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Halotrifluoromethylation of 1,3-Enynes: Access to Tetrasubstituted Allenes

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Cite This: *Org. Lett.* 2021, 23, 2314–2319 Read Online

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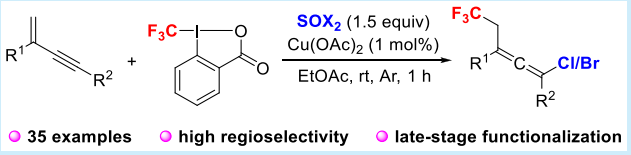
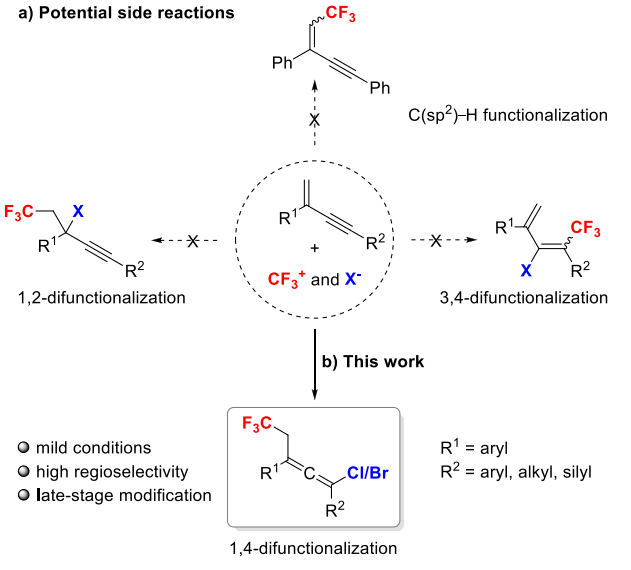
ABSTRACT: A highly regioselective copper-catalyzed 1,4-chloro- and bromotrifluoromethylation of 1,3-enynes has been presented for the first time, which affords an efficient transformation to access halo- and CF_3-containing tetrasubstituted allene derivatives with good to excellent yield. This protocol is practical and convenient, in which a wide range of functional groups are compatible. Applications of this method for the gram-scale preparation and late-stage functionalization of biologically active molecules are also demonstrated.



Owing to the high electronegativity and small atomic radius (similar to hydrogen) of fluorine, as well as the high dissociation energy of C−F bond, fluorine-containing compounds are widely applied in pharmaceuticals, agrochemicals, nuclear imaging, and materials science.[1] In particular, the trifluoromethyl group (CF_3) has gained significant interest in drug discovery, mainly because the CF_3 unit can dramatically improve the lipophilicity, metabolic stability of lead compounds, and ability to cross the blood−brain barrier.[2] Therefore, several highly effective approaches for the direct incorporation of a CF_3 motif into organic molecules have been developed using nucleophilic, electrophilic, and free-radical trifluoromethylation strategies.[3]

Organic halogen has been identified as a versatile skeleton in synthetic chemistry, which can be easily converted into heteroatom functional groups (N, O, S, etc.), hydrocarbons, alkenes, and hydrogen.[4] Thus, it is of great value to construct halogen-containing trifluoromethyl frameworks simultaneously through a one-pot procedure. By the complementary use of nucleophilic halide reagents and electrophilic CF_3 reagents, many elegant works have been well illustrated through a difunctionalization strategy that allows convenient and efficient access to the halogenated trifluoromethyl compounds.[5−7] In these reports, a variety of metal- or organocatalyzed systems were proven to be efficient for the halotrifluoromethylation, and their reactivity toward different multibond compounds, such as alkenes,[5] alkynes,[5c,j,6] and other unsaturated compounds,[7] were investigated. In addition, for the terminal alkenes or (hetero)arenes, a C(sp^2)−H trifluoromethylation may also occur.[8] As a typical unsaturated compound, 1,3-enynes were commonly used to construct valuable allenes.[9] It bears alkenyl and alkynyl residues, which could react with electrophilic trifluoromethyl reagents independently. Thus, when 1,3-enyne was employed as an unsaturated compound for the halotrifluoromethylation, several potential side reactions could occur, such as the competing premature C(sp^2)−H trifluoromethylation of the alkenyl moiety, 1,2-difunctionalization, or 3,4-difunctionalization of the alkenyl and alkynyl moieties, respectively (Scheme 1a). Obviously, a significant challenge for this process is to control the reaction regioselectivity and promote the formation of more favored

