OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

Diphenyl-Diselenide-Mediated Domino Claisen-Type Rearrangement/Cyclization of Propargylic Aryl Ethers: Synthesis of Naphthofuran-2-carboxaldehyde Derivatives

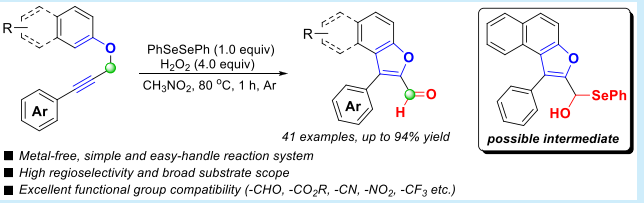
Jun-Dan Fang,[†,§] Xiao-Biao Yan,[‡,§] Wu-Jie Lin,[†] Yi-Chuan Zhao,[†] and Xue-Yuan Liu*[,†]

[†]State Key Laboratory of Applied Organic Chemistry (SKLAOC), College of Chemistry and Chemical Engineering, Lanzhou University, 222 South Tianshui Road, Lanzhou 730000, China

[‡]School of Pharmacy, Anhui Medical University, 81 Meishan Road, Hefei 230032, China

Supporting Information

ABSTRACT: A diphenyl-diselenide-mediated Claisen-type rearrangement/cyclization of propargylic aryl ethers under metal-free conditions is developed, affording various naphthofuran-2-carboxaldehydes in moderate to excellent yield. The broad substrate scope and excellent functional group compatibility suggest that it can be a straightforward and powerful method to access naphthofuran-2-carboxaldehydes in a highly regioselective manner. Moreover, this reaction can be scaled up to the gram scale.



Benzofuran scaffolds are a basic and valuable structural skeleton in natural products.[1] Among them, naphthofuran and its derivatives, such as (±)-laevigatin, (+)-heritol, and furomollugin, represent an important class of biological active compounds due to their significant pharmacological properties (Figure 1).[2] Accordingly, it is of urgent desire to develop a new

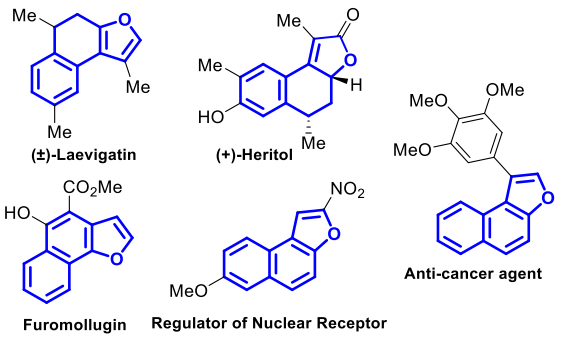
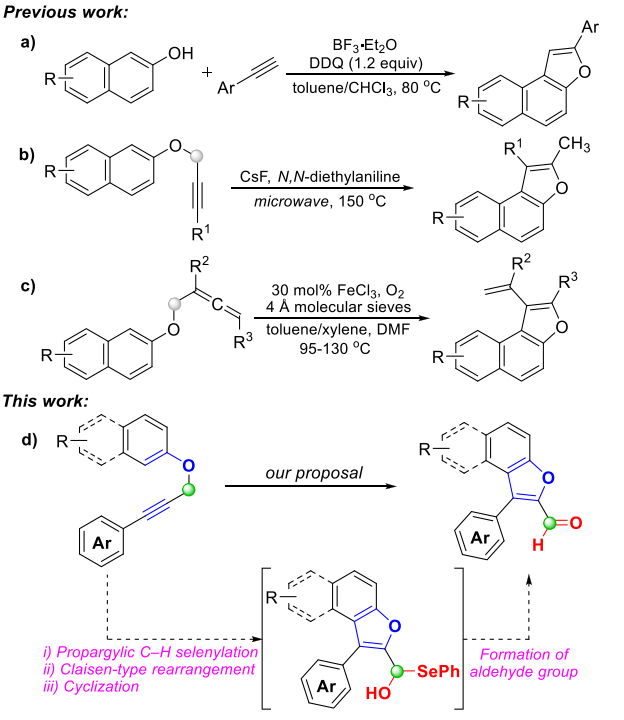


