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Copper-Catalyzed Syntheses of Multiple Functionalizatized Allenes via Three-Component Reaction of Enynes

Yulong Song, Chunling Fu, and Shengming Ma*

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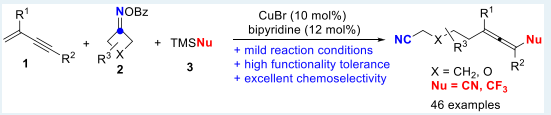
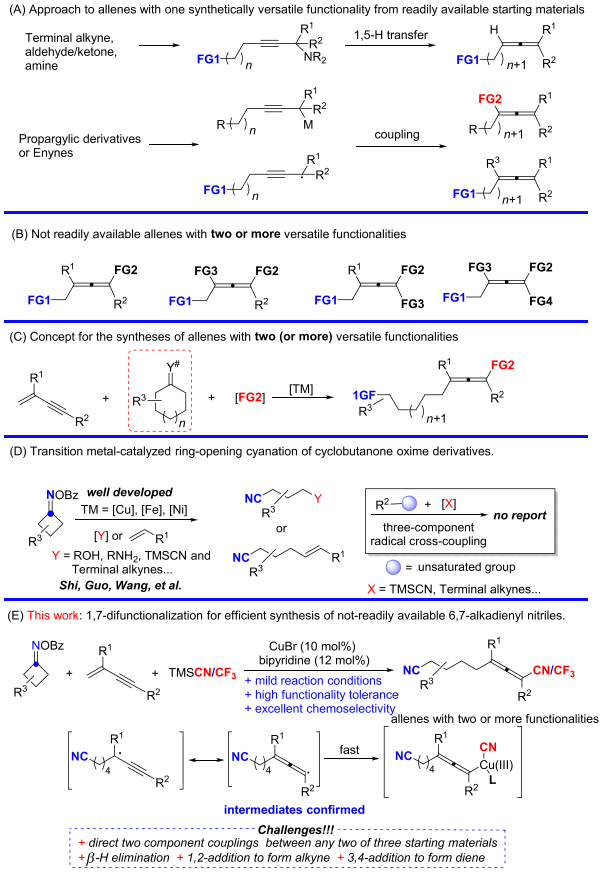
ABSTRACT: A copper-catalyzed three-component reaction of cyclobutanone oxime esters and 1,3-enynes in the presence of TMSCN or $TMSCF_3$ has been developed. This mild protocol enjoys a broad substrate scope tolerating many functional groups, providing a facile access to 1,7-double-functionalized allenes, which are difficult to prepare. The allenyl nitrile products may be easily transformed into allenoic acid derivatives and stereodefined tetrasubstituted alkenes, demonstrating their potentials as platform molecules in synthesis. A mechanism has been proposed on the basis of mechanistic studies.



KEYWORDS: *three-component reaction, multiple functionalizatized allenes, enynes, copper-catalysis, cyclobutanone oximes*

Scheme 1. Enyne Approaches to Functionalized Allenes and Transition-Metal-Catalyzed Two-Component Reactions Involving Cyclobutanone Oxime Derivatives



Organic synthesis is based on the transformation of various functional groups.[1] Therefore, syntheses of various multiple functionalized molecules are of great significance. Allenes have become a class of very important building blocks in organic syntheses,[2] with much attention being paid to their syntheses (Scheme 1A).[3] However, syntheses of multiple-functionalized allenes[4] albeit highly desirable, are still challenging due to the availability of the starting materials for the known syntheses (Scheme 1B).[2] Recently, attention has been paid to the reactions of 1,3-enynes, some of which efficiently afford allenes with a single synthetically reactive functional group (Scheme 1A).[5−7] We envisioned a concept of remote double functionalization based on the C−C cleavage of cyclic precursors, which would generate *in situ* the first functionality FG1 in $FG1-(CH_2)_n$ species[8] and subsequently react with conjugated enynes followed by propargyl−allenyl isomerization and trapping with M−FG2 species to afford not readily available remote double-functionalized allenes (Scheme 1C). Recently, during our study on the ring-opening reactions of cyclic substrates,[9] we noticed two-component reactions of cyclobutanone oximes with other nucleophiles or olefins followed by β-H elimination (Scheme 1D).[10,11] However, there have been no reports on three-component reactions, mostly due to excessive competitive side reactions of the two-component reactions, including direct two-component couplings between any two of the three starting materials and β-H elimination of a radical intermediate to afford the Heck-type product via literature survey.[10,11]

