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Copper-Catalyzed Selective 1,2-Difunctionalization of *N*-Heteroaromatics through Cascade C−N/C═C/C═O Bond Formation

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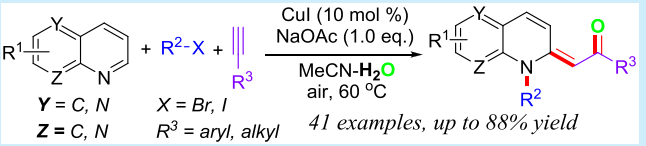
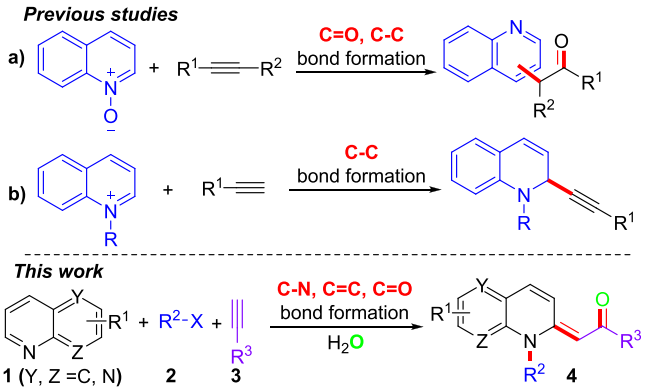
ABSTRACT: This study presents an efficient strategy for constructing 1,2-difunctionalized quinoline derivatives via the multicomponent cascade coupling of *N*-heteroaromatics with alkyl halides and different terminal alkynes. This reaction was achieved through sequential functionalization at the one- and two-positions of quinolines, which displayed a broad substrate scope, environmental friendliness, excellent functional group tolerance, high atom efficiency, and chemoselectivity. The multicomponent coupling involved the abnormal construction of new C−N, C═C, and C═O bonds in one pot. The applicability of this method was further demonstrated by the late-stage functionalization of complex drug molecules under the established conditions.



Quinoline and its derivatives are widely used in the fields of pharmaceutical and organic syntheses owing to their unique properties.[1] Therefore, the development of new and efficient synthetic strategies for functionalized quinoline frameworks is important in both synthetic organic chemistry and medicinal chemistry.[2] In recent years, reactions of alkynes with quinolines or quinoline *N*-oxides to construct quinoline derivatives have been well developed.[3] One of the most well studied reaction routes is the C═O and C−C bond formation between quinoline *N*-oxide and internal alkynes. For instance, Li and Sundararaju have developed a redox-neutral coupling of quinoline *N*-oxide with alkynes to synthesize quinolines with a carbonyl group.[4] Maulide and coworkers reported the oxyarylation of alkynes with pyridine and quinonline *N*-oxides.[5] Furthermore, Zhang reported metal-free reactions of alkynes with isoquinoline and quinoline *N*-oxides (Scheme 1a).[6]

On the contrary, the functionalization of quinolinium salts has been shown to be a useful method for the synthesis of the substituted quinoline skeleton.[2b,7] In general, the addition of electrophiles to (iso)quinoline generates (iso)quinolinium salts that can be captured by nucleophiles (e.g., terminal alkyne), which provides a facile pathway to access quinoline with different functionalities (Scheme 1b).[8] On the basis of the previously described advancements and our recent work on the construction of functionalized *N*-heterocycles,[9] we envisaged a direct transformation of alkynes into functionalized quinolones via in situ quinolinium salt formation. This multicomponent coupling of alkyl halides with different *N*-heteroaromatics and terminal alkynes involved the creation of multiple bonds in one pot, providing various substituted quinolines (Scheme 1c). This reaction realized the 1,2-difunctionalization of *N*-heteroaromatics through cascade C−N/C═C/C═O bond formation.