Figure 1. Naphthofuran-containing biologically active compounds.

strategy to synthesize naphthofurans. In general, the intramolecular cyclization of 2-alkenylphenols catalyzed by transition metals (e.g., Pd, Cu, Co)[3a−d] or promoted by stoichiometric amounts of I_2,[3e] $PhI(OAc)_2$,[3f] and Ag_2O[3g] is a commonly used method to construct the benzo(naphtho)furan cores. In 2016, an elegant work was developed through an intermolecular reaction of naphthols with terminal alkynes in the presence of a catalytic amount of $BF_3{\cdot}Et_2O$ (Scheme 1a).[4] Additionally, the Claisen-type rearrangement of naphthyl-substituted propargylic ethers has been a straightforward method to build naphthofurans, but it usually requires a high temperature or the assistance of microwave irradiation

Scheme 1. Strategies for the Construction of Naphthofuran Skeleton



(Scheme 1b).[5] Very recently, a $FeCl_3$-catalyzed Claisen rearrangement/aerobic dehydrogenative cyclization of allenyl-

Received: August 19, 2019

DOI: 10.1021/acs.orglett.9b02942
Org. Lett. XXXX, XXX, XXX−XXX

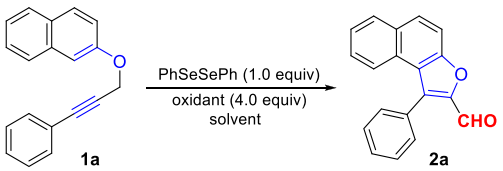
methyl ether has been reported by Jiang and coworkers (Scheme 1c).[6] Despite these formidable advances, the development of an efficient method to access functionalized benzo(naphtho)furans under mild conditions is still in highly demand but remains a challenge.

Over the past decade, the domino or cascade reaction has become a powerful and ingenious strategy for the synthesis of natural products or complex compounds.[7] It has shown undeniable advantages, including extensive functional group compatibility and the economies of labor and cost. As part of our ongoing interest in the transformation of propargylic aryl ethers,[8] we anticipated that the construction of naphthofuran-2-carboxaldehydes would be realized by the following domino process: propargylic C−H selenylation, Claisen-type rearrangement, cyclization reaction, and the formation of aldehyde. Although the organic diselenide has been extensively used in the synthesis of organoselenium compounds,[9] it has rarely been reported as a reaction promoter for the construction of an aldehyde or other functional groups. Herein we report a diphenyl-diselenide-mediated Claisen-type rearrangement/cyclization cascade strategy for the synthesis of naphthofuran-2-carboxaldehyde derivatives (Scheme 1d). To the best of our knowledge, this reaction represents the first highly regioselective domino procedure to construct naphthofuran-2-carboxaldehydes.

We started our investigation by using 2-((3-phenylprop-2-yn-1-yl)oxy)naphthalene (**1a**) as the model substrate and performing the reactions in CH_3CN at 80 °C under an argon atmosphere. To our delight, the desired product (**2a**) was obtained in 83% yield when diphenyl diselenide and TBHP (*tert*-butyl hydroperoxide, 5.0 to 6.0 M in decane) were used (Table 1, entry 1). No desired product was observed in the absence of diphenyl diselenide or TBHP. These results indicated that diphenyl diselenide and oxidant were crucial for this reaction. Screening of the solvents revealed that CH_3NO_2 was the optimal solvent (Table 1, entries 2−8). The effects of different oxidants were also tested (Table 1, entries 9−14). A slightly better yield (92%) was achieved when H_2O_2 (30% in water, w/w) was used (Table 1, entry 14). Further optimization of reaction temperature has shown that the reaction at 80 or 100 °C gave the best results (Table 1, entries 15−17). Changing the loading of H_2O_2 or diphenyl diselenide has failed to increase the yield efficiently (Table 1, entries 18−21). Therefore, the reaction conditions of entry 14 in Table 1 were used as the standard conditions of this transformation.