Scheme 1. Potential Side Reactions and 1,4-Halotrifluoromethylation of 1,3-Enynes



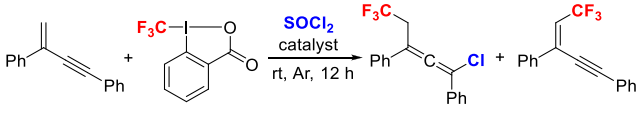
Received: February 5, 2021
Published: March 4, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00449
Org. Lett. 2021, 23, 2314–2319

1,4-difunctionalization. Given the potential issues associated with 1,4-halotrifluoromethylation of 1,3-enynes, their slow progress is fairly understandable and a practical strategy has not yet been successfully established. On the other hand, allenes are not only versatile building blocks for natural products, drug candidates, and materials but also key synthetic intermediates frequently found in various organic transformations.[9] In continuation of our research program to develop difunctionalized fluoroalkylation,[5f,10] we herein report an unprecedented 1,4-halotrifluoromethylation of 1,3-enynes with a nucleophilic halide reagent (SOX_2) and an electrophilic CF_3 reagent. This tandem reaction facilitates the construction of halo- and CF_3-containing tetrasubstituted allene derivatives with high regioselectivity and excellent functional-group tolerance.

At the beginning of this study, 1,3-enyne **1a** was used as a model substrate to investigate reaction conditions (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	solvent	3a[b] (%)	3a′[b] (%)
1	$Cu(OAc)_2$	CH_2Cl_2	21	23
2	$Cu(OAc)_2$	DMF	trace	22
3	$Cu(OAc)_2$	DMSO	trace	19
4	$Cu(OAc)_2$	THF	33	trace
5	$Cu(OAc)_2$	toluene	33	trace
6	$Cu(OAc)_2$	CH_3CN	7	8
7	$Cu(OAc)_2$	dioxane	7	6
8	$Cu(OAc)_2$	EtOAc	91	trace
9	$CuCl_2$	EtOAc	88	trace
10	Cu_2O	EtOAc	86	trace
11	CuI	EtOAc	68	trace
12	$PdCl_2$	EtOAc	19	trace
13[c]	$Cu(OAc)_2$	EtOAc	87	trace
14[d]	$Cu(OAc)_2$	EtOAc	82	trace

[a]Reaction conditions: 1,3-enyne **1a** (0.1 mmol), Togni's reagent **2a** (1.5 equiv), $SOCl_2$ (1.5 equiv), catalyst (20 mol %), solvent (1.0 mL), rt, Ar, 12 h. [b]Yields determined by ^{19}F NMR spectroscopy using trifluoromethylbenzene as an internal standard. [c]$Cu(OAc)_2$ (10 mol %) was used. [d]$Cu(OAc)_2$ (1 mol %) was used; the reaction time was 1 h.

At first, $SOCl_2$ was selected as the nucleophilic halide reagent, and Togni's reagent[11] (**2a**) was chosen as the electrophilic CF_3 source in the presence of a copper catalyst. When the reaction was carried out in CH_2Cl_2 at room temperature under an argon atmosphere for 12 h, the corresponding tetrasubstituted allene **3a** was obtained in 21% yield with an almost equal amount of byproduct **3a′** (Table 1, entry 1). Encouraged by this preliminary result, various solvents were then investigated. It was found that the solvent plays a crucial role in the regioselectivity and reactivity of the reaction. Polar solvents including DMF and DMSO only provided $C(sp^2)$–H trifluoromethylated product **3a′**, albeit in poor yields (entries 2 and 3). In contrast, when THF or toluene was employed as the solvent, only the expected 1,4-halotrifluoromethylation occurred, affording **3a** as the sole product in slightly increased yields (entries 4 and 5). The yield and the regioselectivity did not improve when the reaction was performed in CH_3CN or dioxane (entries 6–7). Interestingly, when EtOAc was employed as the solvent, the reaction system selectively afforded the 1,4-halotrifluoromethylated product with a higher yield (91%), while almost no $C(sp^2)$–H trifluoromethylation product **3a′** was detected (entry 8). Subsequently, other commonly used copper salts, such as $CuCl_2$, Cu_2O, and CuI, were also examined and the expected transformation also occurred, but no superior reactivity was realized (entries 9–11). To our surprise, $PdCl_2$ could also drive the expected reaction, although a lower yield was provided (entry 12). To our delight, when 10 mol % of catalyst loading was employed, the desired product **3a** was obtained without obvious loss of reactivity (entry 13). Finally, a reduction in the catalyst loading to only 1 mol % along with a shorter reaction time (1 h) led to **3a** in 82% yield (entry 14).

