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Copper-catalyzed radical trifluoromethylalkynylation of unactivated alkenes with terminal alkynes☆

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ABSTRACT

A copper-catalyzed three-component radical trifluoromethylalkynylation of unactivated alkenes is realized from Togni-II reagent and readily available terminal alkynes under mild conditions to afford an array of β-trifluoromethylated alkynes. The utilization of a multidentate N,N,N-ligand is crucial for the efficient radical generation and the C(sp^3)–C(sp) bond formation. Facile transformations of the difunctionalization products highlight its potential utility in the synthesis of various trifluoromethyl-containing building blocks.

1. Introduction

The trifluoromethyl (CF_3) group serves as a valuable structural motif in pharmaceuticals and agricultural chemicals due to its unique physical, chemical, and biological properties [1–3]. As such, the development of concise and efficient methods to introduce trifluoromethyl group into organic molecules has attracted great attention of organic chemists [2,3]. Unactivated alkenes are a class of readily available feedstocks and thus the trifluoromethylation of alkenes serves as a powerful tool for upgrading the alkene simple feedstocks into complex trifluoromethylated compounds [4]. In this respect, trifluoromethyl radical-mediated 1,2-trifluoromethylalkynylation of unactivated alkenes, simultaneously incorporating a trifluoromethyl and an alkynyl group in one step [5], has attracted increasing interest because alkynes are versatile synthons for many other functionalities [6] (Scheme 1A). Only a few examples have been reported by utilizing the prefunctionalized alkynes as alkynylating reagents, such as alkynyl triflones [5a, 5b], alkynyl sulfones [5c-5e] or hypervalent iodine reagent [5f]. The key strategy in the C(sp^3)–C(sp) formation is the attacking of the prefunctionalized alkynylating reagents by the in situ generated radical, followed by the β-scission of the functionalized alkenyl radical species [5] (Scheme 1B). Moreover, the cost and availability of the alkynylating reagents may retard their wide application in organic synthesis (Scheme 1B). Therefore, the development of efficient catalysts with low-cost and easily available alkynylating reagents for 1,2-trifluoromethylalkynylation of unactivated alkenes is still highly desirable.

Given that terminal alkynes are widespread building blocks in organic synthesis, we envisioned that they could serve as an ideal alkynylating reagent for the alkene 1,2-trifluoromethylalkynylation. However, the reported mechanism for C(sp^3)–C(sp) bond with prefunctionalized alkynylating reagents [5] is inapplicable for terminal alkynes due to the difficult β-scission of the corresponding alkenyl radical intermediates. As part of our continuous interest in designing novel ligands for copper-catalyzed radical reactions [7], we have developed a copper-catalyzed asymmetric radical 1,2-carboalkynylation of arylated alkenes with terminal alkynes [4h,8]. The crucial step is the utilization of a copper/multidentate N,N,P-ligand catalyst to forge the desired C(sp^3)–C(sp) bond via the interaction of the benzyl radical with copper(II) acetylide complex [4h]. As such, we theorized the same strategy might be utilized for the 1,2-trifluoromethylalkynylation of unactivated alkenes with Togni-II reagent [9] as the CF_3 source. However, several challenges might exist: i) the easily occurring Glaser homocoupling of terminal alkynes [10]; ii) the competing chemoselectivity between trifluoromethyl radical addition to terminal alkynes

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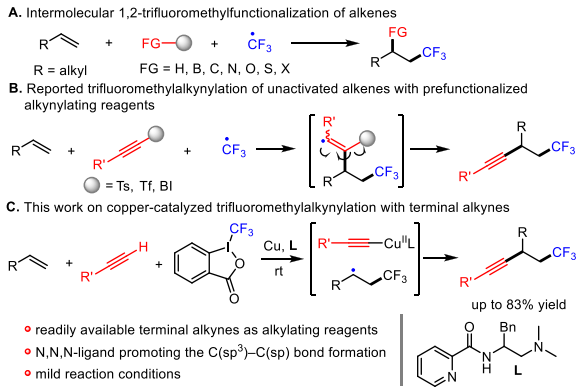


