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Switchable Access to 3-Carboxylate-4-quinolones and 1-Vinyl-3-carboxylate-4-quinolones via Oxidative Cyclization of Isatins and Alkynes

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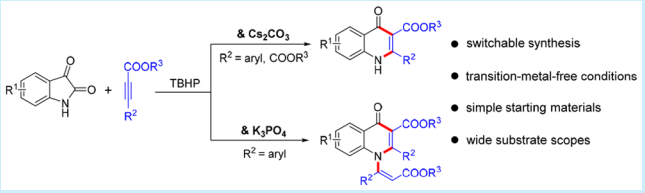
Supporting Information

ABSTRACT: An efficient transition-metal-free oxidative cyclization reaction using isatins and alkynes for the facile synthesis of structurally diverse 4-quinolones has been developed. Intriguingly, switchable access to substituted 3-carboxylate-4-quinolones and 1-vinyl-3-carboxylate-4-quinolones could be achieved by choosing a different base in the reaction. The obtained products could undergo further transformations, increasing the application potential of the method in organic synthesis.



4-Quinolone and its derivatives represent an important and abundant class of nitrogen-containing heterocycles. It is exemplified as a privileged structure motif that is embedded in a wide range of biological active molecules[1] and pharmaceuticals.[2] For example, this structural motif forms the scaffold of drugs such as lvacaftor (treatment of cystic fibrosis),[3] elvitegravir (treatment of HIV infection),[4] nedocromil (crucial antiasthmatic agent),[5] and a vital class of marketed antibiotics such as levofloxacin, norfloxacin and ciprofloxacin (Figure 1).[6]

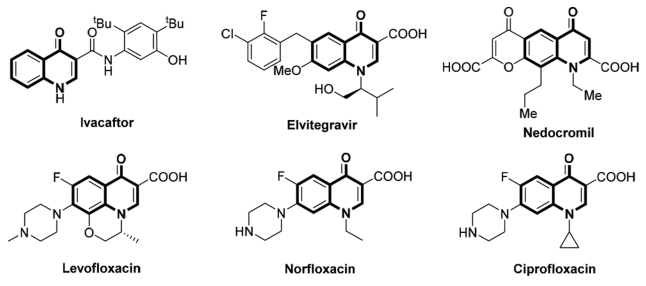


Figure 1. Selected biologically active 4-quinolone derivatives.

Because of their importance, the synthesis of 4-quinolones has attracted the continued interest of chemists and pharmacologists. Currently, the known procedures for the synthesis of 4-quinolone derivatives can be mainly summarized by three types. One type is the classical cyclocondensation reactions such as Niementowski,[7] Conrad−Limpet,[8] and Camps cyclizations[9] (Scheme 1a), which are usually perceived as the most common methods for 4-quinolone synthesis. However, these processes are more or less confined to harsh reaction conditions, low yields, and limited substrate scope. An alternative pathway involves the intramolecular cyclization of *o*-amino acetylenic ketones, and this strategy provides an efficient and straightforward access to 4-quinolones (Scheme 1b).[10] However, these transformations require the substrates to be carefully designed. To address this gap, several superior procedures have been established to construct 4-quinolones from more simple and readily available anilines/alkenes or anilines/alkynes (Scheme 1c).[11] For example, in 2015, Larhed and colleagues described a novel Pd-catalyzed synthesis of 4-quinolones from 2-iodoanilines, alkynes, and molybdenum hexacarbonyl.[11a] In 2017, Zhang and co-workers developed a unique and direct approach for constructing 4-quinolone derivatives from anilines and alkynes.[11b] Moreover, Lee et al. also disclosed an elegant process for the synthesis of 4-quinolones through efficient Cu-catalyzed aza-Michael addition of 2-aminobenzoates to β-substituted α,β-unsaturated ketones followed by cyclization/mild oxidation.[11c] Despite these recent advances, the development of new methods for constructing diverse 4-quinolones from commercially available substrates, especially under transition-metal-free conditions, remains an important goal.