With the optimal reaction conditions developed (Table 1, entry 14), we next studied the scope of 1,3-enynes derived from different alkenyl moieties for this 1,4-difunctionalized transformation, and the results are summarized in Scheme 2. The reaction was performed on a 0.5 mmol scale and gave the expected product **3a** in slightly increased reactivity (95%). The alkenyl moiety containing various substituents such as fluorine, chlorine, and bromine at the aromatic ring's *para* position worked efficiently, resulting in tetrasubstituted allenes **3b–d** in 80–87% yields. The alkenyl moiety bearing a methyl or halogen substituent at the phenyl ring's *meta* position tolerated this trifluoromethylation and were transformed into the expected products **3e–h** in 77–92% yields. Likewise, the alkenyl moiety with a sterically hindered *ortho*-substituted aryl was well tolerated with the same reaction conditions, delivering the targeted product **3i–l** in 73–98% yields. A 1,3-enyne bearing two substituents at the phenyl ring of the alkenyl moiety was converted into the corresponding product **3m** efficiently. When fused ring-derived 1,3-enynes **1n,o** (Ar = 1- or 2-naphthyl) were subjected to this transformation, the desired tetrasubstituted allenes were achieved in satisfactory yields. To further benefit from the current method, the late-stage halotrifluoromethylation of biologically active molecules and natural products could be realized. 1,3-Enynes incorporated with L-menthol, polyethylene glycol (PEG), and propofol were all suitable substrates, providing the corresponding chlorotrifluoromethylated products **3p–s** with good efficiency. Even the 1,3-enyne-derived from complex natural product vitamin E was also a suitable substrate. The desired tetrasubstituted allene **3t** was obtained as the sole adduct in 69% yield and 3:1 diastereoselectivity.

Inspired by the above halotrifluoromethylation reactions, we turned our attention to the unique reactivity of 1,3-enynes and performed the extensive exploration of this 1,4-difunctionalized protocol by employing 1,3-enynes derived from different alkynyl moieties. As displayed in Scheme 3, a wide range of 1,3-enynes were compatible with this transformation. The electronical nature, positional change (*para* or *meta*), and steric hindrance (*ortho*) of the phenyl ring did not have many restrictions on the reaction efficiency; the expected adducts **5a–h** were generated in satisfactory yields. When aliphatic alkynes such as propyl, cyclopropyl, *tert*-butyl, and *n*-hexyl were included in the 1,3-enynes and subjected to the standard conditions, the reactions conducted smoothly to deliver the corresponding products **5i–l** in 75–86% yields. Indeed, the alkynyl moiety containing a silyl group was also a suitable substrate for the chlorotrifluoromethylation to afford the

