Organic LETTERS

Copper-Catalyzed Intermolecular Trifluoromethylazidation and Trifluoromethylthiocyanation of Allenes: Efficient Access to CF_3-Containing Allyl Azides and Thiocyanates

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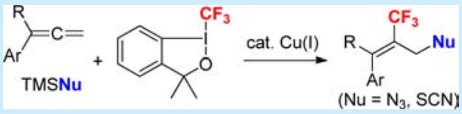
Supporting Information

ABSTRACT: A mild and efficient method for copper-catalyzed trifluoromethylazidation and trifluoromethylthiocyanation of allenes was explored. A series of CF_3-containing allyl azides and thiocyanates were obtained with high yields and good stereoselectivities, which can be used for further transformation to some valuable compounds.



Allyl amines and sulfides are versatile building blocks for the synthesis of organic molecules of higher complexity.[1] These structural motifs are frequently found in natural products and pharmaceuticals and commonly exhibit biological activities.[2] Generally, the introduction of a trifluoromethyl group into lead compounds was considered to modify their activity and biocompatibility.[3] Thus, exploration of new methods for introducing the CF_3 group into organic compounds has been of broad interest.[4] Some CF_3-substituted allyl amines and sulfides have been recognized to be biologically active; some of which are listed in Figure 1.[5] However, traditional strategies for the synthesis of these skeletons suffered from multistep transformations and low efficiency.[5] Thus, new methods for constructing CF_3-containing allyl amines and sulfides are in high demand. Herein, we report a novel copper-catalyzed intermolecular trifluoromethyl-azidation and -thiocyanation of allenes in which azide or thiocyanate and CF_3 group are incorporated simultaneously; a series of CF_3-containing allyl azides and thiocyanates are efficiently synthesized.

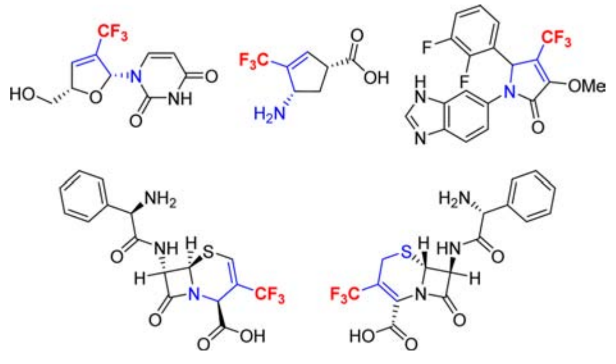


Figure 1. Representative bioactive compounds with CF_3-allylic amines and sulfides.

In the past decade, copper-catalyzed trifluoromethylation of alkenes has been well documented, and an array of new chemical bonds were incorporated, such as C−X, C−O, C−N, C−S, and C−C bonds, depending on the nature of the functional group used to trap the key intermediate.[6,7] The related trifluoromethylation of alkynes has also been achieved to synthesize various CF_3-containing vinyl products.[8] In contrast, the trifluoromethylation of allenes is relatively rare.[9] In 2013, Ma and Yu disclosed a copper-catalyzed intramolecular trifluoromethyloxygenation of 2,3-allenoic acids to provide CF_3-substituted butenolides.[9b] Later, an intermolecular trifluoromethyloxygenation reaction was explored by Liu and co-workers, while the substrate scope was limited to heteroatom substituted allenes.[9c] Recently, our group developed a series of copper-catalyzed intermolecular difunctionalization of alkenes[10] and alkynes,[11] including trifluoromethylated azidation, arylation, cyanation, and thiocyanation, in which a mutual activation model between ether-type Togni's CF_3^+ reagent and TMSNu or $ArB(OH)_2$ was presented to be vital for the success of these reactions (Scheme 1a). With our continuous efforts on this catalytic system, we speculated that if allenes were subjected to our reaction systems, a battery of functional groups, such as azide and thiocyanate, would simultaneously be easily introduced into the products with CF_3 group. However, the reaction of allenes presented more complex reactivity than that of alkenes because of more reaction sites of allene moiety, which could deliver more possible trifluoromethylation products (Scheme 1b). The interesting but questionable selectivity motivated us to investigate this chemistry.