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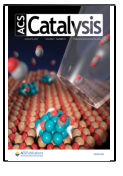

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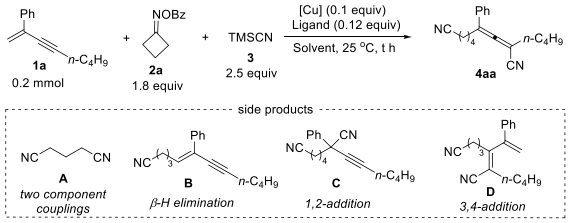
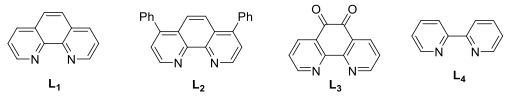
Table 1. Optimization of the Conditions[a]



entry	solvent	C (mol/L)	L	[Cu]	t (h)	yield of **4aa**/**1a** recovered/**2a** recovered (NMR)[b] (%)
1	$CHCl_3$	0.05	L_1	$Cu(CH_3CN)_4PF_6$	12	ND/90/100
2	CH_3CN	0.05	L_1	$Cu(CH_3CN)_4PF_6$	12	ND/79/100
3	MTBE	0.05	L_1	$Cu(CH_3CN)_4PF_6$	11	ND/100/100
4	DMSO	0.05	L_1	$Cu(CH_3CN)_4PF_6$	13	63/18/23
5	NMP	0.05	L_1	$Cu(CH_3CN)_4PF_6$	11	64/32/0
6	DMA	0.05	L_1	$Cu(CH_3CN)_4PF_6$	11	68/32/0
7	DMF	0.05	L_1	$Cu(CH_3CN)_4PF_6$	15.5	70/30/0
8	DMF	0.1	L_1	$Cu(CH_3CN)_4PF_6$	13	72/25/0
9	DMF	0.2	L_1	$Cu(CH_3CN)_4PF_6$	10.5	52/44/0
10	DMF	0.1	L_2	$Cu(CH_3CN)_4PF_6$	16	69/28/0
11	DMF	0.1	L_3	$Cu(CH_3CN)_4PF_6$	13	72/17/0
12	DMF	0.1	L_4	$Cu(CH_3CN)_4PF_6$	16	86/7/0
13	DMF	0.1	L_4	CuI	16	79/1/0
14	DMF	0.1	L_4	CuBr	16	89 (82)/[c]0/0
15	DMF	0.1	L_4	CuCl	16	82/6/0
16	DMF	0.1	L_4	CuOAc	16	80/10/0
17[d]	DMF	0.1	L_4	-	16	ND/98/100
18[e]	DMF	0.1	-	CuBr	16	ND/73/100

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (1.8 equiv), **3** (2.5 equiv), [Cu] (10 mol %), and ligand (12 mol %) in solvent unless otherwise noted.



[b]Determined by ^1H NMR analysis of the crude product using mesitylene or CH_2Br_2 as the internal standard. [c]Isolated yield. [d]No CuBr was added to the reaction system. [e]No ligand was added to the reaction system.

Herein, we describe an efficient copper-catalyzed three-component synthesis of synthetically versatile 6,7-alkadienyl nitriles with an extra nitrile group directly connected to the allene unit (Scheme 1E). They have been demonstrated as versatile platform molecules for the efficient syntheses of allenes and other functional molecules. Mechanistic studies confirmed a radical process.

