OL Organic Letters

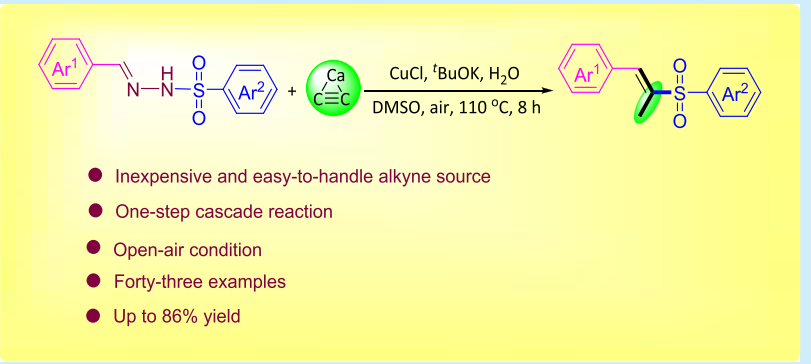
pubs.acs.org/OrgLett Letter

Direct Synthesis of Propen-2-yl Sulfones through Cascade Reactions Using Calcium Carbide as an Alkyne Source

Lei Gao, Zhenrong Liu, Xiaolong Ma, and Zheng Li*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c01915 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

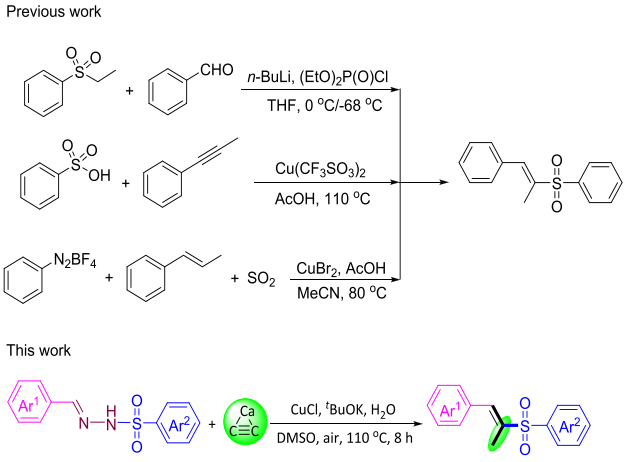


ABSTRACT: A simple method for the construction of propen-2-yl sulfones through cascade reactions of calcium carbide with arylsulfonylhydrazones using copper as a mediator is described. The salient features of this protocol are the use of readily available and easy-to-handle alkyne source, broad substrate scope, open-air condition, and simple operation procedure.

Alkenyl sulfones have long been known for their synthetic utilities in organic chemistry, easily participating in 1,4-addition reactions and cycloaddition reactions. They have also been shown to potently inhibit a variety of enzymic processes providing unique properties for drug design and medicinal chemistry.[1] Various synthetically viable procedures have been used for the construction of alkenyl sulfones in the literature.[2] For example, the recent reported typical methods for the synthesis of propen-2-yl sulfone include (i) the reaction of ethylphenyl sulfone with benzoaldehyde in the presence of *n*-butyllithium and diethyl chlorophosphate,[3] (ii) microwave-assisted copper triflate-catalyzed hydrosulfonylation of alkyne with benzenesulfonic acid,[4] and (iii) the copper(II)-catalyzed three-component reaction of aryldiazonium tetrafluoroborate, sulfur dioxide, and alkene (Scheme 1).[5] However, some drawbacks still exist for the reported methods such as use of unavailable starting materials, rigorous reaction conditions, and complex workup procedures. Therefore, more efficient methods using simple steps and commercially available materials are still necessary.

Calcium carbide is a widely utilized inexpensive industrial material to synthesize acetylene gas. However, research in recent years has found that the direct use of calcium carbide as an alkyne source has a deeper and wider application value in organic synthesis than acetylene gas.[6] Our research group has devoted great efforts to the research on organic synthesis direct using calcium carbide as an alkyne source.[7] Although calcium carbide is safer, easier to operate, more environmentally friendly, and more economical than acetylene gas in the field of organic synthesis, calcium carbide itself is stable and difficult to

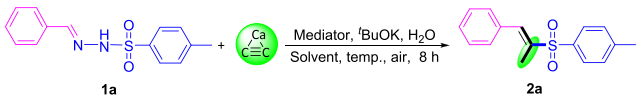
Scheme 1. Synthesis of Propen-2-yl Sulfones



