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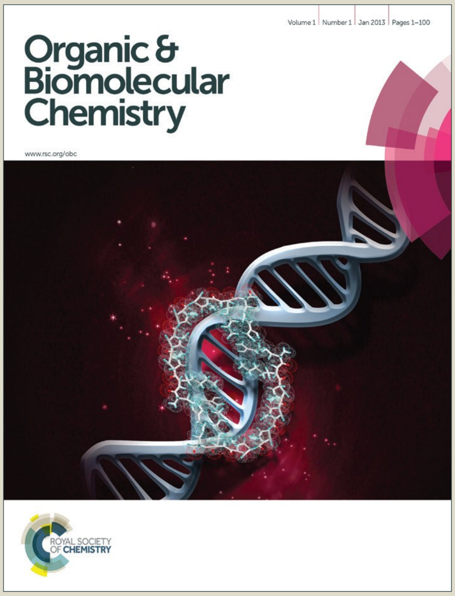

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Copper-Catalyzed Three-Component Cascade Reaction of Alkynes, Sulfonyl Azides and Simple Aldehydes/Ketones

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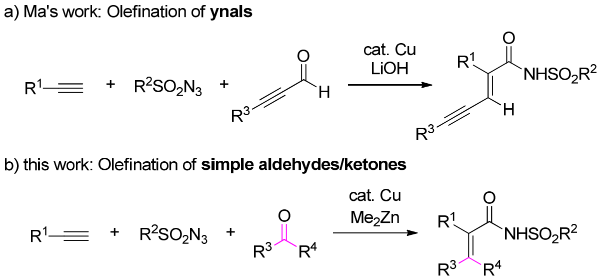
A copper-catalyzed dimethylzinc-promoted three-component cascade reaction of alkynes, sulfonyl azides, and simple aldehydes or ketones is described. Polysubstituted olefins were thus constructed expeditiously in a one-pot procedure under mild conditions.

The multicomponent reactions (MCRs) allow multiple bond-forming processes in one-pot operation with simple and readily available substrates, which shows great advantages in atomic economy, process practicability, low cost, and environmental friendliness.[1] Thus, development of such reactions is highly desirable from the synthetic point of view. In recent years, copper-catalyzed multicomponent reactions concerning sulfonyl azides and alkynes[2] have attracted a vast of attention, in which a ketenimine intermediate is generated in situ[3-12,13] and can be further employed in nucleophilic addition,[3-7] radical addition,[8] and cycloaddition reactions[9-12]. Since Chang and coworkers elegantly disclosed the first three-component coupling of sulfonyl azides, alkynes, and amines to synthesize *N*-sulfonylamidines by utilizing Cu(I)/Et_3N system,[3a] a variety of nucleophiles containing N,[3] C,[4] O,[5] and S[3o,6] as the nucleophilic atom have been successfully engaged in this chemistry. Unsaturated C=N bonds[9a-j,12] and 1,3-dipoles[10] can also serve as efficient reaction partners via [2+2], [2+2+2] or [3+2] cycloaddition patterns. In these events, a copper alkynamide intermediate is often involved. However, this Cu/amine system shows relatively weaker reactivity for carbonyls.[9k-m] In 2012, Ma et al. reported a highly *E*-selective olefination of ynals through coupling with sulfonyl azides and alkynes to achieve conjugated enyne scaffolds (Scheme 1a).[9l] Mechanistically, a lithium ynamidate intermediate was assumed to form in the presence of a stoichiometric amount of LiOH, which attributes to the reaction outcome. Herein, we develop a three-component cascade reaction of alkynes, sulfonyl azides, and simple aldehydes/ketones by using copper-catalysis with the assistance of Me_2Zn (Scheme 1b).[14] The reaction also features mild reaction conditions, broad substrate scopes, and tolerance of a wide range of functional groups.