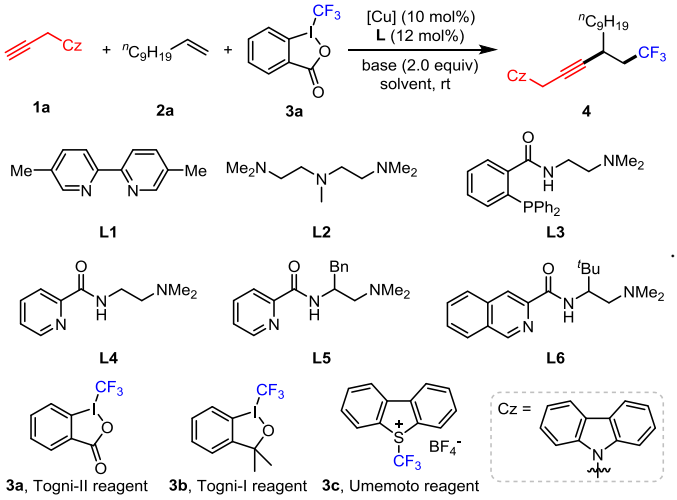
Scheme 1. 1,2-Trifluoromethylalkynylation of unactivated alkenes.

and unactivated alkenes [11]; (3) the competing side reactions of the alkyl radical, such as intramolecular hydrogen atom abstraction (HAA) [12], β-H elimination [13], and single-electron oxidation [14] owing to the inherently high reactivity of the alkyl radical species. We herein report a copper/ethylenediamine-derived N,N,N-ligand catalyst for a radical trifluoromethylalkynylation of unactivated alkenes with Togni-II reagent and terminal alkynes under mild reaction conditions (Scheme 1C). Critical to the success of the reaction is the rational design of a sterically demanded amide-derived multidentate N,N,N-ligand to effectively forge the C(sp^3)–C(sp) bond (Scheme 1C).

2. Results and discussion

Based on the above assumption, we investigated the ligand effect on the model reaction of alkyne **1a**, undec-1-ene **2a**, and Togni-II reagent **3a** in the presence of CuOAc and Cs_2CO_3 in 1,4-dioxane (Table 1). The bipyridine ligand **L1** and tridentate N,N,N-ligand **L2** afforded no trifluoromethylalkynylation product **4** (Table 1, entries 1 and 2). Instead, the amide-derived N,N,P-ligand **L3** [15] that performed well in our previously reported 1,2-carboalkynylation of arylated alkenes [4h,8a] gave rise to the desired product **4** in 8% yield (Table 1, entry 3). The success of amide-derived N,N,P-ligand led us to further examine the performance of the amide-derived N,N,N-ligand **L4** [16], which were shown to be more effective than **L3** and generated **4** in 25% yield (Table 1, entry 4). We surmised that the steric effect adjacent to the amide *N* atom of **L4** might change the coordination sphere of ligand with copper and would further affect reaction efficiency. As such, we then

Table 1
Screening of reaction conditions for model reaction[a].



Entry	[Cu]	L	Base	Solvent	Yield (%)[b]
1	CuOAc	**L1**	Cs_2CO_3	1,4-dioxane	0
2	CuOAc	**L2**	Cs_2CO_3	1,4-dioxane	0
3	CuOAc	**L3**	Cs_2CO_3	1,4-dioxane	8
4	CuOAc	**L4**	Cs_2CO_3	1,4-dioxane	25
5	CuOAc	**L5**	Cs_2CO_3	1,4-dioxane	73
6	CuOAc	**L6**	Cs_2CO_3	1,4-dioxane	43
7[c]	CuOAc	**L5**	Cs_2CO_3	1,4-dioxane	0
8[d]	CuOAc	**L5**	Cs_2CO_3	1,4-dioxane	0
9	CuTc	**L5**	Cs_2CO_3	1,4-dioxane	63
10	CuI	**L5**	Cs_2CO_3	1,4-dioxane	52
11	CuOAc	**L5**	K_2CO_3	1,4-dioxane	11
12	CuOAc	**L5**	LiO^{t}Bu	1,4-dioxane	34
13	CuOAc	**L5**	Cs_2CO_3	THF	35
14	**CuOAc**	**L5**	**Cs_2CO_3**	**MeCN**	**80 (80)**[e]
15[f]	CuOAc	**L5**	Cs_2CO_3	MeCN	78
16[g]	CuOAc	**L5**	Cs_2CO_3	MeCN	75

