Organic LETTERS
Letter
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
pubs.acs.org/OrgLett

Copper-Catalyzed Cascade Aminoalkynylation−Oxidation of Propargylic Alcohols: Stereospecific Synthesis of (*Z*)-2-Amino Conjugated Enynals/Enynones

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Supporting Information

ABSTRACT: Copper-catalyzed cascade aminoalkynylation−oxidation of propargylic alcohols has been realized, sterospecifically providing an array of (*Z*)-2-amino conjugated enynals/enynones in good yields under mild conditions. This transformation involves a rare 1,3-alkynyl migration of propargylic alcohols and simultaneously forms C−C, C−N, and C═O bonds. Furthermore, (*Z*)-2-amino conjugated enynals were applied to efficiently synthesize 3,5-disubstituted-1*H*-pyrrole-2-carbaldehyde and conjugated enynol derivatives.

Conjugated enynals/enynones are important structural units that are widely encountered in synthetic chemistry, medicinal chemistry, and materials science.[1] Consequently, efficient synthesis of these compounds has been increasingly explored.[2−5] The condensation reaction of ynals with ketones with α-H[2] (Scheme 1ia) and the reaction of ynals with Wittig reagents[3] (Scheme 1ib) could efficiently provide access to *E*-conjugated enynals/enynones. Sonogashira coupling reaction of terminal alkynes with β-substituted α,β-unsaturated ketone derivatives could form the conjugated enynones with retention of the unsaturated ketone configuration[4] (Scheme 1ic), but easily coordinating groups were usually incompatible in the presence of Pd-catalyst. Despite these achievements, it is necessary to develop novel methods that allow rapid access to diversely functionalized conjugated enynals/enynones starting from readily available starting materials.

Recently, our group[6] realized aminoarylation and aminovinylation of alkynes via 1,4-aryl or 1,3-vinyl migration triggered by nitrogen-centered radical addition to alkynes. Lately, Zhu[7a] and Studer[7b] described a perfluoroalkylative alkynylation of alkenes via 1,4- or 1,5-alkynyl migration initiated by perfluoroalkyl radical addition to alkenes. As part of our continued interest in functional group migration, we considered the possibility of extending this strategy to functionalization of *gem*-diyne via 1,3-alkynyl migration, thus realizing the alkynylation of unactivated alkynes. Herein, we report a copper-catalyzed cascade radical amination−alkynyl migration−oxidation of 1,4-diyn-3-ols with high stereoselectivity under mild conditions, leading to facile synthesis of (*Z*)-2-amino conjugated enynals/enynones (Scheme 1ii), which are important building blocks for the synthesis of other complex organic structures.

Initially, 1,5-diphenylpenta-1,4-diyn-3-ol (**1a**) was chosen as the model substrate. Treatment of **1a** and *N*-fluorobenzenesulfonimide (NFSI, **2a** 1.2 equiv) with CuCl (10 mol %) and pyridine in $CHCl_3$ at 50 °C led to formation of the desired aminoalkynylation/oxidation product (*Z*)-2-amino conjugated enynal **3a** in 19% isolated yield as the sole stereoisomer (Table 1, entry 1). Upon increasing the amount of NFSI to 2.0 equiv, the yield of **3a** increased to 34% (Table 1, entry 2). Evaluation of the solvent effect was subsequently carried out. Switching to DCE and CH_3CN solvent only diminished the efficiency (Table 1, entries 3−4), while THF, 1,4-dioxane, and toluene were unsuitable for this transformation (Table 1, entries 5−7). Among the various copper catalysts (CuI, CuCN, $CuCl_2$, $CuBr_2$, $Cu(OAc)_2$, and $Cu(OTf)_2$) examined, CuCN gave the best result (Table 1, entries 8−13). Both increasing and decreasing the temperature failed to improve the yield (Table 1, entries 14 and 15). With the screening of other additives such as 4-methylpyridine, 3-bromopyridine, 4-acetylpyridine, 3-nitropyridine, and 2-acetylpyridine, a satisfactory yield of 69% was achieved when 4-acetylpyridine was employed (Table 1, entries 16−20).[8a] Finally, the yield of **3a** was increased to 76% when 4 Å molecular sieves (0.2 g) were introduced (Table 1, entry 21).[8b] It should be noted that this novel reaction involved a rare 1,3-alkynyl migration of propargylic alcohols[9] and simultaneously formed C−C, C−N, and C═O bonds.