Scheme 1. Reaction of Quinolines with Alkynes



This investigation was initiated by screening reaction conditions for the copper-catalyzed three-component coupling of quinoline, benzyl bromide, and phenyl acetylene (Table 1). First, many additives were tested by performing the reaction in CH_3CN-H_2O (1:1 v/v) under open-air conditions for 8 h at 60 °C. Subsequently, different additives including CH_3CO_2K, CH_3CO_2Na, $CH_3CO_2NH_4$, and *t*-BuONa were tested, and the

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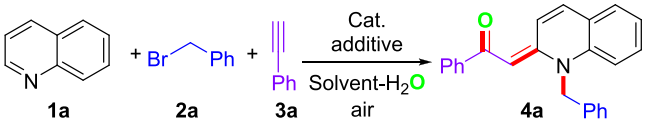
Table 1. Screening Conditions[a]



entry	[Cu]	additives	solvent	yield (%)[b]
1	CuCl	CH_3CO_2K	toluene−H_2O	40
2	CuCl	CH_3CO_2Na	toluene−H_2O	44
3	CuCl	$CH_3CO_2NH_4$	toluene−H_2O	21
4	CuCl	*t*-BuONa	toluene−H_2O	12
5	$CuCl_2$	CH_3CO_2Na	toluene−H_2O	26
6	CuBr	CH_3CO_2Na	toluene−H_2O	22
7	CuI	CH_3CO_2Na	toluene−H_2O	49
8		CH_3CO_2Na	toluene−H_2O	trace
9	CuI		toluene−H_2O	trace
10	CuI	CH_3CO_2Na	MeCN−H_2O	85
11	CuI	CH_3CO_2Na	DMF−H_2O	82
12	CuI	CH_3CO_2Na	DMSO−H_2O	62
13	CuI	CH_3CO_2Na	MeCN−H_2O	80, 82[c]

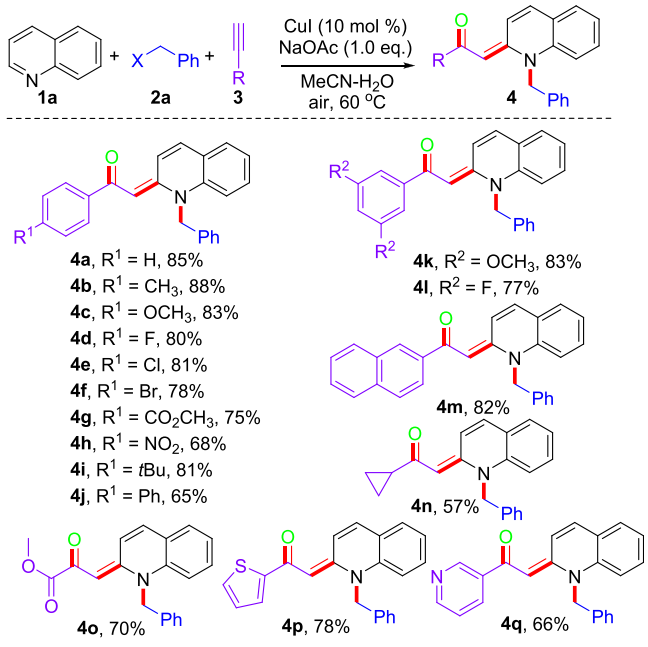
[a]Conditions: Quinoline **1a** (0.3 mmol), [Cu] (10 mol %), benzyl bromide (1.0 equiv), phenylacetylene (1.2 equiv), additive (1.0 equiv), temperature (60 °C), 1.0 mL of mixed solvent (v/v 6/1), 8 h, unless otherwise noted. [b]Isolated yield. [c]**1a**/**2a**/**3a** (1:1.2:1 or 1:1:1.5).

results showed that CH_3CO_2Na was the most effective additive, affording product **4a** in 44% yield (Table 1, entries 1−4). Among the various [Cu] catalysts tested, CuI gave the best results (entries 5−7). Control experiments established the importance of CuI and CH_3CO_2Na in achieving the efficient 1,2-difunctionalization of quinoline (entries 8 and 9). The solvent system used also significantly affected the related reaction efficiency. An investigation of solvent systems (entries 10−12) indicated that MeCN−H_2O (6:1 v/v entry 10) gave the best result.