In the beginning, we conducted the reaction of 2-phenyloct-1-en-3-yne **1a**, cyclobutanone oxime ester **2a**, and TMSCN **3** under the catalysis of $Cu(CH_3CN)_4PF_6$ (10 mol %) and 1,10-phen (12 mol %) at 25 °C in $CHCl_3$ for 12 h (entry 1, Table 1). The expected side reaction products are dinitrile **A** (direct two-component coupling product), nitrile **B** (β-H elimination product), **C** (1,2-addition product), and **D** (3,4-addition product). To our disappointment, we did not obtain the desired product **4aa** or other side products **A**–**D** with 90% recovery of **1a** and 100% recovery of **2a**. The reaction in CH_3CN or MTBE failed to afford the product, and the reaction in DMF delivered better results in comparison to those in NMP, DMSO, or DMA (entries 2–7, Table 1). It was found that when the reaction was conducted in DMF with a concentration of 0.1 mol/L, the yield of **4aa** was 72% with a 25% recovery of **1a** (entry 8, Table 1). Further screening of the ligand effect for the reaction in DMF (entries 10–12, Table 1) led to the observation that bipyridine L_4 was better than 1,10-phen L_1 with a yield of 86%. In comparison with ligands with a rigid tricyclic skeleton, i.e., L_1–L_3, the coordination of bipyridine with copper is more flexible and thus more effective. In the presence of bipyridine L_4, the copper catalyst screening shows a limited difference among $Cu(CH_3CN)_4PF_6$ and noncationic Cu(I) catalysts including CuOAc, CuCl, CuBr, and CuI (entries 12–16, Table 1), and CuBr with the highest yield of 89% was chosen for further study (entry 14, Table 1). Further control experiments suggested that both CuBr and bipyridine L_4 were indispensable to the success of this protocol (entries 17 and 18, Table 1). It is worth mentioning that the selectivity of the reaction was excellent—the formation of **A** was 5% and the other side products **B**–**D** were not observed.[10b−d]

With the optimized reaction conditions in hand (entry 14, Table 1), we next investigated the scope of 1,3-enynes. The reaction tolerated a wide array of functional groups with different electronic natures on the benzene ring of substrate **1** to generate various double-functionalized or multiple-functionalized allenes (Table 2). A variety of different substituents, including electron-donating groups (**4ba**–**4da**) and electron-withdrawing groups (**4ka**), were accommodated to afford double-functionalized allenyl nitriles in moderate to good yields (64–85%). In addition, biologically or synthetically useful groups such as F, Cl, Br, I (**4ea**–**4ja**), and CH_3CO (**4la**) at the para, ortho, or meta position were accommodated to afford the multiple-functionalized allenyl nitriles in moderate