Isatin is a unique structure possessing a γ-lactam and a ketone, which has been extensively employed as an essential building block for the efficient assembly of various N-heterocycles.[12] Recently, we have reported two robust synthetic methods of quinazolines and benzothiazolo[2,3-*b*]quinazolinones via an innovative isatin-based oxidative cyclization strategy.[13] In conjunction with our ongoing research into developing isatin-

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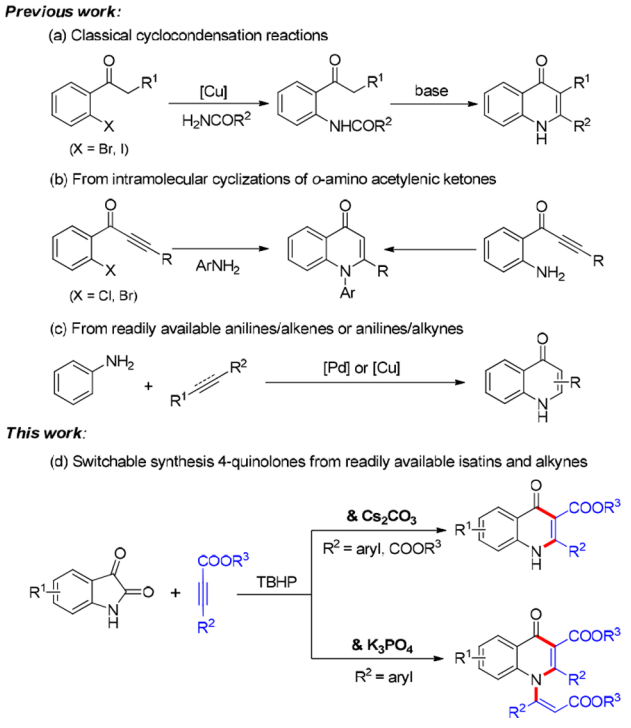
Scheme 1. Methods for the Preparation of 4-Quinolones

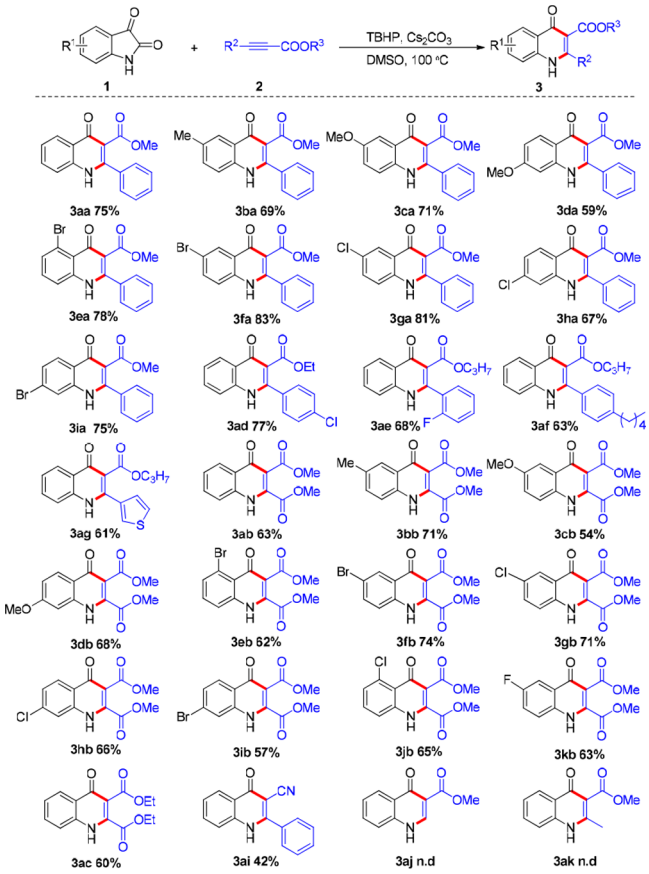


based oxidative cyclization methodologies for the preparation of valuable heterocycles, herein, we report an efficient route to access 4-quinolone derivatives by transition-metal-free oxidative cyclization of isatins and alkynes (Scheme 1d). Notably, this approach enabled switchable construction of 3-carboxylate-4-quinolones and 1-vinyl-3-carboxylate-4-quinolones via the selection of different bases in the reaction.