After the reaction conditions were established, the cascade multicomponent coupling reaction was successfully extended to different terminal alkynes. As shown in Scheme 2, various terminal alkyne classes (including aryl-, alkyl-, and heteroaryl-substituted) were examined. Aromatic alkynes with electron-deficient (*p*-F, *p*-Cl, *p*-Br, *p*-CO_2Me, *p*-Ph, and *p*-NO_2) and electron-rich (*p*-Me, *p*-OMe, *p*-tBu, and 3,5-dimethoxy) groups all reacted well, giving 1,2-difunctionalized products in good yields (**4a**−**4l**). 2-Ethynylnaphthalene and methyl propiolate also showed good compatibility with this reaction, affording **4m** and **4o** in 82 and 70% yields, respectively. Using aliphatic alkyne ethynylcyclopropane (**3n**), the desired product was obtained in moderate yield. Regarding heteroarylacetylenes, 2-thienyl and 3-pyridine acetylenes afforded **4p** and **4q** in moderate yields of 78 and 66%, respectively. However, no reaction occurred when nonterminal alkyne 1,2-diphenylethyne was used as a substrate under the same reaction conditions.

Subsequently, the substrate scopes of *N*-heteroaromatics and alkyl halides were examined (Scheme 3). Various electron-donating, electron-withdrawing, and halogen groups at different positions on the quinoline ring were well tolerated in the coupling with phenylacetylene, with 1,2-difunctionalized products isolated in 58−87% yields. In general, both benzyl bromide and alkyl iodide were suitable for this protocol. Interestingly, the *N*-heteroaromatics were not limited to quinoline systems, with other pyridine-based *N*-heteroaromatics, including 1,5-naphthyridine, 1,8-naphthyridine, and pyrido[2,3-*b*]pyrazine, isolated in moderate to high yields (**5l**−**5p**). The structures of **5a** and **5l** were unambiguously assigned by X-ray crystallography. (See the Supporting Information.) Remarkably, this method was also useful for the addition of hydroxy-substituted quinolines, such as 5-hydroxyquinoline, 6-hydroxyquinoline, and 7-hydroxyquinoline, giving the multifunctionalized products **5q**−**5u** in moderate yield (65−75%). When pyridine and isoquinoline were subjected to the established conditions, no reactions were observed. As shown in Schemes 2 and 3, the method developed had a broad substrate scope, excellent functional group tolerance, and high atom efficiency.

Scheme 2. Substrate Scope of Terminal Alkynes[a]



[a]Conditions: Quinoline **1a** (0.3 mmol), CuI (10 mol %), benzyl bromide **2a** (1.0 equiv), terminal alkynes **3** (1.2 equiv), NaOAc (1.0 equiv), and mixed solvent (1.0 mL; MeCN/H_2O 6:1 v/v) at 60 °C for 8 h under an air atmosphere.

To demonstrate its potential application, this synthetic method was applied to the late-stage functionalization of drug molecules. Specifically, ethisterone and norethindrone were selectively installed at the C2 position of quinoline (**6a**, **6b**). Furthermore, site-selective 1,2-difunctionalization proceeded well when substrates derived from quinoline-based drugs, such as *N*-benzylcinchonidinium chloride, were employed (**6c**). Owing to its generality, this method will likely be useful for fragment couplings, leading to a broad range of complex structures and drug molecules. We were also interested in the subsequent conversion of the target product using a simple method for the selective reduction of the olefinic bonds in the *α*,*β*-unsaturated carbonyl moiety.[10] Reactions were performed using a 1:4:2 ratio of product **4a** (0.2 mmol)/$NaBH_4$/HOAc with 2.5 mol % Pd/C in toluene (2 mL) in open air at room temperature for 2 h, achieving effective reduction of the alkenone and producing the synthetically useful hydrogenated product **4a′** in 78% yield (Scheme 4).