With the optimized reaction conditions in hand, we then studied the reactions with respect to the scope of propargylic aryl ethers derived from *β*-naphthol (Scheme 2). The steric hindrance and electronic effect did not affect the efficiency of this transformation, and a variety of naphthofuran-2-carboxaldehyde derivatives were obtained in good to excellent yield (**2a**−**v**).[10] Notably, a gamut of functionalities such as halogen (−F, Cl, Br), methoxyl, aldehyde, ester (−CO_2Me, CO_2Et), and strong electron-withdrawing groups (−CF_3, CN, NO_2) were well-tolerated. For disubstituted aryl groups attached to the triple bond, the diphenyl-diselenide-promoted reaction system was also efficient, affording the desired products with good yields (**2w**−**ab**). In addition, substrates containing the naphthalene, thiophene, and pyridine groups (**1ac**−**ae**) could also smoothly transform into the naphthofuran-2-carboxaldehydes (**2ac**−**ae**) in moderate to excellent yield. The reaction could be scaled up to the gram scale and produced **2a** in 87% yield under the optimal conditions.

Table 1. Optimization of Reaction Conditions[a]



entry	oxidant	solvent	*T* (°C)	yield (%)[b]
1	TBHP	CH_3CN	80	83, 0,[c] 0[d]
2	TBHP	DCE	80	9
3	TBHP	toluene	80	23
4	TBHP	THF	80	11
5	TBHP	CH_3OH	80	0
6	TBHP	DMF	80	0
7	TBHP	DMSO	80	trace
8	TBHP	CH_3NO_2	80	87
9	DTBP	CH_3NO_2	80	0
10	$K_2S_2O_8$	CH_3NO_2	80	0
11	DCP	CH_3NO_2	80	0
12	BPO	CH_3NO_2	80	72
13	$PhI(OAc)_2$	CH_3NO_2	80	48
14	**H_2O_2**	**CH_3NO_2**	**80**	**92**
15	H_2O_2	CH_3NO_2	40	74[e]
16	H_2O_2	CH_3NO_2	60	81[e]
17	H_2O_2	CH_3NO_2	100	92
18	H_2O_2	CH_3NO_2	80	85[f]
19	H_2O_2	CH_3NO_2	80	89[g]
20	H_2O_2	CH_3NO_2	80	68[h]
21	H_2O_2	CH_3NO_2	80	93[i]

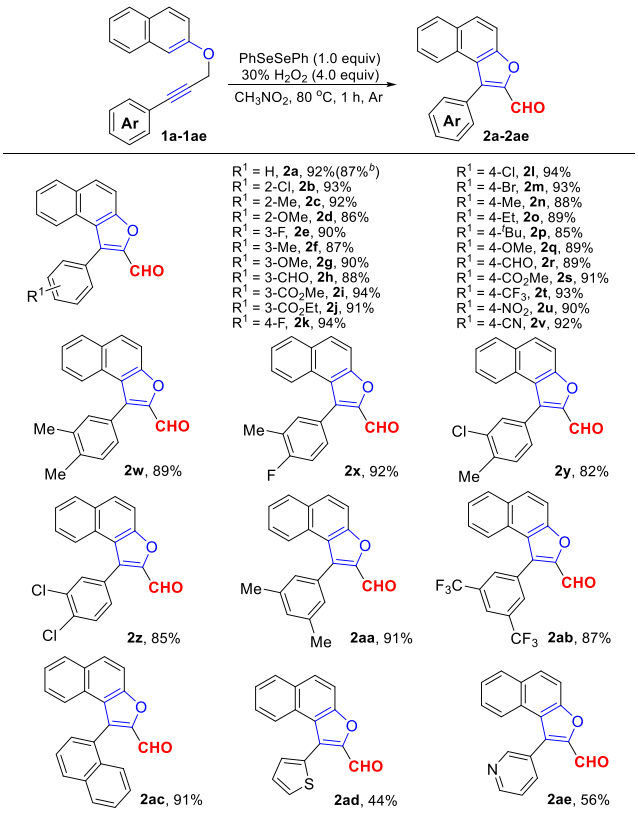
[a]Reaction conditions: **1a** (0.2 mmol scale), diphenyl diselenide, and oxidant (4.0 equiv) in solvent (2.0 mL) were stirred at 80 °C for 1 h under an argon atmosphere. [b]Isolated yields. [c]In the absence of diphenyl diselenide. [d]In the absence of TBHP. [e]Reaction time: 8 h. [f]H_2O_2 (2.0 equiv) was used. [g]H_2O_2 (3.0 equiv) was used. [h]Diphenyl diselenide (0.6 equiv) was used. [i]Diphenyl diselenide (1.2 equiv) was used.