https://dx.doi.org/10.1021/acs.orglett.1c00449
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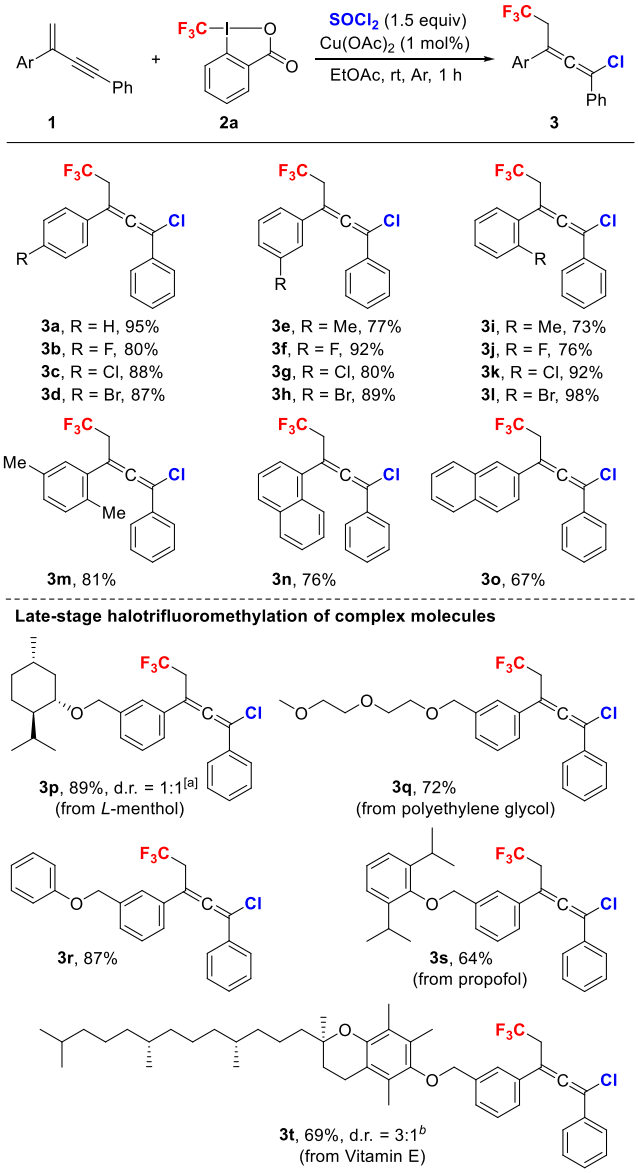
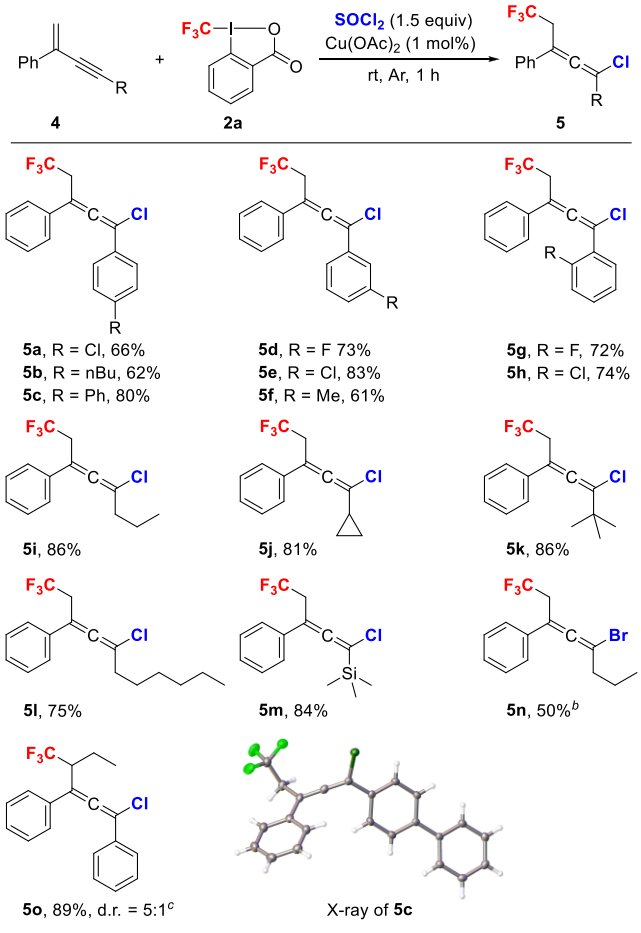
Scheme 2. Scope with Respect to the Alkenyl Moiety of 1,3-enynes[a]



[a]Reaction conditions: 1,3-enyne **1** (0.5 mmol), Togni's reagent **2a** (1.5 equiv), $SOCl_2$ (1.5 equiv), $Cu(OAc)_2$ (1 mol %), EtOAc (5.0 mL), rt, Ar, 1 h; yields are isolated yields. [b]Diastereoselectivity was determined by HPLC analysis of the crude product.

Scheme 3. Scope with Respect to the Alkynyl Moiety of 1,3-Enynes[a]



[a]Reaction conditions: 1,3-enyne **4** (0.5 mmol), Togni's reagent **2a** (1.5 equiv), $SOCl_2$ (1.5 equiv), $Cu(OAc)_2$ (1 mol %), EtOAc (5.0 mL), rt, Ar, 1 h; yields are isolated yields. [b]CH_2Cl_2 was used as solvent, and TMSBr was used as bromine source. [c]Diastereoselectivity was determined by HPLC analysis of the crude product.

expected product **5m** in 84% yield. Noticeably, when TMSBr was employed as a bromine source instead of $SOCl_2$, the resulting brominated adduct **5n** was obtained in 50% yield. When an internal 1,3-enyne **4o** was investigated, the corresponding product **5o** was obtained in 89% yield and good regioselectivity. Finally, the structure of trifluoromethylated tetrasubstituted allene **5c** was unambiguously confirmed by an X-ray crystallographic analysis.