To investigate the reaction mechanism, a series of control experiments were conducted (Scheme 5). First, presynthesized quinolinium salt **4A-1** was reacted with phenylacetylene **3a**

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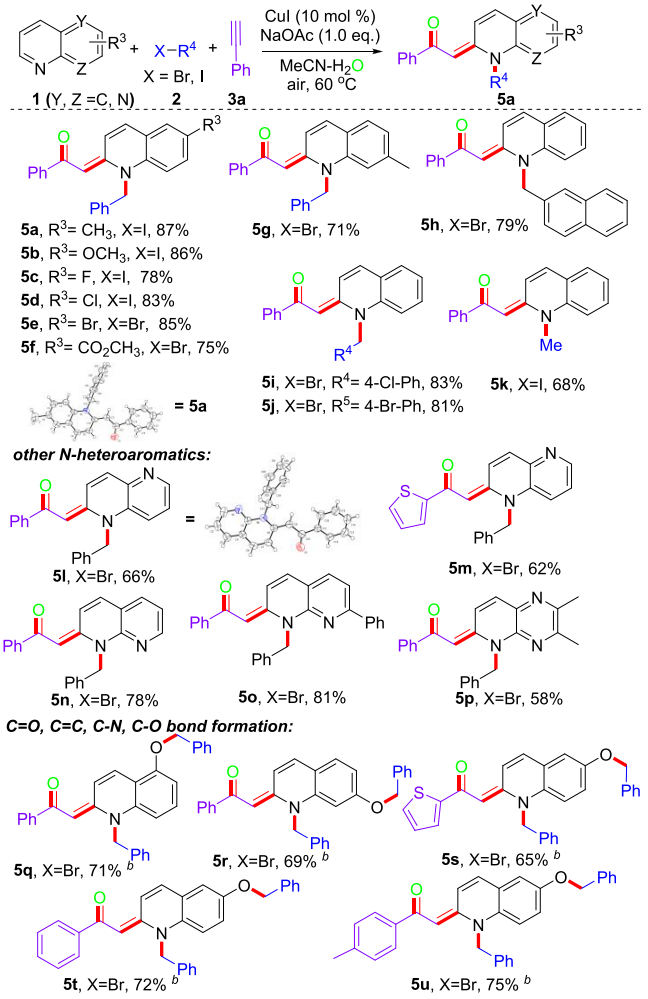
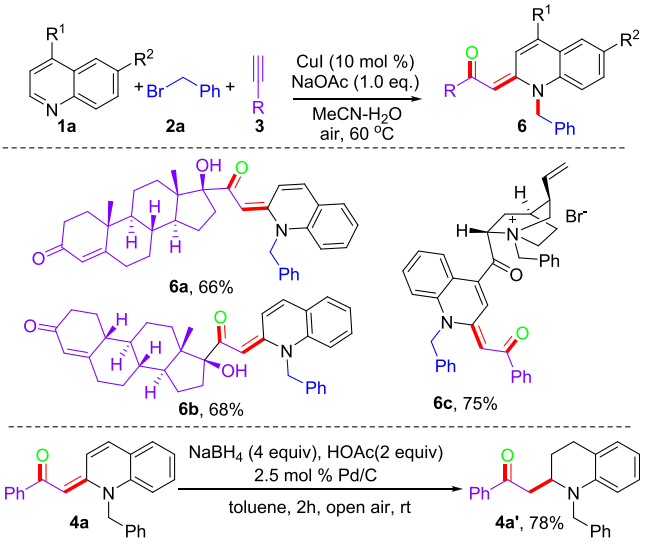
Scheme 3. Substrate Scope of *N*-Heteroaromatics and Alkyl Halides[a]