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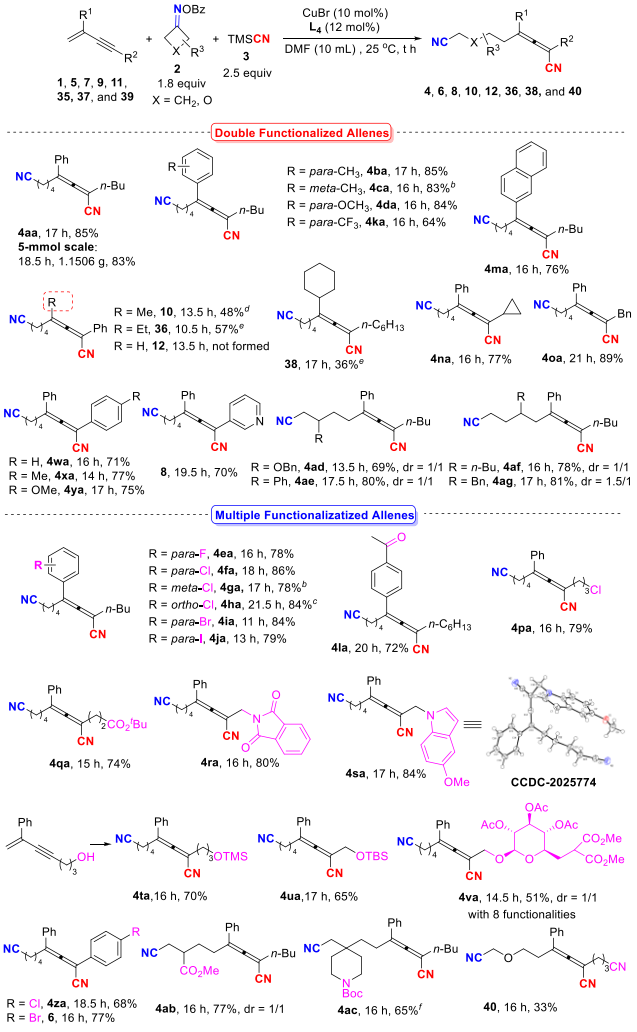
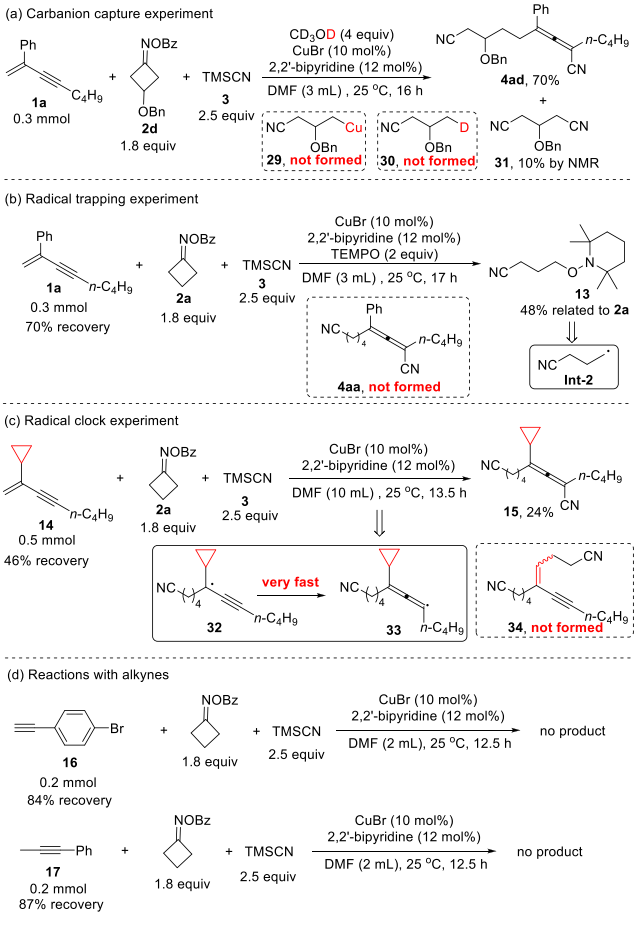
Table 2. Scope of Enynes: Syntheses of Double- or Multiple-Functionalized Allenes[a]



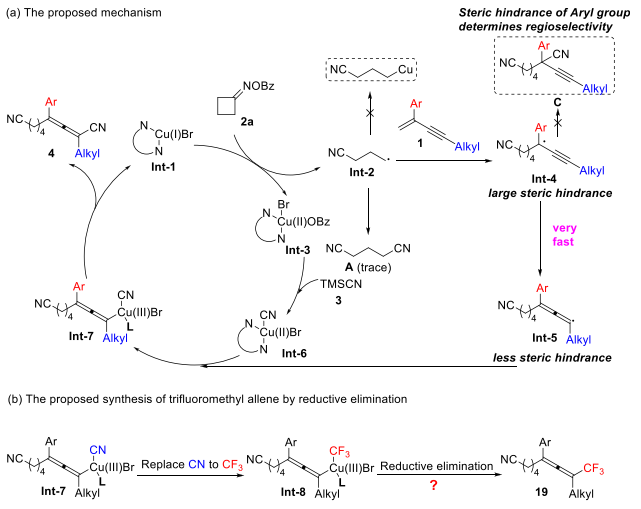
[a]Reaction conditions: **1** (1 equiv), **2** (1.8 equiv), **3** (2.5 equiv), CuBr (10 mol %), and $\mathbf{L_4}$ (12 mol %) in DMF (10 mL) at 25 °C on a 1.0 mmol scale unless otherwise noted. [b]2.0 equiv of **2a** was used. [c]3.0 equiv of **2a** and 2.7 equiv of **3** were used. [d]2.5 equiv of **2a** was used, the reaction was conducted at 40 °C, and the recovery of **9** was 33% by NMR. [e]3.0 equiv of **2a** was used, the reaction was conducted at 40 °C, and the recovery of **35** or **37** was 25% by NMR. [f]The recovery of **1a** was 11% by NMR.