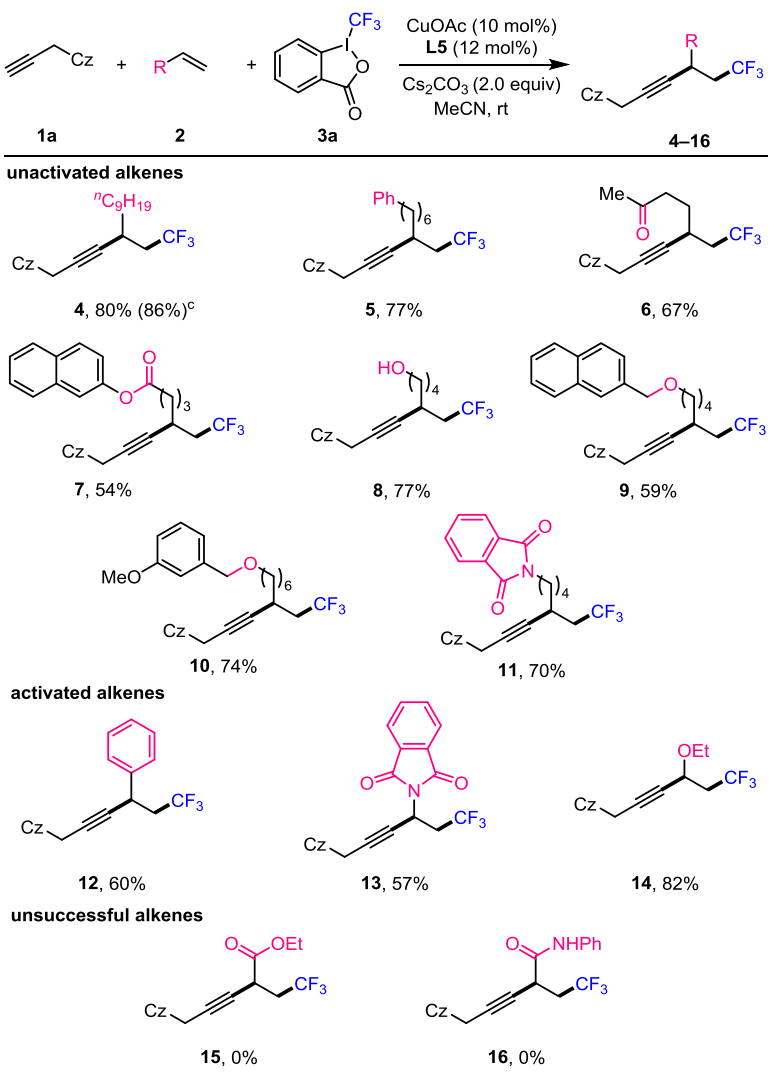
[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.15 mmol), **3a** (0.12 mmol), [Cu] (10 mol%), **L** (12 mol%), and Cs_2CO_3 (2.0 equiv) in solvent (1.0 mL) at room temperature for 3.5 d under argon.
[b] Yields were based on ^{1}H NMR analysis of the crude product using dibromomethane as an internal standard.
[c] **3b** instead of **3a**.
[d] **3c** instead of **3a**.
[e] Isolated yield.
[f] Water (5.0 equiv) was added.
[g] CuOAc (5 mol%), **L** (6 mol%). Cz, carbazoyl.

investigated the analogues of **L4**. We found that the installation of an alkyl group greatly enhanced the yield, with **L5** provided the best result (73% yield, Table 1, entries 5 and 6). Replacing the CF_3 percussor with Togni-I reagent **3b** and Umemoto reagent **3c** [17] indicated that no desired product **4** was observed (Table 1, entries 7 and 8). Further screening of reaction parameters including the copper catalysts, bases as well as solvents led us to identify the optimal conditions as follows: the reaction of **1a** (1.0 equiv), **2a** (1.5 equiv), and **3a** (1.2 equiv) in the presence of CuOAc (10 mol%), **L5** (12 mol%), and Cs_2CO_3 (2.0 equiv) in MeCN at room temperature provided **4** in 80% isolated yield (Table 1, entries 9–14). Notably, we found that water did not significantly affect the reaction efficiency (Table 1, entry 15, and Table S1 in the Supplementary Material), and reducing the catalyst loading to 5 mol% did not significantly affect the reaction efficiency (Table 1, entry 16).

With the optimal conditions in hand, we first investigated the substrate scope of alkenes (Table 2). Aliphatic alkenes bearing unfuntionalized linear chain and a phenyl ring provided **4** and **5** in 80% and 77% yields, respectively. Notably, the reaction could be run on a gram scale to give **4** in 86% yield. Alkenes bearing a carbonyl group as well as an ester group at the remote position of the reactive site were also suitable for the reaction to afford **6** and **7** in 67% and 54% yields, respectively. Notably, the potentially reactive hydroxyl group was tolerated under the standard conditions to generate **8** in 77% yield. A further investigation of the scope showed that alkenes possessing a remote ether group was viable substrates and delivered **9** and **10** in moderate to good yields. Moreover, the substrates with a phthalimidyl group proceeded smoothly under the standard conditions to furnish **11**, thus providing an indirect method for the synthesis of the amino substituted product. It is noteworthy that several activated alkenes, such as styrene, enecarbamate and vinyl ether proceeded smoothly in this reaction, providing the desired products **12**–**14** in good to excellent yields. However, the electron-deficient alkenes, such as ethyl acrylate and N-phenylacryamide could not afford the desired products **15** and **16** under the optimal conditions.