We commenced our study by choosing isatin **1a** (0.5 mmol) and methyl 3-phenylpropiolate **2a** (0.5 mmol) as model substrates to optimize the reaction conditions (Table S1). Pleasingly, this reaction afforded 3-carboxylate-4-quinolone **3aa** in 75% yield when it was conducted in DMSO with 2.0 equiv of Cs_2CO_3 and 1.0 equiv of TBHP at 100 °C in a sealed vessel for 12 h (entry 1). Surprisingly, the reaction produced an interesting N-alkenylated product **4aa** in 6% yield. In view of the above interesting results, this domino reaction was optimized to improve yield and selectivity. We first evaluated the effect of various inorganic and organic bases to the product **3aa**, with Cs_2CO_3 giving the highest yield (entries 1−8). Other oxidants including DDQ, Oxone, and $K_2S_2O_8$ all failed to deliver the product **3aa** (entries 9−11). A diminished yield was obtained when the reaction was performed at lower or higher temperatures (entries 12 and 13). Further solvent screening identified DMSO as the optimum choice, and other solvents gave lower yields (entries 14 and 15). We continued to examine the effect of various bases, temperatures, and solvents in an effort to improve the yield and selectivity of **4aa** (entries 16−25). Eventually, good selectivity and yield for **4aa** were obtained when the reaction conditions were determined as **1a** (0.5 mmol), **2a** (1 mmol), 2.0 equiv of K_3PO_4, and 1.0 equiv of TBHP in 3 mL of DMSO at 100 °C (entry 17).

After the optimized conditions were identifed, we further evaluated the substrate generality for this reaction (Scheme 2). To our delight, the reaction demonstrated good compatibility and proved to be a general method to build various 4-quinolone derivatives. Reactions with isatins bearing electron-neutral (H,

Scheme 2. Scope of 3-Carboxylate-4-quinolones[a,b]



[a]Reactions conditions: **1** (0.5 mmol), **2** (0.5 mmol), Cs_2CO_3 (1 mmol), and TBHP(0.5 mmol) in DMSO (3 mL) at 100 °C in a sealed vessel for 12 h. [b]Isolated yields.

5-Me) and electron-donating (5-OMe, 6-OMe) groups all underwent the desired transformation to deliver the corresponding products in moderate to good yields (**3aa**−**da**, 59%−75%). An array of halogen-substituted isatins (4-Br, 5-Br, 5-Cl, 6-Cl, 6-Br) were all found to be compatible with the reaction (**3ea**−**ia**, 67%−83%), which provided opportunities for further synthetic elaboration. Several substituted alkynes including heteroaryl substrate propyl 3-(thiophene-3-yl)propiolate were also reacted well to deliver the corresponding products in satisfactory yields (**3ad**−**ag**, 61%−77%). The reaction scope was further tested by reacting different isatins with dimethyl but-2-ynedioate. The reaction proceeded smoothly with a variety of isatins to afford the corresponding products (**3ab**−**kb**, 54%−74%). Diethyl but-2-ynedioate was also tolerant to give the target product (**3ac**, 60%). Notably, 3-phenylpropiolonitrile reacted smoothly under the optimized conditions to deliver the product **3ai** in 42% yield. However, the application of the standard conditions to aliphatic alkynoates failed to afford any of the desired products **3aj** and **3ak**.