Received: June 7, 2020

https://dx.doi.org/10.1021/acs.orglett.0c01915
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Reaction Conditions[a]



1a 2a

entry	mediator (eq)	solvent	temp. (°C)	yield[b] (%)
1	none	DMF	120	0
2	$CuCl_2$ (1)	DMF	120	0
3	$Cu(NO_3)_2$ (1)	DMF	120	trace
4	$Cu(OAc)_2$ (1)	DMF	120	trace
5	CuCl (1)	DMF	120	trace
6	CuCl (1.2)	DMF	120	12
7	CuCl (1.5)	DMF	120	58
8	CuCl (2)	DMF	120	65
9	CuBr (2)	DMF	120	61
10	CuI (2)	DMF	120	55
11	$CuNO_3$ (2)	DMF	120	23
12	CuOAc (2)	DMF	120	36
13	CuCl (2)	xylene	120	trace
14	CuCl (2)	chlorobenzene	120	trace
15	CuCl (2)	DMSO	120	68
16	CuCl (2)	DMSO	100	71
17	CuCl (2)	DMSO	110	82
18	CuCl (2)	DMSO	130	35
19[c]	CuCl (2)	DMSO	110	0

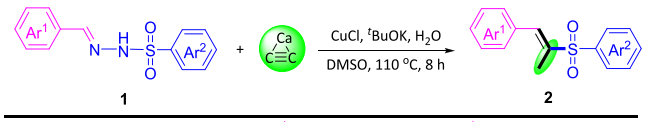
[a]Reaction conditions: **1a** (1 mmol), calcium carbide (3 mmol), water (6 mmol), mediator (appropriate amount), and ^{t}BuOK (2 mmol) in solvent (4 mL) were heated at appropriate temperature for 8 h under open-air condition. [b]Isolated yield. [c]KF was used as an activator.

participate in organic reactions. Therefore, exploring more effective organic reactions involving calcium carbide is still a very challenging subject.

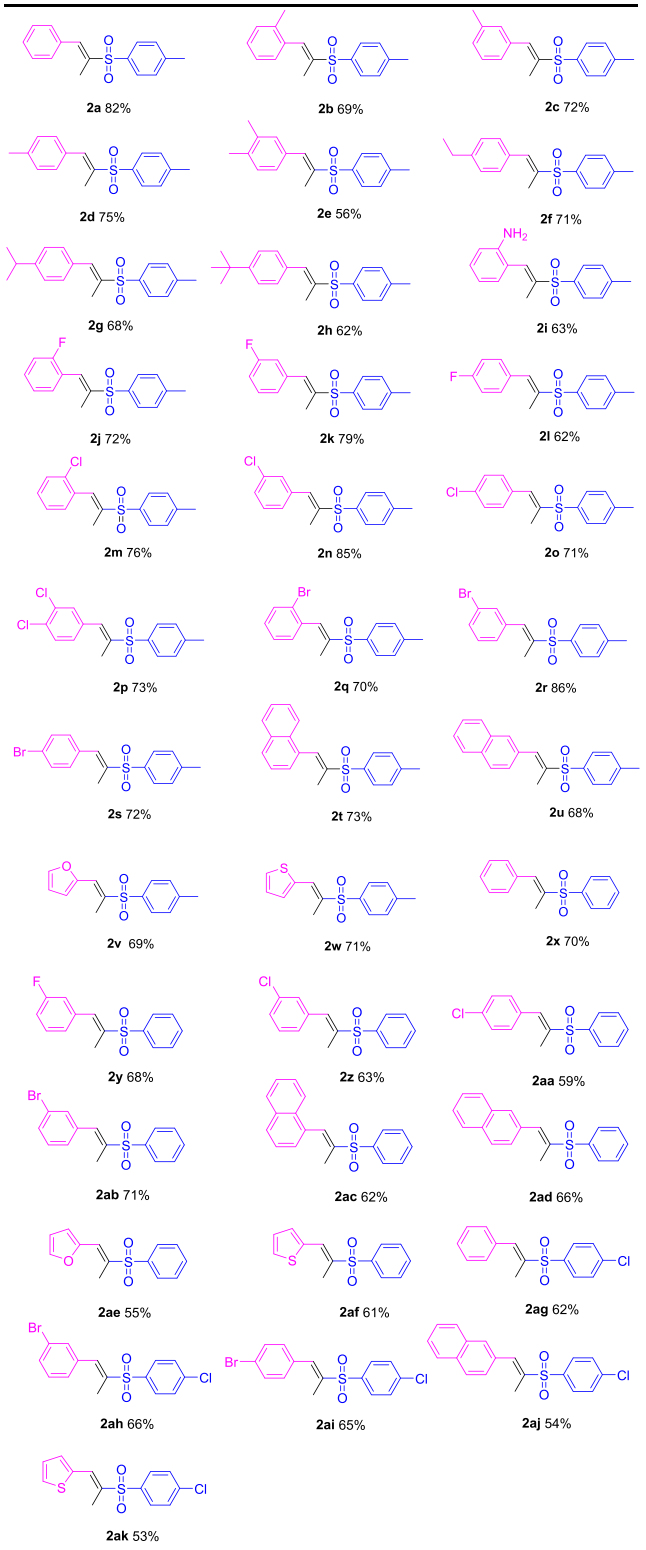
Herein, we report a cascade method for the synthesis of propen-2-yl sulfones using calcium carbide as an alkyne source and sulfonylhydrazones as starting materials.