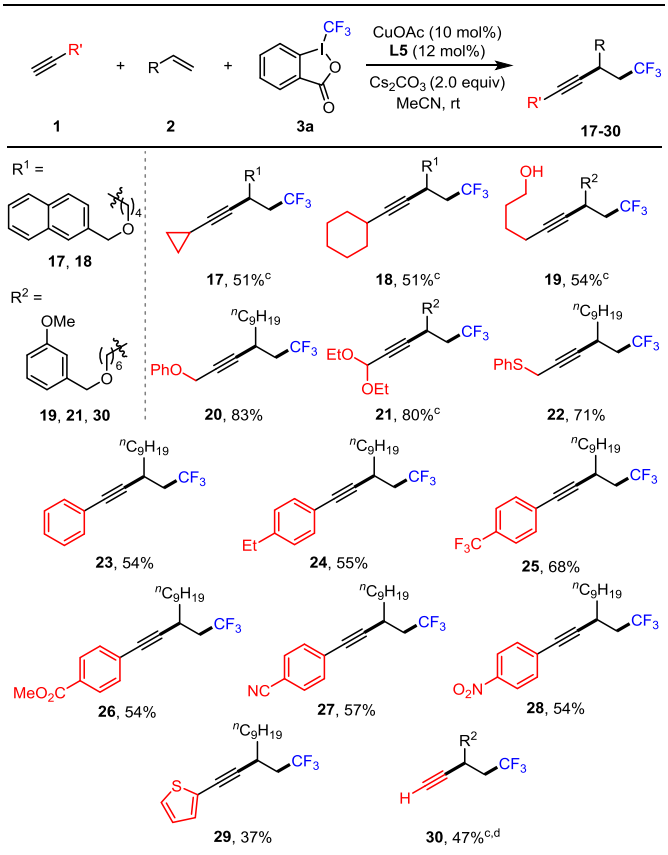
We then examined the scope of alkynes (Table 3). Under the standard conditions, a series of aliphatic alkynes worked well to give the products **17**–**22** in 51–80% yields. Moreover, a range of functional groups, including free alcohol (**19**), ether (**20**), acetal (**21**), and thioether (**22**) were compatible with the reaction conditions. More importantly, aryl alkynes with various electronic properties all worked well to give **23**–**28** in moderate to good yields. Diverse functional groups, such as trifluoromethyl (**25**), methoxylcarbonyl (**26**), cyano (**27**), and nitro (**28**)

Table 2
Substrate scope of alkenes. [a,b].



[a] Reaction conditions: **1a** (0.20 mmol), **2** (0.30 mmol), **3a** (0.24 mmol), CuOAc (10 mol%), **L5** (12 mol%), and Cs_2CO_3 (0.40 mmol) in MeCN (2.0 mL) at rt for 3.5 d
[b] Isolated yield.
[c] **1a** was used on a 5.0 mmol, CuOAc (5 mol%), **L5** (6 mol%) for 5 d

Table 3
Substrate scope of alkynes. [a,b].



[a] Reaction conditions: **1** (0.20 mmol), **2a** (0.30 mmol), **3a** (0.24 mmol), CuOAc (10 mol%), **L5** (12 mol%), and Cs_2CO_3 (0.40 mmol) in MeCN (2.0 mL) at rt for 3.5 d

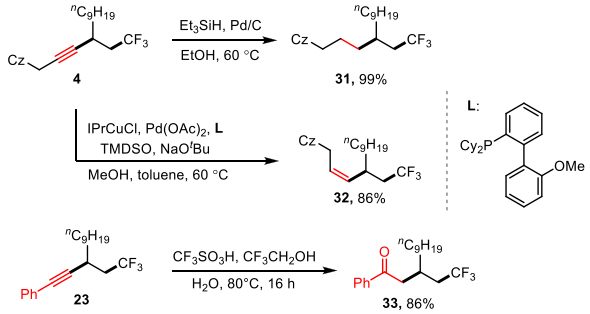
[b] Isolated yield.