Chlorinated allenes are highly useful intermediates and versatile building blocks in organic synthesis. This halotrifluoromethylation could easily be carried out on a gram scale, showing the potential opportunity for further applications. Under the standard reaction conditions, 1,3-enyne **1a** (0.82 g) reacted smoothly with Togni's reagent **2a** and $SOCl_2$, delivering the corresponding allene **3a** without reactivity loss while still maintaining an 81% isolated yield (Scheme 4a).

To demonstrate the utility of these transformations, further derivatizations of the halotrifluoromethylation product were investigated (Scheme 4b). Under basic conditions and the use of $Pd(PPh_3)_2Cl_2$ as a catalyst, a coupling reaction between **3a** and phenylboronic acid could occur in a mixture solvent of dioxane and H_2O, resulting in the formation of triphenyl-substituted allene **6** in 85% yield. The chloro group of the allene undergoes a nucleophilic attack by KSCN to generate expected thiocyanate **7** with 60% yield. Treatment of **3a** with potassium phthalimide in DMF resulted in the elimination of the chloro group, delivering the double bond migration product **3a′** in good yield (71%) and geometric selectivity (Z-alkene). Also, the chloro group could be readily removed via a reduction with zinc powder in acetic acid, and the reduced product **8** was detected in 59% yield.

Several control experiments were performed to gain more mechanistic insight into the process (Scheme 5). When 2,6-di-*tert*-butyl-4-methylphenol (BHT) was added as a radical inhibitor, the chlorotrifluoromethylation was partly prohibited (Scheme 5a). Furthermore, the reaction was almost sup-

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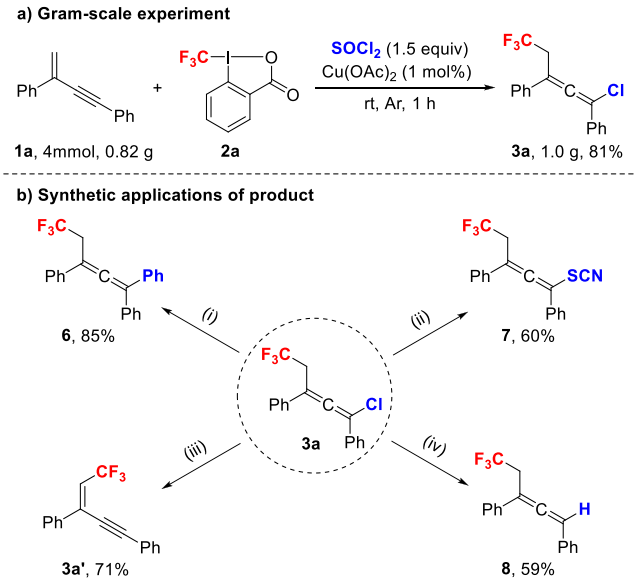
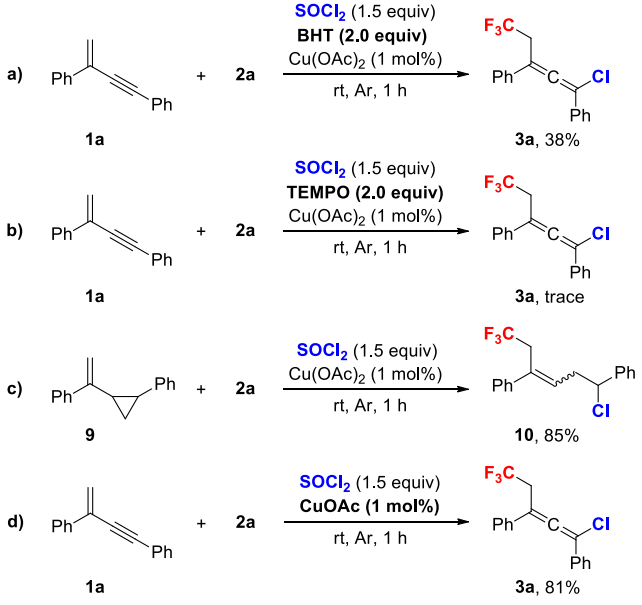
Scheme 4. Scale up and Derivatization Experiments[a]



[a]Reaction conditions: (i) $Pd(PPh_3)_2Cl_2$, Cs_2CO_3, $PhB(OH)_2$, dioxane/H_2O, rt; (ii) KSCN, acetone/H_2O, rt; (iii) potassium phthalimide, DMF, 45 °C (oil bath); (iv) Zn, AcOH, Ar, rt.