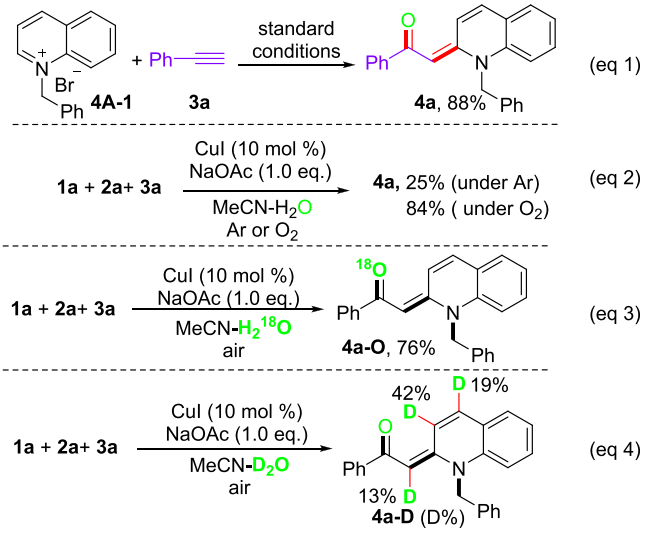


[a]Conditions: *N*-Heteroaromatics **1** (0.3 mmol), CuI (10 mol %), alkyl halides **2** (1.0 equiv), phenylacetylene **3a** (1.2 equiv), NaOAc (1.0 equiv), and mixed solvent (1.0 mL, MeCN/H_2O 6:1 v/v) at 60 °C for 8 h under an air atmosphere. [b]2.0 equiv of alkyl halides **2** was used.

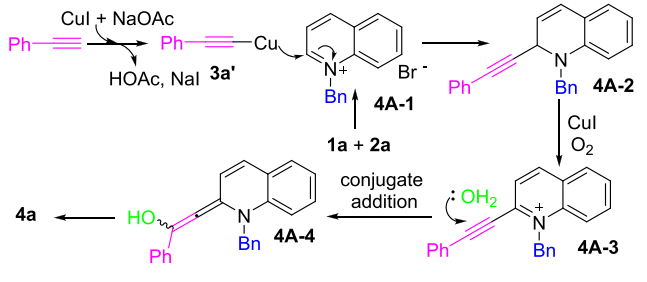
Scheme 4. Potential Application of This Method



Scheme 5. Control Experiments



Scheme 6. Plausible Reaction Pathways



under the established reaction conditions, producing the desired product **4a** in 88% yield (eq 1). This result clearly showed that **4A-1** was a reaction intermediate. The low reaction yield under an argon atmosphere showed that an oxygen atmosphere played an important role in this reaction (eq 2). To prove that water provides a source of oxygen in the reaction, H_2O-labeling experiments were conducted.[11] When conducting the reaction in the presence of ^{18}O-labeled water instead of $H_2{}^{16}O$, the ratio of ^{18}O-labeled product **4a-O** increased accordingly, as determined by LC−MS analysis (eq 3). This suggested that oxygen atoms in the unsaturated ketones mainly originated from H_2O. Furthermore, a D_2O-labeling experiment resulted in product **4a-D** with deuterium incorporated into the conjugated diene unit, showing that D atoms were transferred from D_2O to the alkynyl group (eq 4). Meanwhile, the deuterium ratio in the conjugated diene of **4a** implied that double-bond tautomerization was involved in the reaction.

From these results and LC−MS reaction monitoring, a tentative mechanism was proposed for this cascade transformation, as shown in Scheme 6. Initially, quinoline and benzyl bromide quickly form quinoline salt **4A-1**. Copper activates phenylacetylene to form copper(I) phenylacetylide **3a′**.[12] Next, the addition of the copper(I) phenylacetylide to quinolinium salt **4A-1** forms intermediate **4A-2**. In the presence of oxygen, copper catalyzes the formation of imine-type intermediate **4A-3** through oxidation adjacent to the nitrogen atom.[13] Intermediate **4A-3** undergoes further

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conjugate addition with water to produce intermediate **4A-4**, which isomerizes into the more stable intermediate **4a**.[14]

In summary, we have described an unprecedented *N*-alkylation/alkenylation tandem process for the construction of 1,2-difunctionalized quinoline derivatives. This protocol exhibits a high atom economy, a broad substrate scope, functional group tolerance, and environmental friendliness. The applicability of this method was further demonstrated by the late-stage functionalization of complex drug molecules under the established conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02910.