With the optimized conditions in hand, we next investigated the scope and the limitation of this aminoalkynylation−oxidation reaction (Scheme 2). First, variation of 1,4-diyn-3-ols

Received: July 20, 2018

DOI: 10.1021/acs.orglett.8b02272
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Scheme 1. Synthetic Methods of Conjugated Enynals/Enynones

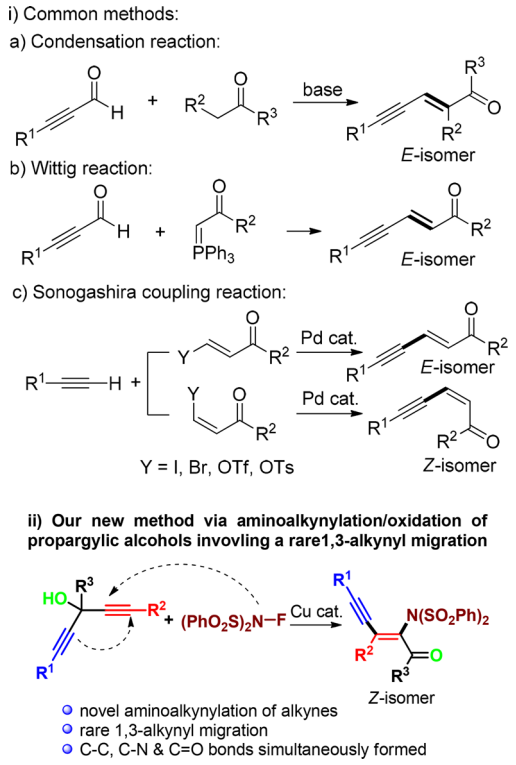
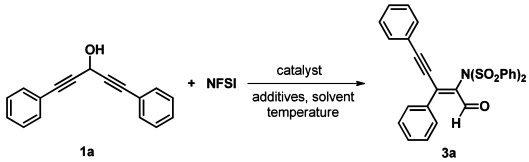


Table 1. Copper-Catalyzed Aminoalkynylation of 1a and NFSI[a,b]



1a 3a

entry	catalyst	additive	solvent	3a (%)[b]
1[c]	CuCl	pyridine	$CHCl_3$	19
2	CuCl	pyridine	$CHCl_3$	34
3	CuCl	pyridine	DCE	30
4	CuCl	pyridine	CH_3CN	25
5	CuCl	pyridine	1,4-dioxane	0
6	CuCl	pyridine	THF	0
7	CuCl	pyridine	toluene	trace
8	CuI	pyridine	$CHCl_3$	12
9	CuCN	pyridine	$CHCl_3$	42
10	$CuCl_2$	pyridine	$CHCl_3$	30
11	$CuBr_2$	pyridine	$CHCl_3$	28
12	$Cu(OAc)_2$	pyridine	$CHCl_3$	20
13	$Cu(OTf)_2$	pyridine	$CHCl_3$	24
14[d]	CuCN	pyridine	$CHCl_3$	36
15[e]	CuCN	pyridine	$CHCl_3$	34
16	CuCN	4-methylpyridine	$CHCl_3$	33
17	CuCN	3-bromopyridine	$CHCl_3$	41
18	CuCN	4-acetylpyridine	$CHCl_3$	69
19	CuCN	3-nitropyridine	$CHCl_3$	31
20	CuCN	2-acetylpyridine	$CHCl_3$	19
21[f]	**CuCN**	**4-acetylpyridine**	**$CHCl_3$**	**76**

[a]Reaction conditions: **1a** (0.2 mmol), NFSI (**2a**, 2.0 equiv), catalyst (10 mol %), additive (1.5 equiv), solvent (2 mL), 50 °C for 8 h under a nitrogen atmosphere. [b]The yield was determined after isolation of products by column chromatography. [c]1.2 equiv NFSI was used. [d]The reaction was conducted at 40 °C. [e]The reaction was conducted at 70 °C. [f]4 Å Molecular sieves (0.2 g) were used.

