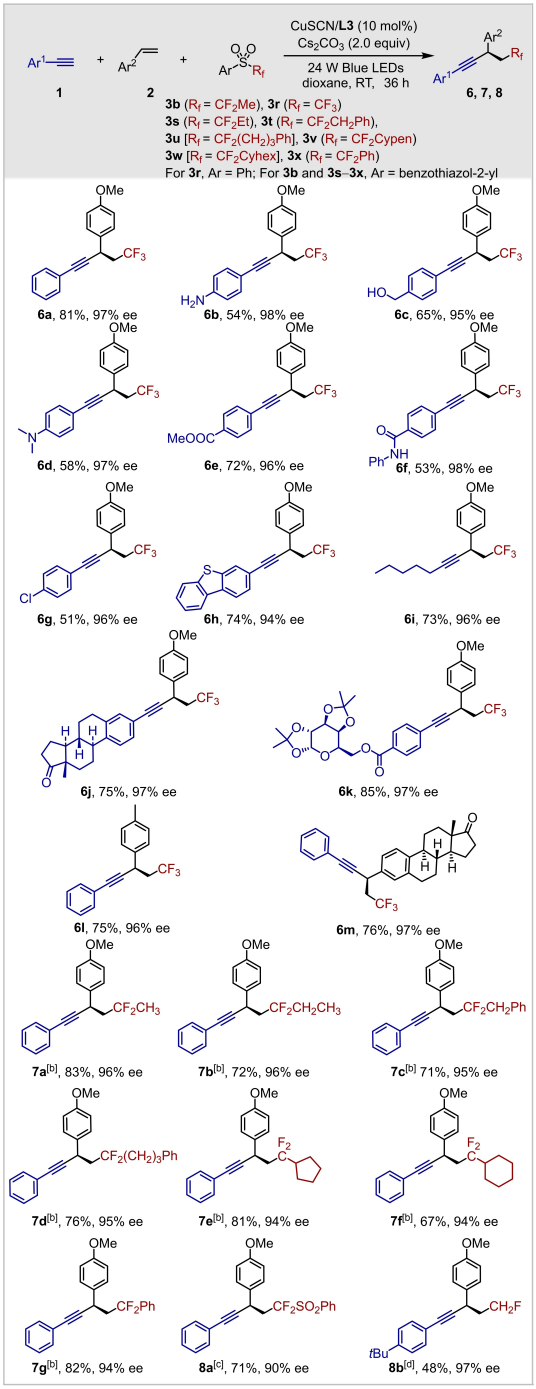
Figure 1. The linear correlation of reduction potential differences Δ*E* (V *vs.* Ag/AgCl) with Hammett substituent constants (σ) of difluoromethyl aryl sulfones **3i-3q** in CH_3CN. $\Delta E = E_R - E_H$.



Scheme 2. Copper-catalyzed enantioselective difluoromethylation-alkynylation of olefins with **3o**. [a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), **3o** (0.3 mmol, 1.5 equiv), CuSCN (0.02 mmol, 0.1 equiv), **L3** (0.02 mmol, 0.1 equiv), Cs_2CO_3 (0.4 mmol, 2.0 equiv), THF (2.0 mL), 24 h; the ee values were determined by chiral HPLC.

$\sigma = 0.66$) leads to high acidity of **3q** and the undesired acid-base reaction between **3q** and Cs_2CO_3.