The scope of substrates for constructing 1-vinyl-3-carboxylate-4-quinolones was next investigated. As shown in Scheme 3, isatins with electron-neutral, electron-donating, and halogen groups at the C-5 or C-6 position delivered products smoothly with moderate to good yields (**4aa**−**ia**, 63%−80%). Ethyl 3-(4-chlorophenyl) propiolate (**4ad**, 69%) and ethyl 3-phenylpropiolate (**4ah**, 67%) were also tolerated. The optimized conditions were also applied to 3-phenylpropiolonitrile, which

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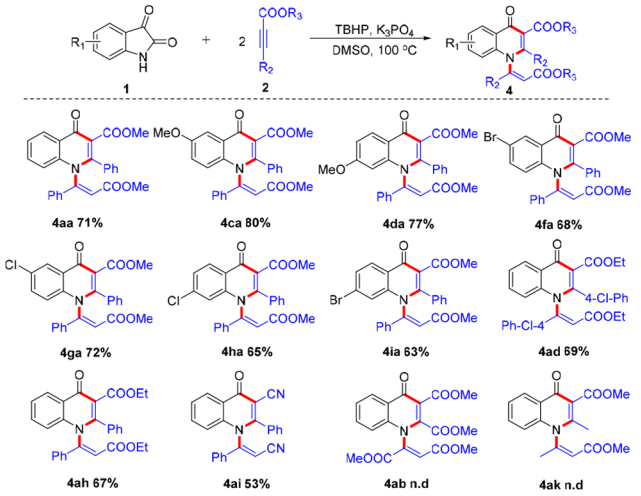
Scheme 3. Scope of N-Substituted 4-Quinolones[a,b]

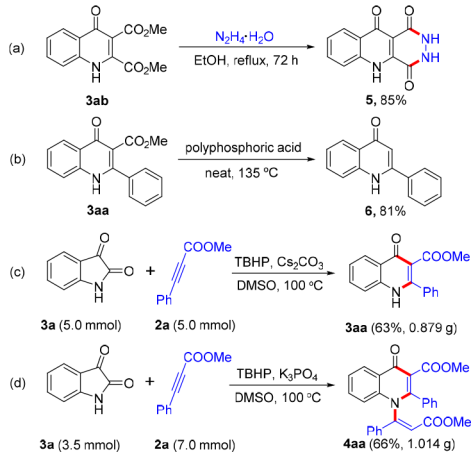


[a]Reactions conditions: **1** (0.5 mmol), **2** (1 mmol), K_3PO_4 (1 mmol), and TBHP (0.5 mmol) in DMSO (3 mL) at 100 °C in a sealed vessel for 12 h. [b]Isolated yields.

gave the corresponding product **4ai** in 53% yield. Unfortunately, no N-alkenylated product formation were observed when dimethyl but-2-ynedioate and aliphatic alkynoates were used. The structures of **3ab**, **4aa**, and **4ga** were unambiguously determined by X-ray crystallographic analysis (see the Supporting Information).

Since the obtained 4-quinolones possessed multiple operable handles, we attempted to conduct further transformations to other structurally novel molecules. For example, 4-quinolone derivative **3ab** could be applied successfully in the convenient synthesis of 2,3-dihydropyridazino[4,5-*b*]quinoline-1,4,10(5*H*)-trione **5** via a condensation reaction with hydrazine hydrate (Scheme 4a). Product **3aa** would also undergo a

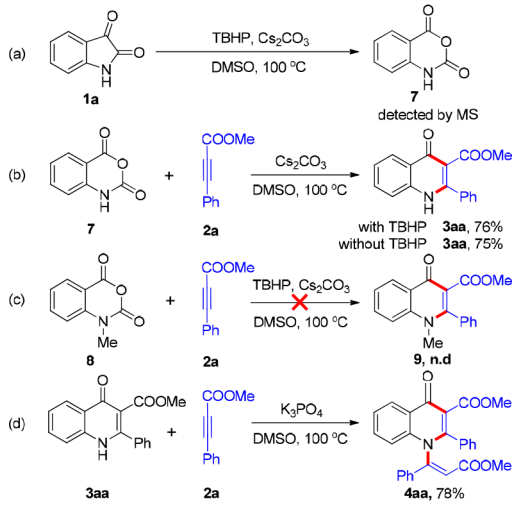
Scheme 4. Follow-up Transformations and Gram-Scale Experiments