To test our hypothesis, the initial investigation was focused on the reaction of substrate **1a**, which was treated with the

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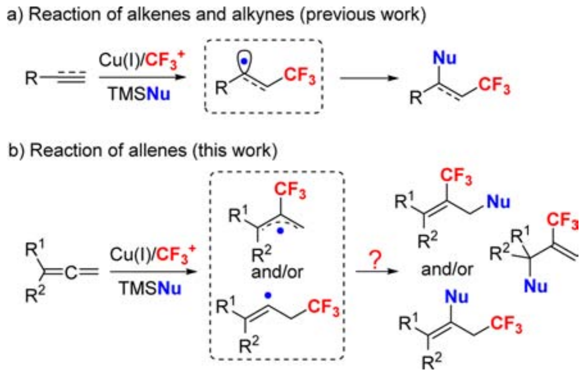
Scheme 1. Copper-Catalyzed Intermolecular Trifluoromethylations



previous reaction conditions of alkenes.[10a] We were delighted to find the desired CF_3-substituted allyl azide product **2a** was detected in 17% yield with excellent regioselectivity but poor stereoselectivity (Table 1, entry 1). Further optimization of the solvent revealed that MeOH provided the best result, giving the corresponding product **2a** in 65% yield with excellent regio- and stereoselectivity (entries 2–5). Later, various Cu(I) and Cu(II) salts were also examined, and $Cu(CH_3CN)_4PF_6$ was determined to be the best. When ester-type Togni's CF_3^+ reagent was used, the reaction also provided product **2a** but with a slightly lower yield (entry 11). In addition, under the lower or elevated temperature, the reactions suffered decreased yields (entries 12–14). It should be noted that the stereoselectivity of the reactions varied with the change of reaction conditions.

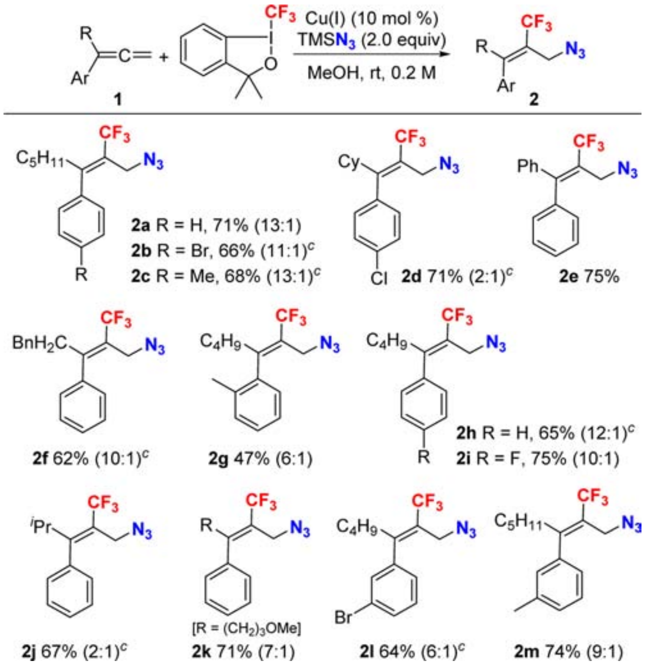
Table 1. Optimization of the Reaction Conditions[a]

entry	solvent	copper	yield (%)[b]	Z/E[b]
1	DMAc	$Cu(CH_3CN)_4PF_6$	17	1/1
2	MeOH	$Cu(CH_3CN)_4PF_6$	65	1/13
3	CH_3CN	$Cu(CH_3CN)_4PF_6$	48	1/23
4	THF	$Cu(CH_3CN)_4PF_6$	30	1/9
5	DCM	$Cu(CH_3CN)_4PF_6$	38	1/22
6	MeOH	$Cu(OTf)_2$	35	1/11
7	MeOH	$Cu(OAc)_2$	18	1/17
8	MeOH	CuI	16	1/14
9	MeOH	$CuCl_2$	50	1/9
10	MeOH	CuOAc	35	1/16
11[c]	MeOH	$Cu(CH_3CN)_4PF_6$	47	1/17
12[d]	MeOH	$Cu(CH_3CN)_4PF_6$	44	1/15
13[e]	MeOH	$Cu(CH_3CN)_4PF_6$	48	1/10
14[f]	MeOH	$Cu(CH_3CN)_4PF_6$	42	1/8

[a] All the reactions were run at 0.1 mmol scale. [b] ^{19}F-NMR yield with CF_3-DMA as an internal standard; E/Z ratio was detected from the crude product. [c] Ester-type Togni's CF_3^+ reagent was used. [d] At 0 °C. [e] At 40 °C. [f] At 60 °C.