Initially, the reaction of benzaldehyde *p*-tosylhydrazone (**1a**) with calcium carbide was selected as a model reaction to screen the optimal conditions. The reaction first tested in DMF at 120 °C, and the result showed that no products were observed in the absence of a mediator (Table 1, entry 1). Then various copper salts with different amount as mediators were tested for the reaction. Cu(II) salt, $CuCl_2$, $Cu(NO_3)_2$, and $Cu(OAc)_2$ as mediators could not give a product (entries 2−4). In contrast, Cu(I) salt, CuCl, as a mediator could afford (*E*)-1-phenyl-propen-2-yl *p*-tolyl sulfone (**2a**) as a product in different yields depending on the amount of CuCl (entries 5−8). The *E*-style structure of **2a** was determined by the comparison with literature data.[4a,8] Among them, 2 equiv of CuCl could obtain the best yield (entry 8). The other Cu(I) salts, such as CuBr, CuI, $CuNO_3$ and CuOAc, as mediators were also examined, and no higher yields of **2a** were observed (entries 9−12). The solvents also played important roles in the reaction. It was found that xylene and chlorobenzene as solvents only gave a trace amount of **2a** (entries 13, 14). DMSO was a more efficient solvent than DMF (entry 15). The appropriate reaction temperature was also necessary for the reaction (entries 16−18). It was found that **2a** could be obtained in highest yield (82%) at 110 °C for 8 h (entry 17). In the case of using fluoride, such as KF, as an activator according to literature,[9] the reaction was inversely inhibited for the formation of **2a** (entry 19). In addition, the reaction was also affected by the amount of water. It was observed that 6

Scheme 2. Synthesis of Propen-2-yl Sulfones[a]



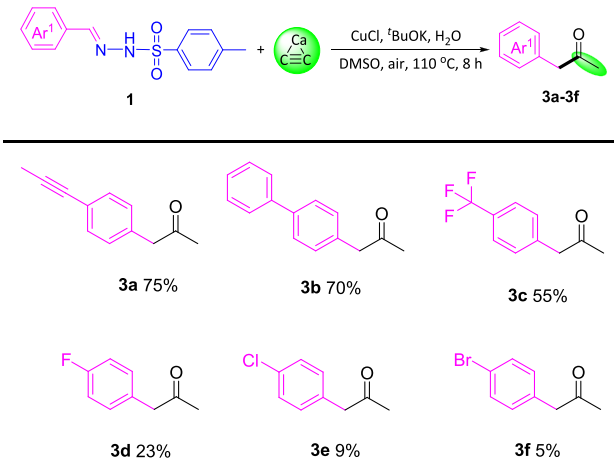
1 2



[a]Reaction conditions: **1** (1 mmol), calcium carbide (3 mmol), water (6 mmol), and ^{t}BuOK (2 mmol) in DMSO (4 mL) were heated at 110 °C for 8 h.