Scheme 1. Cu-Catalyzed Three-Component Reactions of Alkynes, Sulfonyl Azides, and Carbonyls

Recently, we have discovered the important role of dimethylzinc in cooperating with manganese catalyst for direct C-H addition to aldehydes.[15] As part of our continuous interest, we serendipitously found that the reaction of phenylacetylene **1a**, *p*-toluenesulfonyl azide **2a**, and cyclohexanone **3a**, together with 10 mol% $CuBr_2$ and 1.5 equivalents of Me_2Zn in DCE at 60 ^{o}C, afforded three-component coupling product **4aaa** in 74% NMR yield (Table 1, entry 1). Screening of solvents suggested DCE to be the best choice (entries 2-3).[16] To our delight, the reaction proceeded even better at room temperature (entries 4-5). Adjustments of the reaction concentration and ratio of substrates resulted in increased yields of **4aaa** (entries 6-8). Variations on bases highlighted the key role of Me_2Zn in this reaction (entries 9-14). Of note, Et_3N, mostly used in reported Cu-catalyzed multicomponent reactions, couldn't promote this transformation at all. Halving the amount of $CuBr_2$ showed no obvious influence on the reaction outcome (entry 15). No reaction occurred in the absence of the copper catalyst and other Cu(I) and Cu(II) salts were also effective for the reaction (entries 16-18).[16] At last,

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Electronic Supplementary Information (ESI) available: Experimental details, characterization data and NMR spectra for all new compounds, and X-ray data for **4aai** (CCDC 1444389) and **4hak** (CCDC 1444390). See DOI: 10.1039/x0xx00000x

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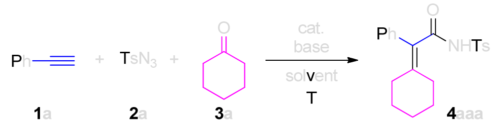
4aaa was obtained in 76% isolated yield with 5 mol% $Cu(NO_3)_2$ as the catalyst (entry 19).

Table 1. Optimization of Reaction Conditions[a]

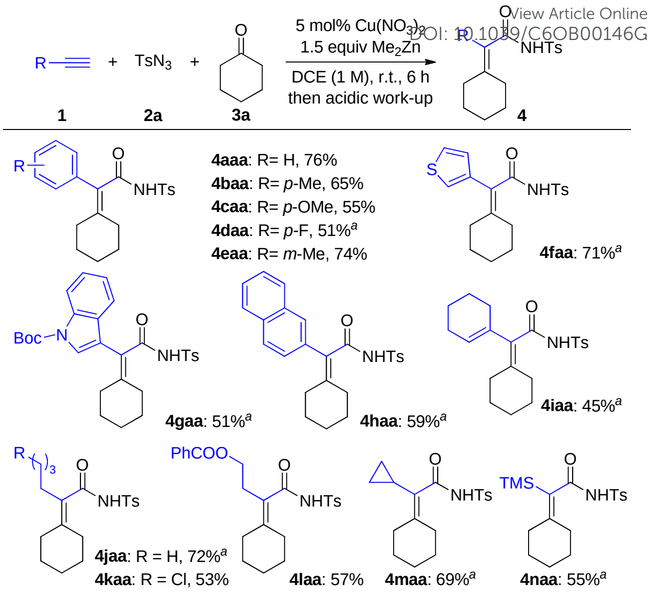


entry	cat.	base	solvent	T (°C)	yield (%)[b]
1	$CuBr_2$	Me_2Zn	DCE	60	74
2	$CuBr_2$	Me_2Zn	Et_2O	60	68
3	$CuBr_2$	Me_2Zn	toluene	60	24
4	$CuBr_2$	Me_2Zn	DCE	r.t.	78
5	$CuBr_2$	Me_2Zn	DCE	80	66
6	$CuBr_2$	Me_2Zn	DCE[c]	r.t.	85
7	$CuBr_2$	Me_2Zn	DCE[d]	r.t.	77
8[e]	$CuBr_2$	Me_2Zn	DCE[c]	r.t.	85
9[e]	$CuBr_2$	-[f]	DCE[c]	r.t.	0
10[e]	$CuBr_2$	Et_2Zn	DCE[c]	r.t.	25
11[e]	$CuBr_2$	MeMgBr	DCE[c]	r.t.	0
12[e]	$CuBr_2$	*n*-BuLi	DCE[c]	r.t.	0
13[e]	$CuBr_2$	LiOH	DCE[c]	r.t.	0
14[e]	$CuBr_2$	Et_3N	DCE[c]	r.t.	0
15[e,g]	$CuBr_2$	Me_2Zn	DCE[c]	r.t.	82
16[e]	-[h]	Me_2Zn	DCE[c]	r.t.	0
17[e,g]	CuBr	Me_2Zn	DCE[c]	r.t.	70
18[e,g]	$Cu(OAc)_2$	Me_2Zn	DCE[c]	r.t.	80
19[e,g]	**$Cu(NO_3)_2$**	**Me_2Zn**	**DCE[c]**	**r.t.**	**88 (76)[i]**