Next, we explored the compatibility of propargylic aryl ethers derived from various naphthols (Scheme 3). Propargylic ethers derived from *β*-naphthols tethered with functional groups, including bromide (**2af**, **2ak**), alkoxyl (**2ai**, **2aj**), aldehyde (**2ag**), and ester (**2ah**), furnished the corresponding products in good yield. *α*-Naphthyl-substituted propargylic ethers were also the efficient substrates whereby the corresponding naphthofuran-2-carboxaldehydes could be isolated in good yield (**2al**−**an**).[10] The propargylic phenyl ether (**1ao**) was less effective than naphthyl ones, and benzofuran-2-carboxaldehyde (**2ao**) was obtained in 32% yield.[11] One possible reason is that unlike the naphthyl-based substrates with the *π*-extended system, the intermediate from the phenyl substrate might be unstable because the dearomatization of phenyl might have occurred in the process of the Claisen-type rearrangement.[5,6]

To illuminate the reaction mechanism of this transformation, several control experiments were carried out (Scheme 4). The reaction was inhibited in the presence of a radical inhibitor such as TEMPO, BHT, or 1,1-diphenylethylene (Scheme 4a). The radical trapping product **3** was obtained in 47% isolated yield. These results indicated that a radical process might be involved in this transformation. Furthermore, we tried to track the reaction process. It is worth pointing out that compound **4** was isolated when the reaction was stirred for 6 min under standard conditions (Scheme 4b).

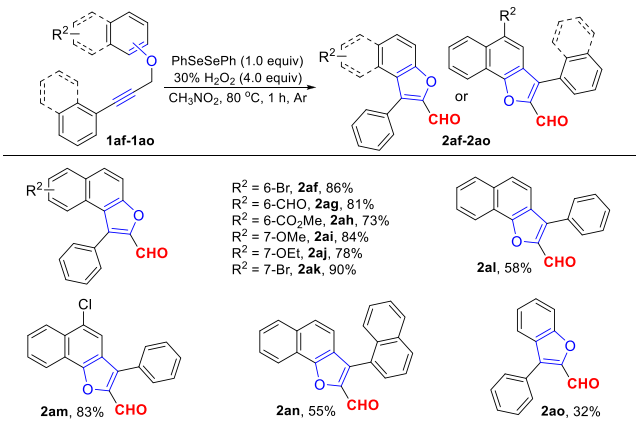
DOI: 10.1021/acs.orglett.9b02942
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 2. Scope of β-Naphthyl-Substituted Propargylic Ethers[a]



[a]Reaction conditions: See Table 1, entry 14. Isolated yields. [b]4.0 mmol scale.

Scheme 3. Scope of Propargylic Aryl Ethers Derived from Various Naphthols[a]