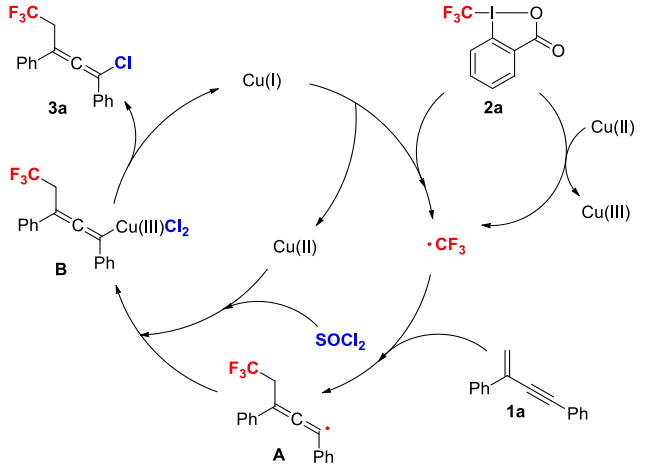
Scheme 5. Control Experiments



pressed, and no expected product **3a** was observed in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, Scheme 5b). Next, compound **9** was subjected to the standard reaction conditions as a radical clock instead of 1,3-enyne **1a**, and the reaction proceeded smoothly to produce the ring-opened product **10** in 85% yield (Scheme 5c). These experimental results reveal that these transformations proceeding through the free-radical pathway would be expected for the classical electrophilic trifluoromethylation process. In addition, a similar yield of **3a** was also observed when CuOAc was employed as the catalyst instead of $Cu(OAc)_2$ (Scheme 5d).

On the basis of the previous observations and previous literature data,[5−7] a mechanism for the halotrifluoromethylation of 1,3-enynes has been proposed in Scheme 6. Initially, an electrophilic trifluoromethyl radical ($^{\bullet}CF_3$) was generated from

Scheme 6. Plausible Mechanism



Togni's reagent **2a** via a single-electron-transfer (SET) caused by the copper(II) complex with concomitant formation of copper(III) species. The radical ($^{\bullet}CF_3$) would then be captured by the 1,3-enyne **1a** to furnish the trifluoromethylated allenyl radical intermediate **A**. The CF_3-allenyl radical species combined with another Cu(II) and $SOCl_2$ to give a CF_3-allenyl-Cu(III)Cl_2 species **B**, which would then undergo reductive elimination to produce the final product **3a** and released Cu(I). Finally, the copper(I) species serves as the real catalyst to recycle the reaction.

In conclusion, we have developed the first copper-mediated 1,4-halotrifluoromethylation of 1,3-enynes with an electrophilic trifluoromethylating reagent and a nucleophilic halide reagent (SOX_2), an approach that previously presented a formidable challenge.[5−7] Various halo- and CF_3-containing tetrasubstituted allenes were formed with high yield and regioselectivity, which can be easily converted into some valuable molecules. This process is readily scaled up, and diverse transformations of 1,3-enynes are being pursued for the late-stage derivatization of biologically relevant compounds. Further development of other kinds of 1,4-difunctionalization of 1,3-enynes involving fluorine chemistry is presently underway in this laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00449.

Experimental procedures, screening of reaction conditions, characterization data, and copies of ^{1}H, ^{13}C, $^{19}FNMR$ (PDF)

Accession Codes

CCDC 2054394 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

https://dx.doi.org/10.1021/acs.orglett.1c00449
Org. Lett. 2021, 23, 2314−2319

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We are thankful for financial support from the National Key Research and Development Program of China (Grant No. 2018YFA0704000) and the National Natural Science Foundation of China (Grant No. 22077098). We are grateful to Dr. Guofu Qiu in the School of Pharmaceutical Sciences at Wuhan University for the NMR analysis.

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https://dx.doi.org/10.1021/acs.orglett.1c00449
Org. Lett. 2021, 23, 2314−2319