to good yields (72−86%). The naphthyl-substituted allenyl nitrile **4ma** could also be prepared in a decent yield. When the substituent at the 2-position (R^1) was an alkyl group, including methyl (**10**), ethyl (**36**), or cyclohexyl (**38**) instead of aryl, the reaction also worked with yields of 36−57%. However, the reaction of an enyne without a substituent at the 2-position (**11**) failed to afford the trisubstituted allene (**12**) with 40% recovery of **11**. We next investigated the reactivity of various 1,3-enynes with R^2 bearing different functional groups, such as cyclopropanyl (**4na**), benzyl (**4oa**), halide (**4pa**), ester (**4qa**), imide (**4ra**), and indole (**4sa**). These were all tolerated, affording double-functionalized or multiple-functionalized allenyl nitriles in yields of 74−89%. An enyne with a free hydroxyl unit, 6-phenylhept-6-en-4-ynol, failed to afford the corresponding allenol; however, with the hydroxy group being protected as a TMS or TBS ether, the reaction worked to

Scheme 2. Mechanistic Experiments



Scheme 3. Proposed Mechanism



afford multiple-functionalized allenyl nitriles **4ta** and **4ua**. A glucose-derived enyne also afforded **4va** in a yield of 51%. R^2 was not limited to alkyl groups, as aryl substituents also worked. A series of double-functionalized or multiple-functionalized allenyl nitriles were prepared in moderate yields (68−77%) with versatile substituent(s) on the aromatic rings: electron-donating groups such as *p*-Me (**4xa**) and *p*-OMe (**4ya**) or electron-withdrawing groups such as *p*-Cl (**4za**) and *p*-Br (**6**). Due to the importance of pyridine in pharmaceuticals

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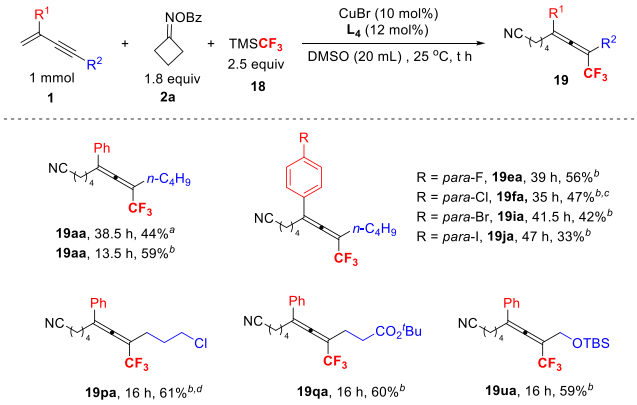
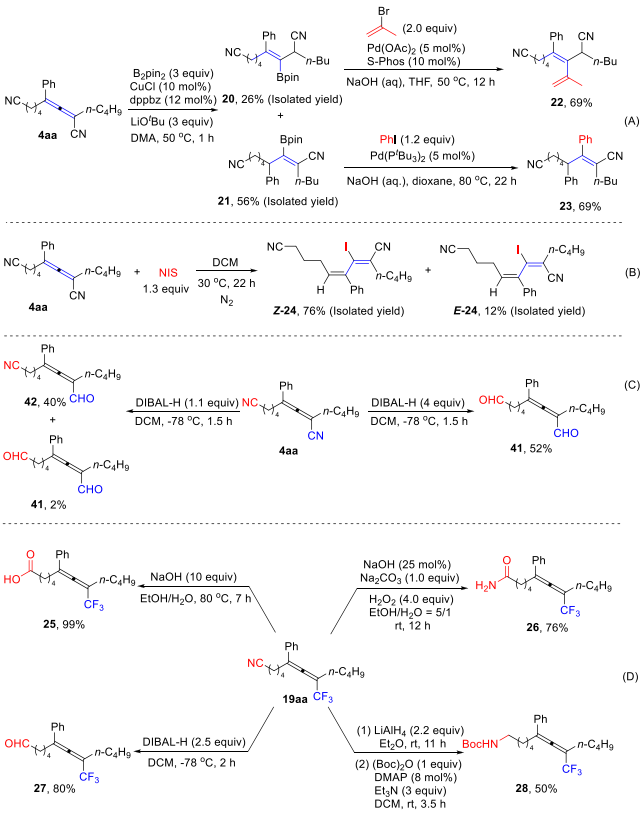
Table 3. Reaction with $TMSCF_3$ instead of TMSCN