1 was performed, with the data being summarized in Scheme 2. Gratifyingly, a range of 1,5-diarylpenta-1,4-diyn-3-ols **1a**−**1o** bearing electron-withdrawing and -donating substituents, such as alkyl, alkoxyl, halide, and trifluoromethyl, led to desired (*Z*)-2-amino conjugated enynals **3a**−**3o** in moderate to high yields. The configuration of **3a** was further confirmed by X-ray analysis (CCDC 1562685). Halogen atoms were tolerant (**3g**, **3h**, **3j**, **3k**, **3n**, **3o**), which offers an opportunity for further transformation. Substrate **1p** with different substituents on the benzene ring of 1,4-diyn-3-ol reacted with **NFSI** smoothly and formed the desired product **3p** and **3p′** in a total yield of 51% with a 5:1 ratio. Furthermore, unsymmetrical 1,4-diyn-3-ols with an aryl substituted alkynyl and alkyl substituted alkynyl group could react smoothly affording product **3q** (51%) and **3r** (43%) with excellent selectivity. Dialkynyl substituted substrate 2,2,8,8-tetramethylnona-3,6-diyn-5-ol (**1s**) were also found to be compatible and afforded product **3s** in 59% yield. In addition, tertiary propargyl alcohols **1t**−**1y** were also tested. To our delight, expected (*Z*)-2-amino conjugated enynones **3t**−**3y** were obtained in moderate yields (61−76%). Notably, during the reactions of tertiary alcohols, 1,3-alkynyl migration was exclusive. Moreover, the novel aminoalkynylation of alkynes showed good stereoselectivity, only giving a *cis*-isomer.

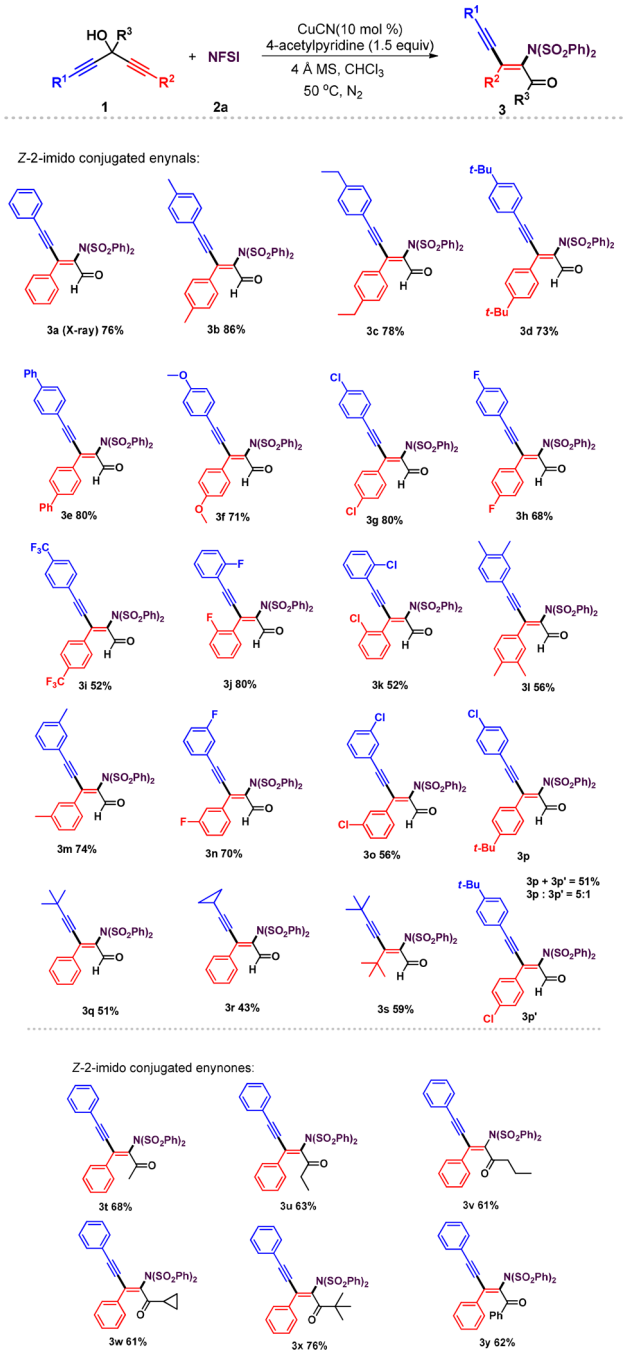
The generality of this aminoalkynylation−oxidation of propargylic alchohols was then examined by screening amination sources. Different NFSI derivatives **2** were investigated under the standard reaction conditions (Scheme 3). NFSI derivatives bearing both electron-donating and -withdrawing substituents at the *para* position (**2b**−**2g**) all reacted smoothly with 1,5-diphenylpenta-1,4-diyn-3-ol (**1a**), and the corresponding Z-2-amino conjugated enynals **4b**−**4g** were isolated in 77%−85% yields.