With the optimized reaction conditions in hand, the substrate scope of the reaction was examined, and the results are summarized in Scheme 2. Various 1,1-disubstituted aryl allenes **1** were suitable for the reaction to yield the corresponding trifluoromethylated allylazides in moderate to good yields with good *E*-isomer selectivity. Among them, a variety of functional groups, such as Br, F, alkyl, methoxyl, were compatible with the reaction conditions. Allene substrates with linear *n*-pentyl, *n*-butyl, and methoxypropyl groups generated the desired products in good yields with good regio- and stereoselectivities. However, substrates **1d** and **1j** with steric bulky groups provided products **2d** and **2j** with poor stereoselectivities around a 2:1 ratio. For the aryl group, both electron-rich and electron-poor are suitable for the transformation, furnishing the corresponding products in good yields and stereoselectivities. In contrast, substrate **1g** with an *ortho*-substituent delivered product **2g** in a slightly lower stereoselectivity. These observations revealed that the stereoselectivity was sensitive to the steric hindrance of both alkyl and aryl groups. Unfortunately, quite limited substrate scope was observed: the reaction of monosubstituted, 1,3-disubstituted allenes provided the corresponding products in low yields with poor regioselectivities. In addition, 1,1-dialkyl substituted allenes also exhibited unsatisfactory reactivity toward this reaction.

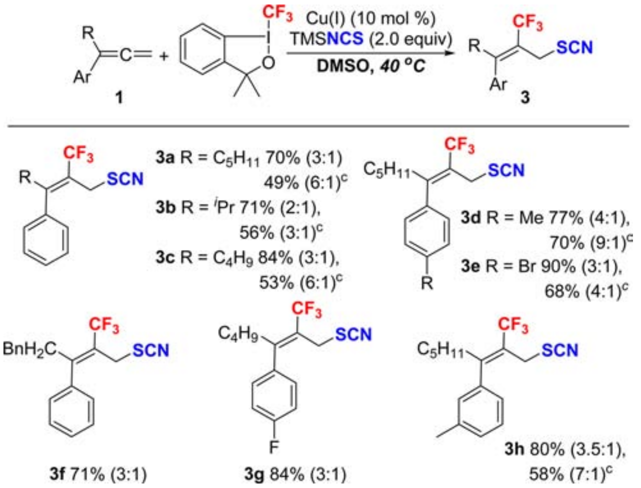
Scheme 2. Substrate Scope for Trifluoromethylazidation of Allenes[a,b]



[a] All the reactions were run at 0.2 mmol scale. [b] Isolated yield. [c] Ester-type Togni's CF_3^+ reagent.

Inspired by the present results, we turned our attention to extending such a system to the trifluoromethylthiocyanation reaction. To our great delight, when substrate **1h** was used as a template by treatment with TMSNCS instead of $TMSN_3$ under the above system, the desired product **3c** was detected in 60% yield. Further optimization demonstrated that the best yield was obtained in DMSO at 40 °C (see the Supporting Information). Next, the scope of the trifluoromethylthiocyanation reaction was evaluated under the modified conditions, and the results are listed in Scheme 3. Generally, similar to the previous transformation, this reaction furnished the desired products in good to excellent yields, but with poor stereoselectivities. Again, the reactions provided *E*-isomer as the main products. In contrast, when MeOH was used as the solvent, the reactions provided a better stereoselectvity, but

Scheme 3. Substrate Scope for the Trifluoromethylthiocyanation Reaction[a,b]

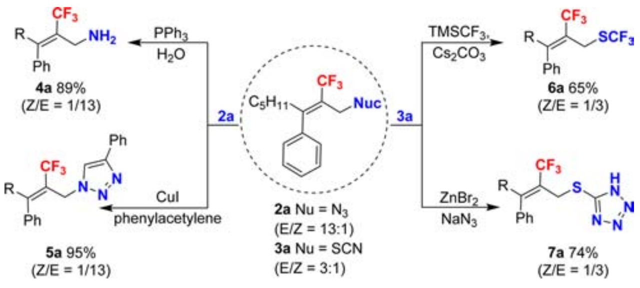


[a]All the reactions were run at 0.2 mmol scale. [b]Isolated yield. [c]MeOH as solvent, at rt.

with slightly lower yields. Finally, the reactions exhibited good functional group compatibility, such as Br, F, and alkyl, under the reaction conditions.