[a]Reaction conditions: **1** (1 equiv), **2** (1.8 equiv), **3** (2.5 equiv), CuBr (10 mol %), and $\mathbf{L_4}$ (12 mol %) in DMF (10 mL) at 25 °C on a 1.0 mmol scale unless otherwise noted. [b]Reaction conditions: **1** (1 equiv), **2** (1.8 equiv), **3** (2.5 equiv), CuBr (10 mol %), and $\mathbf{L_4}$ (12 mol %) in DMSO (20 mL) at 25 °C on a 1.0 mmol scale unless otherwise noted. [c]The recovery of **1f** was 2% by NMR. [d]The recovery of **1p** was 3% by NMR.

Scheme 4. Applications as Platform Molecules



and natural products,[12] a phenyl ring was also replaced with a pyridinyl ring (**7**) and the reaction also worked with a yield of 70% for the corresponding product **8**. The reaction tolerated a diversified range of cyclobutanone oxime esters with biologically relevant functionalities, including ester (**2b**), protected piperidine (**2c**), benzyloxy (**2d**), and phenyl (**2e**) groups at the 3-position, leading to the corresponding allenyl nitriles **4ab**−**4ae** with 65−80% yields. Different groups at the 2-position of cyclobutanone oxime esters, including *n*-butyl (**2f**) and benzyl (**2g**), also worked to afford **4af** in an 78% yield and **4ag** in a 81% yield, respectively. In addition, 3-oxetanone oxime esters **2h** also worked to afford **40**, albeit in 33% yield.

To gain insight into the mechanism, some control experiments have been conducted (Scheme 2). When the reaction was run with a stoichiometric amount of CD_3OD, no deuterated product **30** was observed with a 70% yield of **4ad** and 10% yield of dinitrile **31** (Scheme 2a),[10b−d] illustrating that carbanion **29** was not involved in the reaction. Meanwhile, when the reaction was run in the presence of a stoichiometric amount of the radical trapper TEMPO, the expected reaction was completely inhibited, and the TEMPO-trapped product **13** could be isolated in 48% yield, indicating the formation of radical intermediate **Int-2** (Scheme 2b). With this confirmed, we conducted a radical clock experiment: the reaction of 2-cyclopropylenyne **14** produced cyclopropyl-substituted allenyl nitrile **15** instead of the ring-opening product **34**. Due to the rapid and irreversible ring opening of cyclopropyl,[13] we believe that the propargyl−allenyl isomerization is much faster than the ring-opening, which is the key to the success of such an exclusive allene synthesis (Scheme 2c). In addition, when terminal alkyne **16** and nonterminal alkyne **17** were submitted to the standard conditions, the formation of addition products to alkynes was not observed and 84% and 87% of alkynes were recovered, indicating that the C−C triple bond is NOT reactive under the optimal conditions (Scheme 2d).

On the basis of the aforementioned experimental results, we propose a possible mechanism (Scheme 3a). Initially, the [Cu(I)] species **Int-1** reacts with **2a** to afford the [Cu(II)] species **Int-3** and cyanoalkyl radical **Int-2** via a single-electron-transfer process.[10a−g] The radical **Int-2** could be stabilized via the copper species.[14] Then the addition of this cyanoalkyl radical with the C═C bond in enyne **1** would highly regioselectively produce the propargyl radical **Int-4**. Due to the steric hindrance of the Ar group, the propargyl radical **Int-4** was in rapid resonance with allenyl radical **Int-5** with less steric hindrance, rather than directly coupled with TMSCN to generate propargyl cyanides **C**. Then **Int-6**, which is generated by ligand exchange of **Int-3** with TMSCN, would couple with **Int-5** to generate the allenyl copper(III) species **Int-7**. Subsequent reductive elimination would yield the final product allene **4** and regenerate LCuBr species **Int-1** to complete this catalytic cycle. There is an alternative pathway of abstraction of the CN ligand from **Int-6** to generate the product **4** and **Int-1**. It can be seen from Scheme 3a that the key intermediates **Int-2**, **Int-5**, and **Int-7** are very polar, thus polar aprotic solvents are beneficial to the reaction (entries 1−7, Table 1).