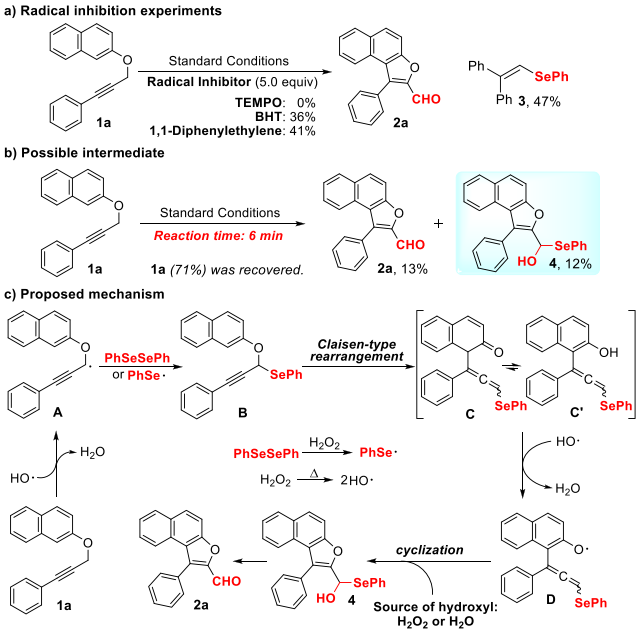


[a]Reaction conditions: See Table 1, entry 14. Isolated yields.

Additionally, when the reaction finished, compound **4** had disappeared and **2a** was obtained in excellent yield. According to this result, we suggest that compound **4** might be the possible intermediate of this reaction.

On the basis of the above control experiments and previous reports,[5,9f,l,n−q] a plausible mechanism was proposed (Scheme 4c). Initially, intermediate **B** might be formed through propargylic C−H selenylation.[8b] Subsequently, intermediate **B** undergoes the Claisen-type rearrangement to give **C**, which can be isomerized to naphthol derivatives **C′**. Then,

Scheme 4. Mechanism Studies



intermediate **4** is formed from **C** or **C′** through hydrogen abstraction and intramolecular cyclization. Finally, the desired product is obtained under oxidative conditions.

In conclusion, we have developed a diphenyl-diselenide-promoted Claisen-type rearrangement/cyclization domino reaction, which affords various naphthofuran-2-carboxaldehyde derivatives in moderate to excellent yield from propargylic aryl ethers under metal-free conditions. The broad substrate scope and excellent functional group compatibility of this method suggest that it can be a straightforward and powerful alternative to the established methodologies for the synthesis of benzo(naphtho)furan-2-carboxaldehydes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02942.

Experimental procedures, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1943585 and 1943766 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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: liuxuey@lzu.edu.cn

ORCID

Xue-Yuan Liu: 0000-0002-8862-9924

Author Contributions

§J.-D.F. and X.-B.Y. contributed equally.

DOI: 10.1021/acs.orglett.9b02942
Org. Lett. XXXX, XXX, XXX−XXX

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from the Natural Science Foundation of China (21871115) is gratefully acknowledged.

■ REFERENCES

(1) Selected references: (a) Stark, J. B.; Walter, E. D.; Owens, H. S. *J. Am. Chem. Soc.* **1950**, *72*, 1819. (b) Wallez, V.; Durieux-Poissonnier, S.; Chavatte, P.; Boutin, J. A.; Audinot, V.; Nicolas, J.-P.; Bennejean, C.; Delagrange, P.; Renard, P.; Lesieur, D. *J. Med. Chem.* **2002**, *45*, 2788. (c) Lin, S.-Y.; Chen, C.-L.; Lee, Y.-J. *J. Org. Chem.* **2003**, *68*, 2968. (d) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett.* **2004**, *6*, 4755. (e) Mori-Hongo, M.; Takimoto, H.; Katagiri, T.; Kimura, M.; Ikeda, Y.; Miyase, T. *J. Nat. Prod.* **2009**, *72*, 194. (f) La Clair, J. J.; Rheingold, A. L.; Burkart, M. D. *J. Nat. Prod.* **2011**, *74*, 2045. (g) Chiummiento, L.; Funicello, M.; Lopardo, M. T.; Lupattelli, P.; Choppin, S.; Colobert, F. *Eur. J. Org. Chem.* **2012**, *2012*, 188. (h) Roumeliotis, T. I.; Halabalaki, M.; Alexi, X.; Ankrett, D.; Giannopoulou, E. G.; Skaltsounis, A. L.; Sayan, B. S.; Alexis, M. N.; Townsend, P. A.; Garbis, S. D. *J. Proteome Res.* **2013**, *12*, 1591.