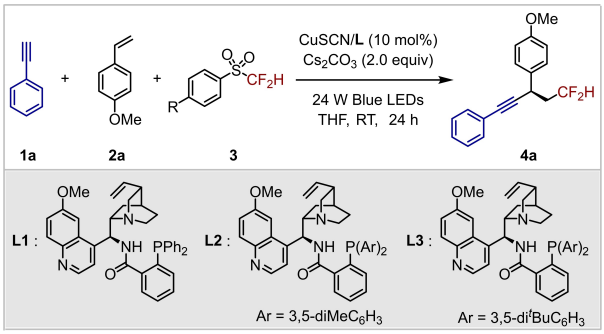
In light of previous work on the linear relationship between reduction potential differences (ΔE) and substituent constants (σ),[3,4] we measured the reduction potentials of nine difluoromethyl aryl sulfones (Table 1), and the correlation of ΔE and σ is shown in Figure 1. The linear regression coefficient r is 0.99 (for details, see SI), indicating that there is a linear relationship between reduction potential differences (ΔE) and substituent constants (σ) of difluoromethyl aryl sulfones **3i–3q** (Table 1 and Figure 1). Using Figure 1 as a guidance, we set out to solve the dilemma between acidities and reduction potentials of difluoromethylating agents by choosing a proper difluoromethyl aryl sulfone that locates at a point between **3m** (R=H) and **3q** (R=CN) in Figure 1. Accordingly, when sulfones **3n** (R=F) and **3p** (R=CF_3) were applied in the present reaction, the yields of **4a** were 47 % and 38 %, respectively (Table 2, entries 5 and



Scheme 3. Enantioselective fluoroalkylation-alkynylation of olefins with trifluoromethyl and difluoroalkyl sulfones. [a] Reaction conditions: **1** (0.2 mmol, 1.0 equiv), **2** (0.3 mmol, 1.5 equiv), $PhSO_2CF_3$ (**3r**) (0.3 mmol, 1.5 equiv), dioxane (2.0 mL), 36 h; the ee values were determined by chiral HPLC. [b] $BTSO_2CF_2R$ (**3b** or **3s**–**3x**) were used. [d] $PhSO_2CF_2Br$ (**3y**) was used. [e] $4\text{-}ClC_6H_4SO(NTs)CH_2F$ (**3z**) was used.

6). Finally, we were delighted to find that, when the difluoromethyl 4-chlorophenyl sulfone **3o** (R=Cl, see Figure 1) was used in the reaction, product **4a** was afforded in 81 % yield with 96 % ee (Table 2, entry 7). In this reaction, the conversion of **3o** was found to be 59 %, indicating that

Table 2: Screening the conditions of enantioselective difluoromethylation-alkynylation of olefin **2a** with difluoromethyl aryl sulfones **3**.[a]

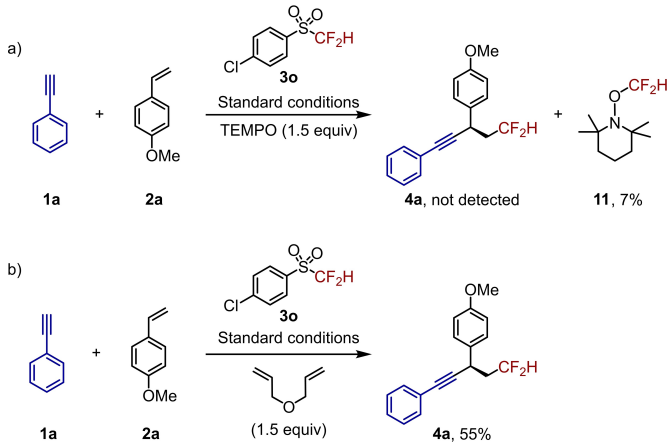


Entry	R	L	Yield (%)[b]	ee (%)[c]
1	H, **3m**	**L1**	13	90
2	H, **3m**	**L2**	21	92
3	H, **3m**	**L3**	37	96
4	CN, **3q**	**L3**	N.D.	–
5	F, **3n**	**L3**	47	96
6	CF_3, **3p**	**L3**	38	96
7	Cl, **3o**	**L3**	81	96