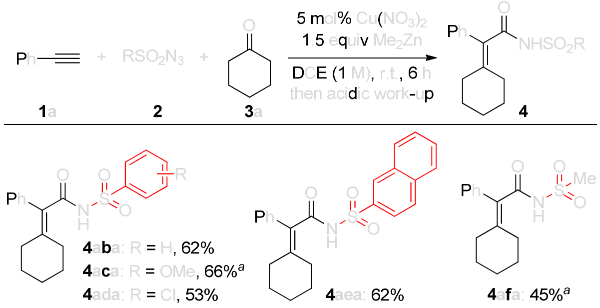
[a] Reaction conditions unless otherwise noted: **1a** (0.2 mmol), **2a** (0.8 mmol), **3a** (0.4 mmol), catalyst (0.02 mmol), base (0.3 mmol), solvent (0.5 mL), 60 °C, 6 h, under N_2 atmosphere. [b] Yields determined by ^1H NMR analysis. [c] 0.2 mL. [d] 1.0 mL. [e] **1a/2a/3a** = 1:2:2. [f] No base. [g] catalyst (0.01 mmol). [h] No catalyst. [i] Isolated yield on 0.5 mmol scale.

With the optimized conditions in hand, we first investigated the scope of alkynes (Scheme 2). Both electron-donating and -withdrawing groups on aromatic alkynes were tolerated affording the expected products in good yields (**4aaa–eaa**). 3-Ethynylthiophene and 3-ethynylindole as well as 2-ethynylnaphthalene were all amenable to this protocol under slightly modified reaction conditions (**4faa–haa**). Furthermore, enyne and aliphatic alkynes were also suitable reaction partners (**4iaa–maa**). Functional groups like halogen atoms (**4daa**, **4kaa**), ester (**4laa**), and silyl group (**4naa**) were all compatible with the reaction conditions.

We next tested the scope of azides with phenylacetylene **1a** and cyclohexanone **3a** as model coupling partners (Scheme 3). Aryl sulfonyl azides bearing electronically varied substituents were all successfully involved in this cascade reaction (**4aba–ada**). 2-Naphthalene sulfonyl azide **2e** showed comparable reactivity affording the three-component coupling product smoothly (**4aea**). Methanesulfonyl azide **2f** was also an effective substrate to deliver the corresponding product (**4afa**), albeit with relatively lower reactivity.



Scheme 2. Substrate Scope for Alkynes. Reaction conditions: **1** (0.5 mmol), **2a** (1.0 mmol), **3a** (1.0 mmol), $Cu(NO_3)_2$ (0.025 mmol), Me_2Zn (0.75 mmol), DCE (0.5 mL), r.t., 6 h. Isolated yields are shown. [a] $Cu(NO_3)_2$ (0.05 mmol).



Scheme 3. Substrate Scope for Azides. Reaction conditions: **1a** (0.5 mmol), **2** (1.0 mmol), **3a** (1.0 mmol), $Cu(NO_3)_2$ (0.025 mmol), Me_2Zn (0.75 mmol), DCE (0.5 mL), r.t., 6 h. Isolated yields are shown. [a] $Cu(NO_3)_2$ (0.05 mmol).