The synthetic utility of the reaction was investigated by performing gram-scale preparation of the conjugated enynals. Under identified conditions, the reaction of **1a** (3 mmol) and **2a** provided 1.10 g of **3a** (Scheme 4). To further demonstrate synthetic applications of this method, we next investigated the follow-up chemistry using **3a** as the starting material (Scheme 5). Desulfonylation was conducted by treatment of **3a** with *n*-Bu_4NF in THF 70 °C. Pleasingly, desulfonylation and cyclization product 3,5-diphenyl-1*H*-pyrrole-2-carbaldehyde **5** was smoothly isolated in 42% yield.[10] Chemoselective reduction of the carbonyl group in **3a** was achieved using $NaBH_4$ at room temperature to provide conjugated enynol **6** in 75% yield.

To gain insight into the reaction mechanism, radical inhibition experiments were performed (see Supporting Information). When 2,6-di-*tert*-butyl-4-methylphenol (BHT, 1.5 equiv) or 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO, 1.5 equiv) was added under the standard conditions, the reaction of **1a** and NFSI was completely suppressed and no desired **3a** was observed. These results suggested that the transformation might involve radical intermediates. On the basis of the experimental results and our previous studies,[6,11] a possible mechanism is proposed in Scheme 6. Initially, nitrogen-centered radical **A′** was generated through the interaction of CuCN and NFSI. Oxygen coordination of the propargylic alcohol **1a** with HF removal gives intermediate **B**.

DOI: 10.1021/acs.orglett.8b02272
Org. Lett. XXXX, XXX, XXX−XXX

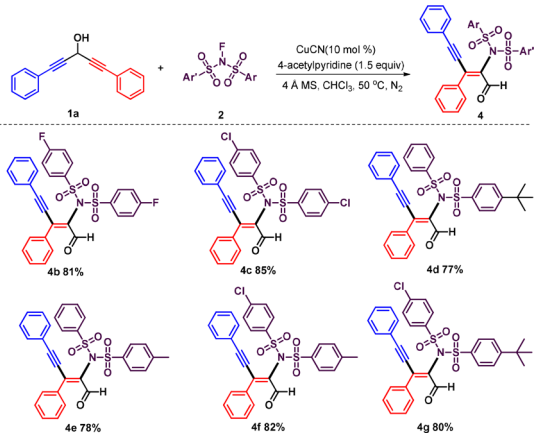
Scheme 2. Scope of Aminoalkynylation of Alkynes[a]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (NFSI, 2.0 equiv), CuCN (10 mol %), 4-acetylpyridine (1.5 equiv), 0.2 g of 4 Å molecular sieves, $CHCl_3$ (2 mL), 50 °C, N_2, 8 h. The yield was determined after isolation of products by column chromatography.

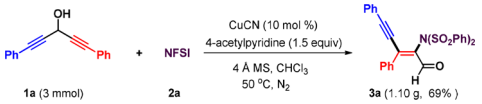
Next, highly selective intermolecular addition of the nitrogen-centered radical to the C≡C bond takes place to generate a linear vinyl radical **C**. For the unsymmetrical 1,4-diyn-3-ols **1p**−**1r**, the radical addition preferentially occurs at the (electron-rich) aryl alkynyl unit. Then, **C** rapidly undergoes 1,3-alkynyl migration to form a radical **D**, which is further transformed into a more stable radical **F** through resonance structure **E**.[12] Finally, homolysis of Cu−O bond of **F** affords stable Z-2-amino conjuated enynal **3a** together with con-

Scheme 3. Reaction of NFSI Derivatives[a]

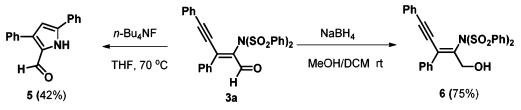


[a]Reaction conditions: **1a** (0.2 mmol), **2** (2.0 equiv), CuCN (10 mol %), 4-acetylpyridine (1.5 equiv), 0.2 g of 4 Å molecular sieves, $CHCl_3$ (2 mL), 50 °C, N_2, 8 h. The yield was determined after isolation of products by column chromatography.