(2) Selected references: (a) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1977**, *110*, 487. (b) Salmon, R. J.; Buisson, J. P.; Zafrani, B.; Aussepe, L.; Royer, R. *Carcinogenesis* **1986**, *7*, 1447. (c) Miles, D. H.; Lho, D. S.; De la Cruz, A. A.; Gomez, E. D.; Weeks, J. A.; Atwood, J. L. *J. Org. Chem.* **1987**, *52*, 2930. (d) Irie, H.; Matsumoto, R.; Nishimura, M.; Zhang, Y. *Chem. Pharm. Bull.* **1990**, *38*, 1852. (e) Lumb, J.-P.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 2870. (f) Lardic, M.; Patry, C.; Duflos, M.; Guillon, J.; Massip, S.; Cruzalegui, F.; Edmonds, T.; Giraudet, S.; Marini, L.; Leonce, S. J. *J. Enzyme Inhib. Med. Chem.* **2006**, *21*, 313. (g) Srivastava, V.; Negi, A. S.; Kumar, J. K.; Faridi, U.; Sisodia, B. S.; Darokar, M. P.; Luqman, S.; Khanuja, S. P. S. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 911. (h) Son, J. K.; Jung, S. J.; Jung, J. H.; Fang, Z.; Lee, C. S.; Seo, C. S.; Moon, D. C.; Min, B. S.; Kim, M. R.; Woo, M. H. *Chem. Pharm. Bull.* **2008**, *56*, 213. (i) Lumb, J.-P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230. (j) Le Guével, R.; Oger, F.; Lecorgne, A.; Dudasova, Z.; Chevance, S.; Bondon, A.; Barath, P.; Simonneaux, G.; Salbert, G. *Bioorg. Med. Chem.* **2009**, *17*, 7021. (k) Sastry, M. N. V.; Claessens, S.; Habonimana, P.; De Kimpe, N. *J. Org. Chem.* **2010**, *75*, 2274. (l) Shashikala Devi, K.; Ramaiah, M.; Vanita, G. K.; Veena, K.; Vaidya, V. P. *J. Chem. Pharm. Res.* **2011**, *3* (4), 445−451.

(3) (a) Guo, L.; Zhang, F.; Hu, W.; Li, L.; Jia, Y. *Chem. Commun.* **2014**, *50*, 3299. (b) Yang, D.; Zhu, Y.; Yang, N.; Jiang, Q.; Liu, R. *Adv. Synth. Catal.* **2016**, *358*, 1731. (c) Xu, T.; Zhang, E.; Wang, D.; Wang, Y.; Zou, Y. *J. Org. Chem.* **2015**, *80*, 4313. (d) Ghorai, J.; Reddy, A. C. S.; Anbarasan, P. *Chem. - Eur. J.* **2016**, *22*, 16042. (e) Pan, C.; Yu, J.; Zhou, Y.; Wang, Z.; Zhou, M. *Synlett* **2006**, *2006*, 1657. (f) Singh, F. V.; Wirth, T. *Synthesis* **2012**, *44*, 1171. (g) Huang, J.; Wang, W.; He, H.-Y.; Jian, L.; Fu, H.-Y.; Zheng, X.-L.; Chen, H.; Li, R.-X. *J. Org. Chem.* **2017**, *82*, 2523.

(4) Liu, L.; Ji, X.; Dong, J.; Zhou, Y.; Yin, S.-F. *Org. Lett.* **2016**, *18*, 3138.

(5) (a) Prasada Rao Lingam, V. S.; Dahale, D. H.; Mukkanti, K.; Gopalan, B.; Thomas, A. *Tetrahedron Lett.* **2012**, *53*, 5695. (b) Mishra, A. K.; Biswas, S. *J. Org. Chem.* **2016**, *81*, 2355.

(6) Zhang, C.; Zhen, L.; Yao, Z.; Jiang, L. *Org. Lett.* **2019**, *21*, 955.