The generality of carbonyls **3** was further examined through the reactions with alkyne **1a** and azide **2a** (Scheme 4). Both cyclic ketones of varied ring sizes and acyclic ketones were competent to participate in the tandem reaction giving the corresponding products successfully (**4aab-g**). The employment of unsymmetrical ketone 2-pentanone **3h** and acetophenone **3i** resulted in a mixture of two stereoisomers with **4aah** and **4aai** as the major product respectively. The structure of **4aai** was unambiguously confirmed by single crystal X-ray diffraction analysis. Besides, both aromatic and aliphatic aldehydes were suitable substrates for this protocol (**4aaj-k**, **4hak**). Notably, these reactions showed an excellent stereoselectivity favoring the formation of *E*-configured products. The structure of **4hak** was again confirmed by single crystal X-ray diffraction analysis. Functionalities such as olefin and bromo groups were well compatible (**4aal-m**). When complex aldehyde **3n** derived from ursodeoxycholic acid was subjected to the reaction conditions, the three-component coupling product **4aan** was obtained in excellent chemo- and stereoselectivity with the ketone moieties remaining intact.

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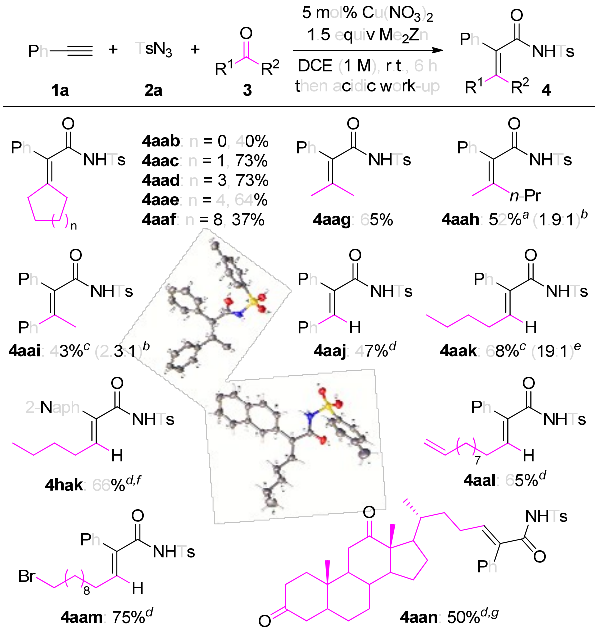
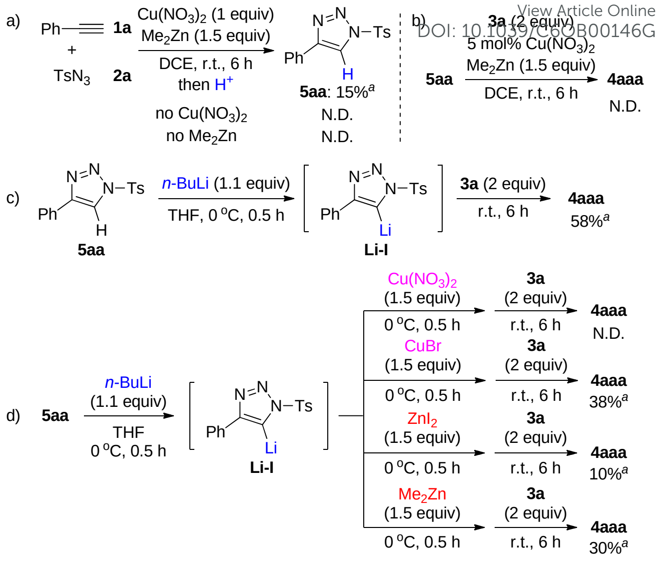
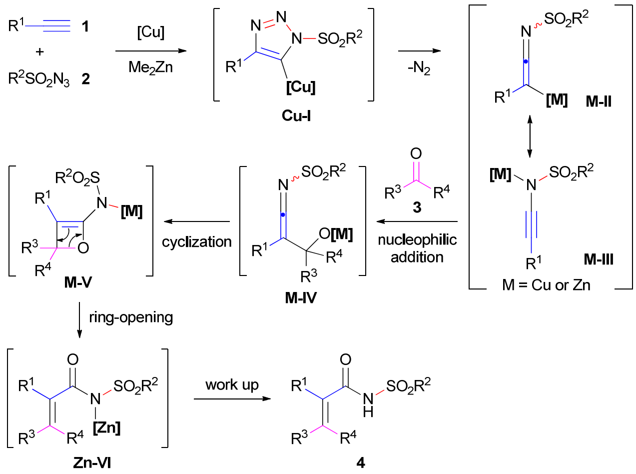