decarboxylation process to afford 2-phenylquinolin-4(1*H*)-one **6** in the presence of polyphosphoric acid (Scheme 4b). The gram-scale synthesis of methyl 4-oxo-2-phenyl-1,4-dihydroquinoline-3-carboxylate **3aa** and (*Z*)-methyl 1-(3-methoxy-3-oxo-1-phenylprop-1-en-1-yl)-4-oxo-2-phenyl-1,4-dihydroquinoline-3-carboxylate **4aa** were carried out to further make this reaction more attractive in terms of synthetic practicality. The reactions proceeded well and the desired products were isolated in 63% and 66% yields, respectively.

To shed light on the mechanism of this oxidative cyclization reaction, a series of control experiments were performed (Scheme 5). Only a trace of the oxidative product isatoic

Scheme 5. Control Experiments



anhydride **7** was detected by mass spectroscopy when isatin **1a** was conducted under the optimized conditions (Scheme 5a). Next, reaction of isatoic anhydride **7** with methyl 3-phenylpropiolate **2a** under the standard conditions delivered the desired product **3aa** in 76% yield, which indicated that the isatoic anhydride might act as the key intermediate involved in this domino process. In the absence of TBHP, the reaction still reacted smoothly to give the target product, indicating that TBHP is mainly responsible for the transformation of isatin to isatoic anhydride (Scheme 5b). Moreover, we attempted to react *N*-methyl isatoic anhydride **8** with **2a** for this annulation reaction. Unfortunately, **8** was not suitable for this process, probably because the nucleophilicity of the nitrogen atom is indispensable for the subsequent reaction (Scheme 5c). Further treatment of **3aa** in the presence of K_3PO_4 in DMSO at 100 °C gave the desired product **4aa** in 78% yield, and this result indicated that **3aa** was the possible intermediate to achieve final N-alkenylation (Scheme 5d).

On the basis of the above results and the literature precedents,[13] a possible mechanism is proposed using isatin **1a** and methyl 3-phenylpropiolate **2a** as an example (Scheme 6). Initially, intermolecular nucleophilic attack of TBHP to isatin **1a** affords intermediate **B**, and intramolecular cyclization followed by rearrangement leads to the formation of the intermediate isatoic anhydride **7**, the product of a Baeyer−Villiger-type oxidation.[14] Subsequently, the nucleophilic addition of isatoic anhydride **7** with methyl 3-phenylpropiolate **2a** provides the intermediate **C**, which undergoes a decarboxylative cyclization to yield intermediate **D**. Isomerization of **D** occurs to deliver methyl 4-oxo-2-phenyl-1,4-dihydroquinoline-3-carboxylate **3aa** as desired. In the presence of K_3PO_4, intermediate **3aa** would further undergo nucleophilic addition with another equivalent of methyl 3-phenylpropiolate **2a** to afford product **4aa**.

In summary, we have developed an efficient transition-metal-free oxidative cyclization for the facile synthesis of 4-quinolone derivatives from commercially available isatins and alkynes. This approach enabled switchable construction of 3-carboxylate-4-

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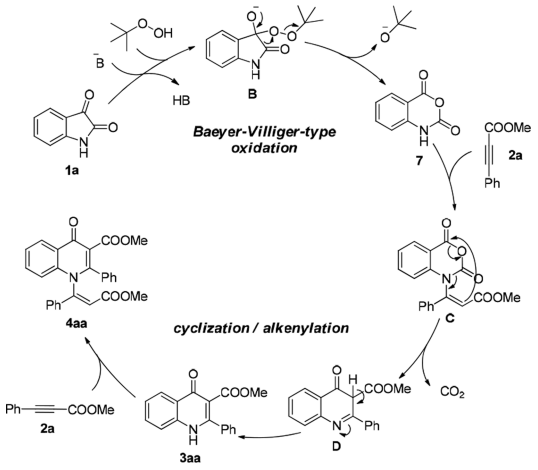
Scheme 6. Possible Mechanism for the Formation of 3 and 4