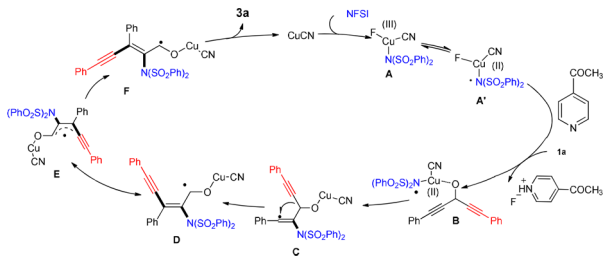
Scheme 4. Gram-Scale Preparation of 3a



Scheme 5. Follow-up Chemistry



Scheme 6. Plausible Mechanism



comitant regeneration of the Cu(I) species, thus completing the catalytic cycle.

In conclusion, an unprecedented aminoalkynylation−oxidation of propargylic alcohols has been realized with copper as catalyst, stererospecifically providing access to various Z-2-amino enynals/enynones. This novel transformation involves a rare 1,3-alkynyl migration of propargylic alcohols and simultaneously forms C−C, C−N, and C═O bonds. The reactions proceed under mild conditions and show good functional group compatibility. The strategy for alkyne aminoalkynylation via 1,3-alkynyl migration might provide a new avenue toward alkynylative functionalization of unsaturated substrates. Furthermore, (*Z*)-2-amino conjugated enynals were applied to efficiently synthesize 3,5-disubstituted-1*H*-pyrrole-2-carbaldehyde and conjugated enynol derivatives.

DOI: 10.1021/acs.orglett.8b02272
Org. Lett. XXXX, XXX, XXX−XXX

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02272.

Experimental procedures, spectral data for new compounds, and crystallographic data for **3a** (PDF)

Accession Codes

CCDC 1562685 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.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We acknowledge the financial support from the Jilin Province Natural Science Foundation (20160519003JH) and the Changbai Mountain Scholarship Program.

■ REFERENCES

(1) (a) Xia, Y.; Liu, Z.; Ge, R.; Xiao, Q.; Zhang, Y.; Wang, J. *Chem. Commun.* **2015**, *51*, 11233. (b) Hojo, D.; Tanaka, K. *Org. Lett.* **2012**, *14*, 1492. (c) Miki, K.; Yokoi, T.; Nishino, F.; Kato, Y.; Washitake, Y. *J. Org. Chem.* **2004**, *69*, 1557. (d) Clark, J. S.; Boyer, A.; Aimon, A.; García, P. E.; Lindsay, D. M.; Symington, A. D. F.; Danoy, Y. *Angew. Chem., Int. Ed.* **2012**, *51*, 12128. (e) Zhan, H.; Lin, X.; Qiu, Y.; Du, Z.; Li, P.; Li, Y.; Cao, H. *Eur. J. Org. Chem.* **2013**, *2013*, 2284. (f) Xia, Y.; Qu, S.; Xiao, Q.; Wang, Z.-X.; Qu, P.; Chen, L.; Liu, Z. *J. Am. Chem. Soc.* **2013**, *135*, 13502. (g) Kuroda, H.; Hanaki, E.; Izawa, H.; Kano, M.; Itahashi, H. *Tetrahedron* **2004**, *60*, 1913. (h) Hu, F.; Xia, Y.; Ma, C.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2016**, *81*, 3275. (i) Dong, J.; Bao, L.; Hu, Z.; Ma, S.; Zhou, X.; Hao, M.; Li, N.; Xu, X. *Org. Lett.* **2018**, *20*, 1244. (j) Xu, C.; Wittmann, S.; Gemander, M.; Ruohonen, V.; Clark, J. S. *Org. Lett.* **2017**, *19*, 3556.

(2) (a) Periasamy, M.; Karunakar, G. V. *J. Chem. Res.* **2006**, *2006*, 566. (b) Golovanova, A. A.; Latypovab, D. R.; Bekina, V. V.; Pisarevaa, V. S.; Vologzhaninac, A. V.; Dokichevb, V. A. *Russ. J. Org. Chem.* **2013**, *49*, 1282.

(3) Hack, D.; Chauhan, P.; Deckers, K.; Hermann, G. N.; Mertens, L.; Raabe, G.; Enders, D. *Org. Lett.* **2014**, *16*, 5188.

(4) (a) Yu, S.; Cho, E.; Kim, J.; Lee, S. *J. Org. Chem.* **2017**, *82*, 11150. (b) Molander, G. A.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 3106. (c) Hoshi, M.; Yamazaki, H.; Okimoto, M. *Synlett* **2010**, *2010*, 2461.