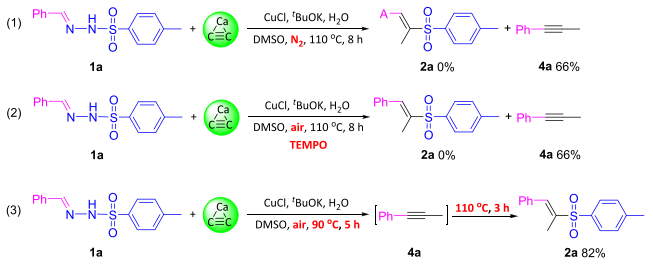
https://dx.doi.org/10.1021/acs.orglett.0c01915
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 3. Synthesis of 1-Arylacetones[a]



[a]Reaction conditions: **1** (1 mmol), calcium carbide (3 mmol), water (6 mmol), and ^{t}BuOK (2 mmol) in DMSO (4 mL) were heated at 110 °C for 8 h.

Scheme 4. Control Experiments

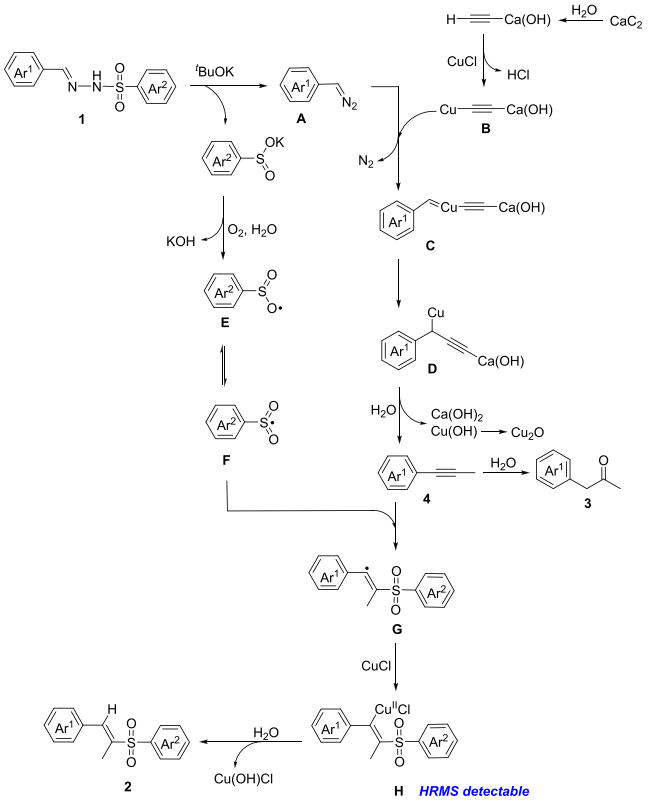


equiv of water based on **1a** was a suitable amount for the formation of **2a** (see Supporting Information, Table S1).

By using the optimized conditions, syntheses of a series of propen-2-yl sulfones were conducted by the reactions of various sulfonylhydrazones with calcium carbide at 110 °C in DMSO using CuCl as a mediator and ^{t}BuOK as a base. The results are summarized in Scheme 2. It was found that the reactions could be suitable to a wide range of substrates including various aromatic rings Ar^1 and Ar^2 to give the corresponding propen-2-yl sulfones in moderate to good yield. For example, Ar^1 not only could be unsubstituted phenyl (**2a**, **2x**, **2ag**) but also could be extended to aromatic rings bearing electron-donating groups such as Me, Et, ^{i}Pr, ^{t}Bu, and NH_2 (**2b**−**2i**), and electron-withdrawing groups such as F, Cl, and Br (**2j**−**2s**, **2y**−**2ab**, **2ah**, **2ai**). Ar^1 could also be extended to fused ring, for example, naphthyl (**2t**, **2u**, **2ac**, **2ad**, **2aj**), and heterocycle, for example, furyl (**2v**, **2ae**) and thienyl (**2w**, **2af**, **2ak**). Ar^2 was suitable to 4-tolyl (**2a**−**2w**), phenyl (**2x**−**2af**), and 4-chlorophenyl (**2ag**−**2ak**) and afforded the expected products in satisfactory yield.

In particular, it was noteworthy to mention that when the substrates including *para*-propyn-1-yl, phenyl, or trifluoromethyl substituted aromatic rings in sulfonylhydrazones, the corresponding propen-2-yl sulfones were not isolated under standard conditions; instead, 1-aryl substituted acetones were obtained in 75%, 70%, and 55% yields (**3a**−**3c**) (Scheme 3). These results were attributed to the strong conjugate effect of corresponding substituents on the aromatic rings, which resulted in the reaction intermediates more readily to be hydrolyzed to produce the substituted acetones. Similar

Scheme 5. Proposed Mechanism for Synthesis of Propen-2-yl Sulfone or 1-Arylacetone



situations were also observed for the substrates including *para*-fluoro-, chloro-, and bromo-substituted aromatic rings, which led to the formation of corresponding *para*-halophenylacetones as byproducts of **2l**, **2o**, or **2s** in low yields (**3d**−**3f**).