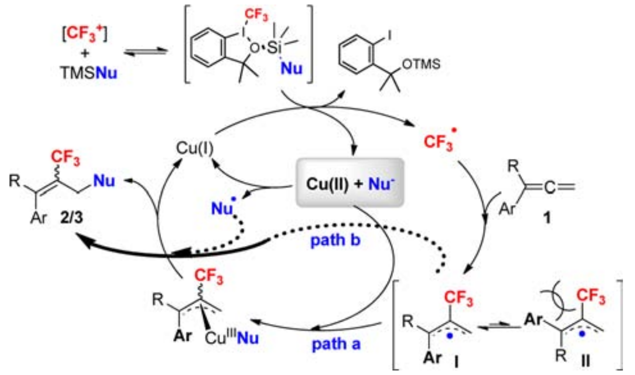
To demonstrate the practicability of the present methods, further transformation of **2a** and **3a** were investigated (Scheme 4). We found that **2a** could be readily converted to the corresponding allylamine **4a** in 89% yield in the presence of PPh$_3$ and H$_2$O. In addition, treatment of **2a** and phenylacetylene with Cu catalyst delivered the triazole **5a** in 95% yield.[10a] Furthermore, allylthiocyanate **3a** could react with TMSCF$_3$ through nucleophilic trifluoromethylation to generate related SCF$_3$-substituted product **6a** in 65% yield. Very interestingly, the reaction of **3a** and NaN$_3$ resulted in the corresponding product **7a** in 74% yield.[10d] Notably, these CF$_3$-decorated *tetra*-substituted olefins were synthesized efficiently from simple allenes, which was difficult to achieve through previously reported methods.

Scheme 4. Further Transformations of Products



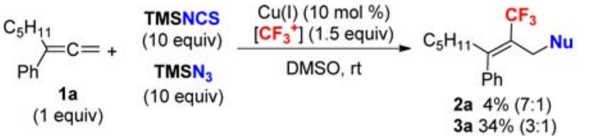
Based on our previous reports on the mutual activation model,[10] the proposed mechanism is provided in Scheme 5: the activated CF$_3^+$ reagent by TMSNu could react with Cu(I) catalyst to release Cu(II), Nu$^-$, and CF$_3$ radical species, which was then trapped by allenes, giving a CF$_3$-allyl radical species with high regioselectivity.[12] For the further process of CF$_3$-allyl radical with Cu(II)/Nu$^-$, two scenarios could be used to address final C−N and C−S bonds formation: (1) The N$_3$ or SCN radical species might be generated from the oxidation of Nu$^-$ with Cu(II) then coupled with CF$_3$-allyl radical species to give final products (path b). (2) CF$_3$-allyl radical species combined with Cu(II)/Nu$^-$ to give a CF$_3$-allyl-Cu(III) species, which underwent reductive elimination to furnish the final products (path a). Both processes seem to be reasonable; however, at present, it is difficult to draw a conclusion.

Scheme 5. Plausible Mechanism



We assumed that the addition of CF$_3$ radical to allene originally generated the corresponding two allyl radical intermediates (**int.I** and **int.II**) with poor selectivity. Then, species **int.II** would isomerize to **int.I**, which is relatively thermodynamically stable, because of the steric hindrance between the aryl and CF$_3$ group. For the trifluoromethylazidation, good stereoselectivity was observed when R is a less bulky group, while poor selectivty was provided when a sterically hindered alkyl group was incorporated (such as **2d** and **2j**). We reasoned that the poor selectivity may result from the steric effect between R and CF$_3$ groups, which pushed the equilibrium from **int.I** to **int.II** (Scheme 5). Compared to the azidation, the related thiocynation reaction was obtained with poor stereoselectivities (around 3:1). Although a detailed mechanistic understanding cannot currently be given to address these differences, we speculated that trapping CF$_3$-allyl radical intermediates by heteroatom radicals or Cu(II) species might be responsible for the selectivity. When the coupling reaction of CF$_3$-allyl radical is faster than its isomerization (between **int.I** and **int.II**), poor stereoselectivity might be expected. Otherwise, high stereoselectivity will be observed.

With this in mind, we hold that the coupling reaction of Cu(II)/SCN$^-$ with allylic radical should be faster than that of Cu(II)/N$_3^-$, resulting in poor stereoselectivity in products **3**. To test this hypothesis, the competition reaction was conducted, and results indicated that the reaction of thiocynation is indeed much faster than azidation eq 1.



(1)

In conclusion, we have developed a novel copper-catalyzed trifluoromethylazidation and trifluoromethylthiocyanation of allenes. Various CF$_3$-allyl azides and thiocyanates were obtained with good yields and regioselectivities, which can be readily transformed to some valuable compounds. Further investigation into the mechanism and application is in progress.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, characterization, and additional data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01677.

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Notes

The authors declare no competing financial interest.

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(12) When Tempo was used as radical scavenger, the reaction provided adducts of tempo-CF_3 and tempo-allyl, which suggests the possibility of the CF_3 and allyl radical in a catalytic cycle. For details, see the Supporting Information.