(5) (a) Chinta, B. S.; Baire, B. *J. Org. Chem.* **2015**, *80*, 10208. (b) Chen, J.; Fan, G.; Liu, Y. *Org. Biomol. Chem.* **2010**, *8*, 4806. (c) Trost, B. M.; Masters, J. T.; Taft, B. R.; Lumb, J.-P. *Chem. Sci.* **2016**, *7*, 6217.

(6) (a) Sun, J.; Zheng, G.; Xiong, T.; Zhang, Q.; Zhao, J.; Li, Y.; Zhang, Q. *ACS Catal.* **2016**, *6*, 3674. (b) Sun, J.; Zheng, G.; Zhang, Q.; Wang, Y.; Yang, S.; Zhang, Q.; Li, Y.; Zhang, Q. *Org. Lett.* **2017**, *19*, 3767. For another recent vinyl migration example via a radical pathway, see: (c) Li, L.; Li, Z.-L.; Gu, Q.-S.; Wang, N.; Liu, X.-Y. *Sci. Adv.* **2017**, *3*, e1701487.

(7) (a) Xu, Y.; Wu, Z.; Jiang, J.; Ke, Z.; Zhu, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 4545. (b) Tang, X.; Studer, A. *Chem. Sci.* **2017**, *8*, 6888.

(8) (a) Inorganic bases such as K_2CO_3 and NaOAc did not work, and **1a** was recovered completely. (b) 4 Å Molecular sieves might remove a very small amount of water in the reaction to improve the yield of **3a**.

(9) (a) Wang, T.; Shi, S.; Rudolph, M.; Hashmi, A. S. K. *Adv. Synth. Catal.* **2014**, *356*, 2337. (b) Wang, T.; Huang, L.; Shi, S.; Rudolph, M.; Hashmi, A. S. K. *Chem. - Eur. J.* **2014**, *20*, 14868. (c) Wang, T.; Shi, S.; Hansmann, M. M.; Rettenmeier, E.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2014**, *53*, 3715. (d) Namba, T.; Kawauchi, S.; Shibata, Y.; Kanno, H.; Tanaka, K. *Angew. Chem., Int. Ed.* **2017**, *56*, 3004. (e) Wang, J.; Shen, C.; Wang, T.; Mo, S.; Li, X.; Zhang, Z. *Adv. Synth. Catal.* **2016**, *358*, 3943. (f) Eisler, S.; Chahal, N.; McDonald, R.; Tykwinski, R. R. *Chem. - Eur. J.* **2003**, *9*, 2542.

(10) Yasuhara, A.; Kameda, M.; Sakamoto, T. *Chem. Pharm. Bull.* **1999**, *47*, 809.

(11) (a) Zhang, H.; Pu, W.; Xiong, T.; Li, Y.; Zhou, X.; Sun, K.; Liu, Q.; Zhang, Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 2529. (b) Zhang, H.; Song, Y.; Zhao, J.; Zhang, J.; Zhang, Q. *Angew. Chem., Int. Ed.* **2014**, *53*, 11079. (c) Zheng, G.; Li, Y.; Han, J.; Xiong, T.; Zhang, Q. *Nat. Commun.* **2015**, *6*, 7011. (d) Zhang, G.; Xiong, T.; Wang, Z.; Xu, G.; Wang, X.; Zhang, Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 12649. (e) Li, Y.; Zhou, X.; Zheng, G.; Zhang, Q. *Beilstein J. Org. Chem.* **2015**, *11*, 2721. (f) Sun, J.; Zheng, G.; Fu, Y.; Zhang, Q.; Wang, Y.; Zhang, Q.; Li, Y.; Zhang, Q. *Chin. J. Catal.* **2018**, *39*, 138−145.

(12) For the substrate **1w**, the ring-opening reaction of cyclopropyl group was not observed, which might be attributed to the better stability of radical intermediate **D** generated from **1w** than that of the resultant radical via ring openging of **D**. For some radical clocks, ring-opening reactions are reversible, and the cyclic forms are thermodynamically favored; see:Newcomb, M. In *Radicals in Organic Synthesis*, Vol. 2; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH, Weinheim, 2001; pp 317−336.

DOI: 10.1021/acs.orglett.8b02272
Org. Lett. XXXX, XXX, XXX−XXX