Furthermore, CF_3-containing compounds have broad applications in fluorinated agrochemicals and pharmaceuticals owing to their potential for improving the metabolic stability, lipophilicity, and selectivity of bioactive molecules.[15] Copper-catalyzed or -mediated trifluoromethylation has emerged as an attractive approach to generate C−CF_3 bonds[16,17] with very limited success for the corresponding allene synthesis.[18,19] Therefore, we wondered whether trifluoromethyl allene **19** could be obtained through the reductive elimination of the intermediate **Int-8** (Scheme 3b). Interestingly, when $TMSCF_3$ replaced TMSCN under the standard conditions, the corresponding trifluoromethyl allene **19aa** was afforded, albeit in 44% yield (Table 3). A further screening of the solvent and concentration led to the observation that the reaction in DMSO with a concentration of 0.05 mol/L afforded **19aa** in 59% yield (Table 3). *p*-F, *p*-Cl, and *p*-Br on the benzene ring

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survived under the modified reaction conditions (**19ea**−**19ia**). Even the very reactive *p*-I functionality (**1j**) was tolerated to give **19ja**, albeit in a yield of 33%. Different R^2 groups bearing halide, ester, or TBS ether were accommodated, affording trifluoromethyl-substituted allenes **19pa**, **19qa**, and **19ua** in yields of 59−61% (Table 3).

In order to showcase the synthetic utility of the method, transformations of the allenyl nitrile products were demonstrated (Scheme 4). Easily separated trisubstituted regioisomeric alkenyl boron compounds **20** and **21** could be readily prepared through the borylcupration of **4aa**.[20] Such alkenyl boron reagents could be further transformed to tetrasubstituted olefins **22** and **23**, which are difficult to prepare yet very useful (Scheme 4A).[21,22] In addition, **4aa** could be readily converted into easily separated *Z* and *E* isomers of 3-iodoalka-2,4-dienyl nitrile **24** in 88% yield with 1.3 equiv of NIS (Scheme 4B). Such alkenyl nitriles are commonly found in bioactive natural products as well as pharmaceutical compounds.[23] Moreover, the reduction of **4aa** using 4 equiv of DIBAL-H provided dialdehyde **41**. When 1.1 equiv of DIBAL-H was used, the nitrile group attached to the allene unit could be reduced highly selectively to monoaldehyde **42** in 40% yield with 2% of **41** (Scheme 4C).[10g] Furthermore, the trifluoromethyl-substituted allenyl nitrile **19aa** was been demonstrated as the starting material for the efficient synthesis of trifluoromethyl-substituted allenoic acid **25**,[24] allenyl amide **26**,[25] aldehyde **27**,[10g] and *N*-allenyl amide **28**[10g] via hydrolysis or reductions under different conditions (Scheme 4D). Such allenoic acid derivative units are widely present in many natural products.[4]

In summary, we have developed the first example of remote double functionalization of 1,3-enynes, which provides an efficient protocol for 7-trifluoromethyl- or 7-cyano-substituted allenyl nitriles. This method uses a readily available catalyst and starting materials, has high catalytic activity, uses mild conditions, and has a broad substrate scope, tolerating many potentially useful functional groups. Mechanistic studies suggested that the reaction proceeded via a radical pathway involving the resonance of a propargyl radical with an allenyl radical and the involvement of Cu species of different oxidation states. Further studies on the new remote difunctionalizations shown in Scheme 1C are being actively pursued in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.1c02140.

Experimental details, characterization data, and spectra (PDF)

Crystallographic data (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Shengming Ma − *Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027 Zhejiang, People's Republic of China*; orcid.org/0000-0002-2866-2431; Email: masm@sioc.ac.cn

Authors

Yulong Song − *Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027 Zhejiang, People's Republic of China*

Chunling Fu − *Laboratory of Molecular Recognition and Synthesis, Department of Chemistry, Zhejiang University, Hangzhou 310027 Zhejiang, People's Republic of China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acscatal.1c02140

Notes

The authors declare no competing financial interest.

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