Detailed experimental procedures, characterization data, crystallographic data for **5a** and **5l**, and copies of NMR spectra for all isolated compounds (PDF)

Accession Codes

CCDC 2024307 and 2024309 contain 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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Author Contributions

†Q.H. and F.X. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Colomb, J.; Becker, G.; Fieux, S.; Zimmer, L.; Billard, T. *J. Med. Chem.* **2014**, *57*, 3884−3890. (b) Jentsch, N. G.; Hart, A. P.; Hume, J. D.; Sun, J.; McNeely, K. A.; Lama, C.; Pigza, J. A.; Donahue, M. G.; Kessl, J. J. *ACS Med. Chem. Lett.* **2018**, *9*, 1007−1012. (c) Kaur, K.; Jain, M.; Reddy, R. P.; Jain, R. *Eur. J. Med. Chem.* **2010**, *45*, 3245−3264.

(2) (a) Shirai, T.; Kanai, M.; Kuninobu, Y. *Org. Lett.* **2018**, *20*, 1593−1596. (b) Grozavu, A.; Hepburn, H. B.; Smith, P. J.; Potukuchi, H. K.; Lindsay-Scott, P. J.; Donohoe, T. J. *Nat. Chem.* **2019**, *11*, 242−247. (c) Xie, F.; Xie, R.; Zhang, J.-X.; Jiang, H.-F.; Du, L.; Zhang, M. *ACS Catal.* **2017**, *7*, 4780−4785. (d) Xie, L.-Y.; Duan, Y.; Lu, L.-H.; Li, Y.-J.; Peng, S.; Wu, C.; Liu, K.-J.; Wang, Z.; He, W.-M. *ACS Sustainable Chem. Eng.* **2017**, *5*, 10407−10412. (e) Xie, L.-Y.; Qu, J.; Peng, S.; Liu, K.-J.; Wang, Z.; Ding, M.-H.; Wang, Y.; Cao, Z.; He, W.-M. *Green Chem.* **2018**, *20*, 760−764.

(3) (a) Chen, X.; Yang, F.; Cui, X.; Wu, Y. *Adv. Synth. Catal.* **2017**, *359*, 3922−3926. (b) Yang, W. W.; Chen, L. L.; Chen, P.; Ye, Y. F.; Wang, Y. B.; Zhang, X. *Chem. Commun.* **2020**, *56*, 1183−1186. (c) Sharma, S.; Kumar, M.; Vishwakarma, R. A.; Verma, M. K.; Singh, P. P. *J. Org. Chem.* **2018**, *83*, 12420−12431. (d) Wu, L.; Sun, J.; Yan, C. *Chin. J. Chem.* **2012**, *30*, 590−596. (e) Xu, Z.; Ni, F.; Han, J.; Tao, L.; Deng, H.; Shao, M.; Chen, J.; Zhang, H.; Cao, W. *Eur. J. Org. Chem.* **2016**, *2016*, 2959−2965.

(4) (a) Barsu, N.; Sen, M.; Premkumar, J. R.; Sundararaju, B. *Chem. Commun.* **2016**, *52*, 1338−1341. (b) Zhang, X.; Qi, Z.; Li, X. *Angew. Chem., Int. Ed.* **2014**, *53*, 10794−10798.

(5) Chen, X.; Ruider, S. A.; Hartmann, R. W.; Gonzalez, L.; Maulide, N. *Angew. Chem., Int. Ed.* **2016**, *55*, 15424−15428.

(6) Zhang, B.; Huang, L.; Yin, S.; Li, X.; Xu, T.; Zhuang, B.; Wang, T.; Zhang, Z.; Hashmi, A. S. K. *Org. Lett.* **2017**, *19*, 4327−4330.