(7) Selected reviews: (a) Patil, N. T.; Yamamoto, Y. *Metal Catalyzed Cascade Reactions*; Müller, T. J. J., Ed.; Springer: Berlin, Heidelberg, 2006. (b) Xu, P.-F.; Wei, H. *Catalytic Cascade Reactions*; Wiley: Hoboken, NJ, 2013. (c) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (d) Moyano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. (e) Grossmann, A.; Enders, D. *Angew. Chem., Int. Ed.* **2012**, *51*, 314. (f) Wille, U. *Chem. Rev.* **2013**, *113*, 813.

(8) (a) Guo, C.-H.; Chen, D.-Q.; Chen, S.; Liu, X.-Y. *Adv. Synth. Catal.* **2017**, *359*, 2901. (b) Fang, J.-D.; Yan, X.-B.; Zhou, L.; Wang, Y.-Z.; Liu, X.-Y. *Adv. Synth. Catal.* **2019**, *361*, 1985.

(9) Selected references: (a) Beletskaya, I. P.; Ananikov, V. P. *Chem. Rev.* **2011**, *111*, 1596. (b) Stein, A. L.; Bilheri, F. N.; da Rocha, J. T.; Back, D. F.; Zeni, G. *Chem. - Eur. J.* **2012**, *18*, 10602. (c) Sperança, A.; Godoi, B.; Zeni, G. *J. Org. Chem.* **2013**, *78*, 1630. (d) Chatterjee, T.; Ranu, B. C. *J. Org. Chem.* **2013**, *78*, 7145. (e) Mantovani, A. C.; Goulart, T. A. C.; Back, D. F.; Menezes, P. H.; Zeni, G. *J. Org. Chem.* **2014**, *79*, 10526. (f) Sun, K.; Wang, X.; Lv, Y.; Li, G.; Jiao, H.; Dai, C.; Li, Y.; Zhang, C.; Liu, L. *Chem. Commun.* **2016**, *52*, 8471. (g) Prasad, C. D.; Sattar, M.; Kumar, S. *Org. Lett.* **2017**, *19*, 774. (h) Gandeepan, P.; Koeller, J.; Ackermann, L. *ACS Catal.* **2017**, *7*, 1030. (i) Shi, Q.; Li, P.; Zhang, Y.; Wang, L. *Org. Chem. Front.* **2017**, *4*, 1322. (j) Hu, Y.; Ma, J.; Li, L.; Hu, Q.; Lv, S.; Liu, B.; Wang, S. *Chem. Commun.* **2017**, *53*, 1542. (k) Goulart, T. A. C.; Back, D. F.; Zeni, G. *Adv. Synth. Catal.* **2017**, *359*, 1901. (l) Liu, Y.; Zheng, G.; Zhang, Q.; Li, Y.; Zhang, Q. *J. Org. Chem.* **2017**, *82*, 2269. (m) Shen, Z.-J.; Wu, Y.-N.; He, C.-L.; He, L.; Hao, W.-J.; Wang, A.-F.; Tu, S.-J.; Jiang, B. *Chem. Commun.* **2018**, *54*, 445. (n) Sahoo, H.; Mandal, A.; Dana, S.; Baidya, M. *Adv. Synth. Catal.* **2018**, *360*, 1099. (o) Sahoo, H.; Singh, S.; Baidya, M. *Org. Lett.* **2018**, *20*, 3678. (p) Yang, D.; Li, G.; Xing, C.; Cui, W.; Li, K.; Wei, W. *Org. Chem. Front.* **2018**, *5*, 2974. (q) Sun, L.; Yuan, Y.; Yao, M.; Wang, H.; Wang, D.; Gao, M.; Chen, Y.-H.; Lei, A. *Org. Lett.* **2019**, *21*, 1297.

(10) The structures of **2a** (CCDC 1943766) and **2al** (CCDC 1943585) were confirmed by X-ray crystallography.

(11) To increase the yield of **2ao**, we carefully optimized the reaction conditions (including oxidants, solvents, temperature, and additives) again. Unfortunately, we failed to obtain a better yield.

DOI: 10.1021/acs.orglett.9b02942
Org. Lett. XXXX, XXX, XXX−XXX