quinolones and 1-vinyl-3-carboxylate-4-quinolones by changing the base in the reaction. The easily accessible starting materials, mild reaction conditions, and simple manipulation render this an attractive methodology. Further applications of this isatin-based oxidative cyclization strategy for the synthesis of other interesting heterocycles are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01645.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)

Accession Codes

CCDC 1831362 and 1831365−1831366 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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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Mugnaini, C.; Pasquini, S.; Corelli, F. *Curr. Med. Chem.* **2009**, *16*, 1746. (b) Huse, H.; Whiteley, M. *Chem. Rev.* **2011**, *111*, 152. (c) Manfroni, G.; Cannalire, R.; Barreca, M. L.; Kaushik-Basu, N.; Leyssen, P.; Winquist, J.; Iraci, N.; Manvar, D.; Paeshuyse, J.; Guhamazumder, R.; Basu, A.; Sabatini, S.; Tabarrini, O.; Danielson, U. H.; Neyts, J.; Cecchetti, V. *J. Med. Chem.* **2014**, *57*, 1952. (d) Chang, Y. H.; Hsu, M. H.; Wang, S. H.; Huang, L. J.; Qian, K.; Morris-Natschke, S. L.; Hamel, E.; Kuo, S. C.; Lee, K. H. *J. Med. Chem.* **2009**, *52*, 4883. (e) Chou, L. C.; Tsai, M. T.; Hsu, M. H.; Wang, S. H.; Way, T. D.; Huang, C. H.; Lin, H. Y.; Qian, K.; Dong, Y.; Lee, K. H.; Huang, L. J.; Kuo, S. C. *J. Med. Chem.* **2010**, *53*, 8047. (f) Chen, C. T.; Hsu, M. H.; Cheng, Y. Y.; Liu, C. Y.; Chou, L. C.; Huang, L. J.; Wu, T. S.; Yang, X.; Lee, K. H.; Kuo, S. C. *Eur. J. Med. Chem.* **2011**, *46*, 6046.

(2) (a) Wiles, J. A.; Bradbury, B. J.; Pucci, M. *Expert Opin. Ther. Pat.* **2010**, *20*, 1295. (b) Overington, J. P.; Al-Lazikani, B.; Hopkins, A. L. *Nat. Rev. Drug Discovery* **2006**, *5*, 993. (c) Pommier, Y.; Johnson, A. A.; Marchand, C. *Nat. Rev. Drug Discovery* **2005**, *4*, 236.

(3) Accurso, F. J.; et al. *N. Engl. J. Med.* **2010**, *363*, 1991.

(4) (a) Hazuda, D. J.; Hazuda, D. J.; Felock, P.; Witmer, M.; Wolfe, A.; Stillmock, K.; Grobler, J. A.; Espeseth, A.; Gabryelski, L.; Schleif, W.; Blau, C.; Miller, M. D. *Science* **2000**, *287*, 646. (b) Smith, R. A.; Raugi, D. N.; Pan, C.; Coyne, M.; Hernandez, A.; Church, B.; arker, K.; MPullins, J. I.; Sow, P. S. *PLoS One* **2012**, *7*, e45372.

(5) Cairns, H.; Cox, D.; Gould, K. J.; Ingall, A. H.; Suschitzky, J. L. *J. Med. Chem.* **1985**, *28*, 1832.

(6) Manfroni, G.; Cannalire, R.; Barreca, M. L.; Kaushik-Basu, N.; Leyssen, P.; Winquist, J.; Iraci, N.; Manvar, D.; Paeshuyse, J.; Guhamazumder, R.; Basu, A.; Sabatini, S.; Tabarrini, O.; Danielson, U. H.; Neyts, J.; Cecchetti, V. *J. Med. Chem.* **2014**, *57*, 1952.