[c] Reacted for 7 d

[d] Trimethylsilylacetylene was used.

were left untouched. Furthermore, 2-thiophenyl acetylene was also suitable for the reaction to deliver **29**, albeit in 37% yield. Notably, trimethylsilyl acetylene also worked well under the standard conditions to provide alkyne **30**, which was derivatized from the in situ removal of the trimethylsilyl group under the basic conditions.

To demonstrate the synthetic utility of this approach, the target products were easily converted to other CF_3-substituted building blocks. As shown in Scheme 2, the complete hydrogenation of **4** resulted in **31** featuring an aliphatic chain. The stereoselective hydrogenation of alkyne **4** gave rise to *Z*-alkene **32** in good yield. Furthermore, hydration of **23** efficiently afforded CF_3-substituted ketone **33**. These results showed that alkyne moiety in the products was easily converted to many



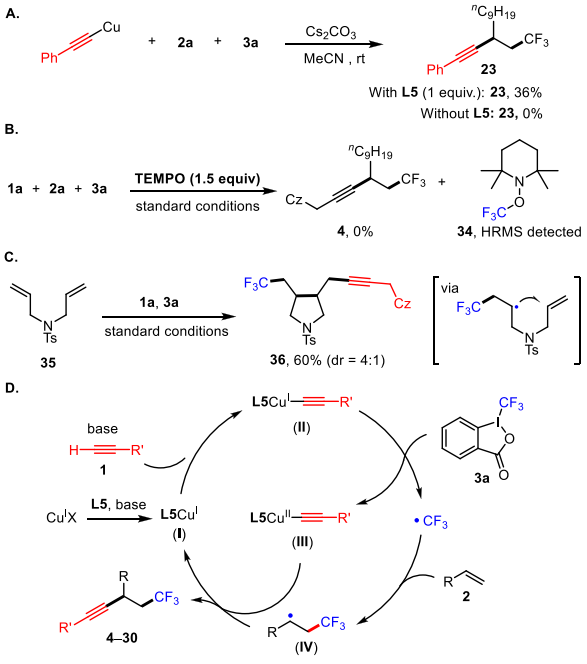
Scheme 2. Synthetic utility.

functional groups, showcasing the potential application in the discovery of pharmaceuticals and agricultural chemicals.

To gain insights into the reaction mechanism, a series of control experiments were conducted (Scheme 3). First, the reaction of the copper acetylide complex with **2a** and **3a** afforded the desired product **23** in 36% yield in the presence of **L5** but afforded no **23** without **L5** (Scheme 3A). This result indicated that the ligand-coordinated copper (I) acetylide is likely the catalyst for the single electron reduction of Togni-II reagent **3a**. Second, the reaction was completely inhibited under standard conditions with a radical scavenger TEMPO, and the TEMPO-CF_3 adduct **34** was detected, suggesting the involvement of a CF_3 radical in this reaction system (Scheme 3B). Finally, a radical clock experiment using diene **35** successfully afforded the cyclization product **36**, which is in support of the radical addition to alkene process (Scheme 3C). Based on above results and our previous reports [4h,8a], a possible mechanism was proposed in Scheme 3D. Cu^I, terminal alkynes **1** and **L5** reacted to form a Cu^I intermediate **II** in the presence of a base [18]. The intermediate **II** reacted with Togni-II reagent **3a** to generate a Cu^{II} complex **III** and a CF_3 radical possibly via a single electron reduction process. Next, the CF_3 radical selectively added to unactivated alkenes **2** to provide an alkyl radical **IV**. Finally, $C(sp^3)$–C(sp) bond formation gives rise to the β-CF_3 alkynes and Cu(I) complex **I** via interaction of the Cu^{II} complex **III** and alkyl radical **IV**.

3. Conclusions

In summary, we have developed a copper-catalyzed three-component radical 1,2-trifluoromethylalkynylation of unactivated alkenes with Togni-II reagent and readily available terminal alkynes under mild conditions. The key to the success of the strategy relies heavily on the utilization of a sterically demanded N,N,N-ligand to efficiently generate the CF_3 radical and forge the $C(sp^3)$–C(sp) bond mediated by the copper catalyst. More importantly, the obtained β-CF_3 substituted alkynes could be easily converted to many other CF_3-containing building blocks. Further efforts for the exploration of the asymmetric radical 1,2-trifluoromethylalkynylation of unactivated alkenes are ongoing in our laboratory.



Scheme 3. Mechanistic investigation.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jfluchem.2023.110107.

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