Scheme 4. Substrate Scope for Carbonyls. Reaction conditions: **1a** (0.5 mmol), **2a** (1.0 mmol), **3** (1.0 mmol), $Cu(NO_3)_2$ (0.025 mmol), Me_2Zn (0.75 mmol), DCE (0.5 mL), r.t., 6 h. Isolated yields are shown. [a] Combined yield of two isomers. [b] Determined by ^1H NMR analysis and the major product is shown. [c] Isolated yield of the major isomer. [d] only *E*-configured product was detected by ^1H NMR analysis of the crude reaction mixture. [e] Determined by GC-MS. [f] $Cu(NO_3)_2$ (0.05 mmol). [g] DCE (0.4 M).

To elucidate the possible reaction mechanism, a series of experiments was conducted. First, the two-component reaction of alkyne **1a** and azide **2a** gave 1-sulfonyltriazole **5aa** in 15% NMR yield after hydrolysis (Scheme 5a). No formation of **5aa** was observed in the absence of either $Cu(NO_3)_2$ or Me_2Zn, which indicated the crucial roles of $Cu(NO_3)_2$ and Me_2Zn in this reaction. Then, the reaction of 1-sulfonyltriazole **5aa** and cyclohexanone **3a** was carried out under the standard conditions (Scheme 5b). No expected product **4aaa** was detected, which ruled out the intermediacy of **5aa** in the three-component coupling reaction. We assumed that 5-metalated-1-sulfonyltriazole might be the key intermediate of the three-component reaction.[17] Therefore, lithiation of 1-sulfonyltriazole **5aa**[9f] followed by addition of cyclohexanone **3a** was conducted, which afforded the expected product **4aaa** in 58% NMR yield (Scheme 5c). However, the direct use of *n*-BuLi for the three-component coupling reaction was unsuccessful presumably due to its incompatibility with the reaction substrates and/or catalyst (Table 1, entry 12). To ascertain the key metal species, lithiated triazole **Li-I** was first treated with $Cu(NO_3)_2$, CuBr, ZnI_2, and Me_2Zn respectively[18-19] and then reacted with cyclohexanone **3a** (Scheme 5d). No product **4aaa** was detected in the reaction of copper(II) species and **3a** while those of copper(I) and zinc species delivered **4aaa** in 38%, 10%, and 30% yield, respectively. These results implied that the roles of Me_2Zn might be complicated in the reaction such as being the base, transmetalation reagent, reductant (Cu^{II} to Cu^{I}) or Lewis acid (activating carbonyls) and awaited further investigations.[20]



Scheme 5. Mechanism Studies. [a] Yields determined by ^1H NMR analysis. N.D. = Not Detected.



Scheme 6. A Plausible Mechanism.

Based on the above experiments and literature clues,[9,17,21] a plausible mechanism is shown in Scheme 6. Initial Cu-catalyzed cycloaddition of alkynes and sulfonyl azides in the presence of Me_2Zn affords copper intermediate **Cu-I**, which then releases dinitrogen to generate metal ynamidate **M-II** or its isomer ketenimine **M-III** (M = Cu, Zn). Subsequent nucleophilic addition to aldehydes/ketones gives metal alkoxide **M-IV**. An intramolecular cyclization of **M-IV** leads to four-membered species **M-V**, which further undergoes a ring-opening step furnishing product **4** after hydrolysis of amide zincate **Zn-VI**.[20,21]

In conclusion, we have developed a three-component one-pot procedure for efficient synthesis of polysubstituted olefins from common and easily available alkynes, sulfonyl azides, and simple aldehydes/ketones by the combinative use of the copper catalyst and Me_2Zn. This protocol showcases broad substrate scopes, mild reaction conditions, and good compatibility of functional groups.

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