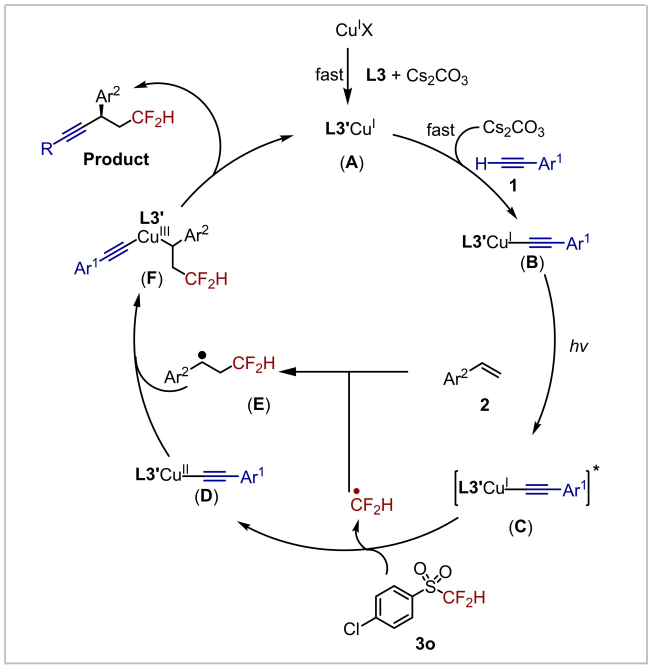
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), **3** (0.3 mmol), CuSCN (0.02 mmol), **L** (0.02 mmol), Cs_2CO_3 (0.4 mmol), THF (2.0 mL). [b] Determined by ^{19}F NMR spectroscopy using trifluoromethoxybenzene as an internal standard. [c] Determined by chiral HPLC. N.D. = not detected.

3o could generate difluoromethyl radical efficiently through an SET process with alkynylcopper species; and the by-products were $PhCCCF_2H$ (**9**, 1 %) and CH_2CF_2 (**10**, 1 %) (for details, see SI). The overall efficiency of **3o** in generating difluoromethyl radical was found to be 94 % (for details, see SI), suggesting that the consumed sulfone **3o** was generating difluoromethyl radical rather than being decomposed by Cs_2CO_3 to produce difluorocarbene. Therefore, when **3o** was used as the difluoromethyl radical precursor, a chiral anionic ligand was able to be generated in the presence of Cs_2CO_3, which is a key factor for the success of this enantioselective fluoroalkylation-alkynylation of olefin **2a**.

With the optimized reaction conditions (Table 2, entry 7) in hand, next we investigated the substrate scope of alkynes in this copper-catalyzed enantioselective transformation. As shown in Scheme 2, the reaction was not sensitive to electronic or steric nature of the substrates, and the ee values of the reaction were generally higher than 90 %. Various aryl alkynes, including those having monosubstituted phenyl rings (with electron-neutral, -rich, or -deficient functional groups at different positions (*ortho*, *meta*, or *para*) and disubstituted phenyl rings, were all suitable for this reaction to afford the desired products **4a**–**4n** in good yields and with excellent enantioselectivities. Many functional groups, such as methoxyl (**4d**), phenoxyl (**4f**), methylthio (**4g**), morpholinyl (**4j**), trifluoromethyl (**4m**), carbonyl (**4o**) were well tolerated under the reaction conditions. Encouraged by the above results, we next switched our attention to examining the scope of alkenes (**5a**–**5n**). The reactions with aryl-substituted alkenes bearing



Scheme 4. Radical capture experiments.



Scheme 5. Proposed mechanism.

ortho-, *meta*- and *para*-substituents on the aryl groups gave the corresponding products in good yields and with excellent ee values (**5a**–**5c**). Many functional groups, such as methylthio (**5f**) phenoxyl (**5g**), ester (**5i**), amide (**5j**), halogens (**5k**–**5m**) were found to be amenable to the current reaction conditions. The natural product derivative can also be applied as a substrate in this reaction (**5n**).