(7) (a) Wang, Y.; Liu, Y.; Zhang, D.; Wei, H.; Shi, M.; Wang, F. *Angew. Chem., Int. Ed.* **2016**, *55*, 3776−3780. (b) Jung, S.; Shin, S.; Park, S.; Hong, S. *J. Am. Chem. Soc.* **2020**, *142*, 11370−11375. (c) Tan, Z.; Ci, C.; Yang, J.; Wu, Y.; Cao, L.; Jiang, H.; Zhang, M. *ACS Catal.* **2020**, *10*, 5243−5249.

(8) (a) Lin, W.; Cao, T.; Fan, W.; Han, Y.; Kuang, J.; Luo, H.; Miao, B.; Tang, X.; Yu, Q.; Yuan, W.; Zhang, J.; Zhu, C.; Ma, S. *Angew. Chem., Int. Ed.* **2014**, *53*, 277−281. (b) Dasgupta, S.; Liu, J.; Shoffler, C. A.; Yap, G. P.; Watson, M. P. *Org. Lett.* **2016**, *18*, 6006−6009. (c) Pappoppula, M.; Cardoso, F. S. P.; Garrett, B. O.; Aponick, A. *Angew. Chem., Int. Ed.* **2015**, *54*, 15202−15206. (d) Zurro, M.; Asmus, S.; Bamberger, J.; Beckendorf, S.; Garcia Mancheno, O. *Chem. - Eur. J.* **2016**, *22*, 3785−3793. (e) Jeganmohan, M.; Bhuvaneswari, S.; Cheng, C. H. *Chem. - Asian J.* **2010**, *5*, 153−159.

(9) (a) Chen, X.; Zhao, H.; Chen, C.; Jiang, H.; Zhang, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 14232−14236. (b) Chen, X.; Yang, Z.; Chen, X.; Liang, W.; Zhu, Z.; Xie, F.; Li, Y. J. *J. Org. Chem.* **2020**, *85*, 508−514. (c) Zhu, Z.; Lin, H.; Liang, B.; Huang, J.; Liang, W.; Chen, L.; Huang, Y.; Chen, X.; Li, Y. *Chem. Commun.* **2020**, *56*, 5621−5624. (d) Liang, W.; Xie, F.; Yang, Z.; Zeng, Z.; Xia, C.; Li, Y.; Zhu, Z.; Chen, X. *Org. Lett.* **2020**, DOI: 10.1021/acs.orglett.0c02924.

(10) Russo, A. T.; Amezcua, K. L.; Huynh, V. A.; Rousslang, Z. M.; Cordes, D. B. *Tetrahedron Lett.* **2011**, *52*, 6823−6826.

(11) (a) Zhang, J.; Chen, H.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2768−2771. (b) Zhao, Y.; Huang, B.; Yang, C.; Chen, Q.;

Xia, W. *Org. Lett.* **2016**, *18*, 5572−5575. (c) Liu, Y.; Meng, Y.-N.; Huang, X.-J.; Qin, F.-H.; Wu, D.; Shao, Q.; Guo, Z.; Li, Q.; Wei, W.-T. *Green Chem.* **2020**, *22*, 4593−4596.
(12) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810−11811.
(13) (a) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997−4999. (b) Gogoi, A.; Modi, A.; Guin, S.; Rout, S. K.; Das, D.; Patel, B. K. *Chem. Commun.* **2014**, *50*, 10445−10447.
(14) (a) Egi, M.; Yamaguchi, Y.; Fujiwara, N.; Akai, S. *Org. Lett.* **2008**, *10*, 1867−1870. (b) Wang, D.; Zhang, Y.; Harris, A.; Gautam, L. N. S.; Chen, Y.; Shi, X. *Adv. Synth. Catal.* **2011**, *353*, 2584−2588.

https://dx.doi.org/10.1021/acs.orglett.0c02910
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