(7) Alexandre, F. R.; Berecibar, A.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 3911.

(8) (a) Reitsema, R. H. *Chem. Rev.* **1948**, *43*, 43. (b) Brouet, J. C.; Gu, S.; Peet, N. P.; Williams, J. D. *Synth. Commun.* **2009**, *39*, 1563. (c) Romek, A.; Opatz, T. *Eur. J. Org. Chem.* **2010**, *2010*, 5841.

(9) (a) Jones, C. P.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 7968. (b) Huang, J.; Chen, Y.; King, A. O.; Dilmeghani, M.; Larsen, R. D.; Faul, M. M. *Org. Lett.* **2008**, *10*, 2609.

(10) (a) Seppänen, O.; Muuronen, M.; Helaja, J. *Eur. J. Org. Chem.* **2014**, *2014*, 4044. (b) Zhou, N.; Yan, Z.; Zhang, H.; Wu, Z.; Zhu, C. *J. Org. Chem.* **2016**, *81*, 12181. (c) Zhao, T.; Xu, B. *Org. Lett.* **2010**, *12*, 212. (d) Xu, B.; Shao, J.; Huang, X.; Hong, X.; Liu, B. *Synthesis* **2012**, *44*, 1798.

(11) (a) Åkerbladh, L.; Nordeman, P.; Wejdemar, M.; Odell, L. R.; Larhed, M. *J. Org. Chem.* **2015**, *80*, 1464. (b) Xu, X.; Zhang, X. *Org. Lett.* **2017**, *19*, 4984. (c) Kang, S.; Park, S.; Kim, K. S.; Song, C.; Lee, Y. *J. Org. Chem.* **2018**, *83*, 2694. (d) Xu, X.; Sun, R.; Zhang, S.; Zhang, X.; Yi, W. *Org. Lett.* **2018**, *20*, 1893.

(12) (a) Liu, Y. L.; Wang, X.; Zhao, Y. L.; Zhu, F.; Zeng, X. P.; Chen, L.; Wang, C. H.; Zhao, X. L.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13735. (b) Zeng, R.; Dong, G. *J. Am. Chem. Soc.* **2015**, *137*, 1408. (c) Liu, M.; Shu, M.; Yao, C.; Yin, G.; Wang, D.; Huang, J. *Org. Lett.* **2016**, *18*, 824. (d) Kaishap, P. P.; Sarma, B.; Gogoi, S. *Chem. Commun.* **2016**, *52*, 9809. (e) Wang, C.; Zhang, L.; Ren, A.; Lu, P.; Wang, Y. *Org. Lett.* **2013**, *15*, 2982. (f) Wang, L.; Huang, J.; Peng, S.; Liu, H.; Jiang, X.; Wang, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 1768. (g) Liu, Y. L.; Wang, B. L.; Cao, J. J.; Chen, L.; Zhang, Y. X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176. (h) Jia, F. C.; Xu, C.; Wang, Y. W.; Chen, Z. P.; Chen, Y. F.; Wu, A. X. *Org. Biomol. Chem.* **2018**, *16*, 4223. (i) Sabbaghan, M.; Yavari, I.; Hossaini, Z.; Souri, S. *Helv. Chim. Acta* **2010**, *93*, 946.

(13) (a) Jia, F. C.; Zhou, Z. W.; Xu, C.; Wu, Y. D.; Wu, A. X. *Org. Lett.* **2016**, *18*, 2942. (b) Zhou, Z. W.; Jia, F. C.; Xu, C.; Jiang, S. F.; Wu, Y. D.; Wu, A. X. *Chem. Commun.* **2017**, *53*, 1056.

(14) (a) Reissenweber, G.; Mangold, D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 222. (b) Reissenweber, G.; Mangold, D. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 882.

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Org. Lett. XXXX, XXX, XXX−XXX