In addition to the difluoromethyl group, other fluoroalkyl groups (such as trifluoromethyl,[13] difluoroalkyl,[14] difluorobenzyl,[15] monofluoromethyl[16]) are also highly important for biologically relevant molecules. As shown in Scheme 3, when we applied trifluoromethyl phenyl sulfone (**3r**, instead of expensive Togni's reagent[6e,17]) in enantioselective trifluoromethylation-alkynylation of olefins, trifluoromethylated products **6a**–**6m** were obtained efficiently. It is important to note that, similar to aryl-substituted alkynes, alkyl-substituted alkyne is also applicable in this reaction (**6i**, 73% yield, 96% ee). We also synthesized 1,1-difluoroalkyl benzothiazol-2-yl sulfones (**3b** and **3s**–**3w**) and were pleased to find that these sulfone reagents were able to undergo enantioselective 1,1-difluoroalkylation-alkynylation of olefins (**7a**–**7f**). Furthermore, the enantioselective reaction proceeded smoothly with 1,1-difluorobenzyl benzothiazol-2-yl sulfone (**3x**) to give **7g** in 71% yield and with 94% ee. Interestingly, when bromodifluoromethyl phenyl sulfone (**3y**) was applied in this reaction, (benzenesulfonyl)difluoromethyl radical (instead of bromodifluoromethyl radical) was generated via SET,[18] giving product **8a** in 71% yield and with 90% ee. It is noteworthy that the monofluoromethylation-alkynylation of olefin was also realized by using monofluoromethyl sulfoximine **3z** as the monofluoromethyl radical precursor, affording product **8b** in 48% yield with 97% ee.[19]

Next, we performed the radical capture experiments (Scheme 4, For details, See SI). When TEMPO (1.5 equiv) was added, the reaction was completely suppressed and 7% of **11** was detected, indicating that the difluoromethyl radical was generated during the reaction (Scheme 4a). We also found that the addition of diallyl ether (1.5 equiv) led to the decrease of yield; however, the reaction was not completely inhibited, probably owing to the high reactivity of *p*-methoxy styrene (Scheme 4b).

Based on the radical capture experiments and related literature,[6,7] a working mechanism is proposed (as shown in Scheme 5). First, the proton on the amide group in ligand **L3** is grabbed by Cs_2CO_3 to form anionic chiral ligand **L3′**, and the deprotonation process on **L3** is faster than that on **3o**. Species **A** is formed through the interaction between CuSCN and **L3′**. Then, species **A** reacts with alkyne and base to form species **B**, which is excited by irradiation with blue light to form species **C**. Subsequently, single electron transfer (SET) from Cu^I species **C** to sulfone **3o** readily occurs to afford Cu^{II} species **D** and difluoromethyl radical ($^{\bullet}CF_2H$). Next, the difluoromethyl radical ($^{\bullet}CF_2H$) selectively adds to alkene **2** to produce a prochiral benzyl radical **E**. Finally, benzyl radical **E** and the species **D** undergo $C(sp^3)$–C(sp) bond formation (possibly via a Cu^{III} species **F**)[20] to deliver the enantioenriched products, while releasing the Cu^I species **A** for the next catalytic cycle.

In summary, we have developed a copper-catalyzed three-component enantioselective fluoroalkylation-alkynylation of olefins for the expedited synthesis of structurally diverse chiral fluoroalkylated propargylic compounds, which showcase the first example of a highly enantioselective reaction involving fluoroalkyl sulfones. One striking feature of this method is the ready accommodation of easily available alkynes (aryl-, hetero-aryl and alkyl-substituted ones) and terminal alkenes as well as various fluoroalkyl radical precursors (trifluoromethyl, difluoromethyl, difluoroalkyl, difluorobenzyl, (benzenesulfonyl)difluoromethyl, and monofluoromethyl sulfones and sulfoximines). More importantly, we found there is a linear relationship between reduction potential differences (ΔE) and substituent constants (σ) of difluoromethyl aryl sulfones, which is the key to

solving the dilemma between acidities and reduction potentials of difluoromethylating agents. To our knowledge, this is the first case that this new type of $\Delta E/\sigma$ Hammett plot is used to tackle an organic reaction problem. We believe that the $\Delta E/\sigma$ Hammett plot promises to find wide applications in a broad range of organic reactions involving radical species. Our work not only demonstrates the importance of using physical organic chemistry to address the challenges in organic synthesis, it also showcases the synthetic power of fluoroalkyl sulfones as privileged fluoroalkylation reagents. Further study in this direction is underway in our laboratory.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: Alkynylation · Difluoromethylation · Enantioselectivity · Multicomponent · Sulfones

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