To investigate the reaction mechanism, several control experiments were designed and conducted (Scheme 4). If the reaction of **1a** with calcium carbide was conducted under nitrogen atmosphere, the desired product **2a** was not observed, and instead 1-phenylprop-1-yne (**4a**) was formed (Scheme 4, eq 1). This result indicated that oxygen in the air was an indispensable condition for the reaction. If the reaction was conducted under air condition in the presence of TEMPO (2 equiv), the product was also 1-phenylprop-1-yne (**4a**), and **2a** was not observed. This implied that the reaction might proceed through a free-radical process (Scheme 4, eq 2). In addition, if the reaction was first conducted under air condition at 90 °C for 5 h, the formation of 1-phenylprop-1-yne (**4a**) could be detected in the reaction system. Then the system was further stirred at 110 °C for 3 h, and the desired product **2a** could be isolated in good yield. This result meant that 1-phenylprop-1-yne (**4a**) might be the intermediate for the formation of **2a**.

On the basis of these observations, a plausible mechanism for the reaction of sulfonylhydrazones **1** with calcium carbide to afford **2** or **3** is proposed in Scheme 5. Initially, diazomethyl arene (**A**) is formed *in situ* by the reaction of arylhydrazone with ^{t}BuOK through the release of potassium arylsulfinate (Bamford−Stevens reaction).[10] Simultaneously, calcium carbide reacts with water to form calcium acetylide hydroxide first,[6d,e] and then transforms into copper calcium acetylide (**B**) in the presence of cuprous chloride,[11] which further reacts with **A** to form copper carbene species **C**.[12] The α-migration of

https://dx.doi.org/10.1021/acs.orglett.0c01915
Org. Lett. XXXX, XXX, XXX−XXX

acetylide in species **C** forms intermediate **D**.[12] Intermediate **D** obtains hydrogen ion from water in the reaction system to afford 1-arylprop-1-yne (**4**) as an intermediate. Meanwhile, potassium arylsulfinate is transformed into free-radical **E** via single electron transfer in the presence of air.[4,13] **E** can easily tautomerize to free-radical **F**. **F** reacts with 1-arylprop-1-yne (**4**) by free-radical addition to afford radical species **G**. **G** further reacts with Cu(I) to yield propen-2-yl sulfone copper(II) complex **H**, which can be detected by HRMS (see Supporting Information). Finally, the demetalation−protonation of **H** with water results in the formation of propen-2-yl sulfone **2** as the final product. In addition, for special intermediate **4**, the hydrolysis can more readily take place to yield 1-arylacetone **3** as the final product.

In conclusion, an efficient method for the synthesis of propen-2-yl sulfones by cascade reactions of calcium carbide with sulfonylhydrazones has developed. The advantages of this protocol are the easy-to-handle and inexpensive alkyne source, open-air conditions, wide scope of substrates with high functional group tolerance, and simple workup procedures. This method will provide a good alternative to synthesize propen-2-yl sulfones.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01915.

Additional data on general experimental information, synthetic procedure, characterization data and $^{1}H/^{13}C$ NMR spectra of all products (PDF)

■ AUTHOR INFORMATION

Corresponding Author

Zheng Li − *College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P. R. China;* orcid.org/0000-0003-1944-8270; Email: lizheng@nwnu.edu.cn

Authors

Lei Gao − *College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P. R. China*

Zhenrong Liu − *College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P. R. China*

Xiaolong Ma − *College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu 730070, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c01915

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors thank the National Natural Science Foundation of China (21462038) for the financial support of this work.

■ REFERENCES

(1) (a) Lopez-Jaramillo, F. J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Integr. Proteomics* **2012**, 301−326. (b) Dunny, E.; Evans, P. *Curr. Bioact. Compd.* **2011**, *7*, 218−236. (c) Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793−814. (d) Forristal, I. *J. Sulfur Chem.* **2005**, *26*, 163−195. (e) Carretero, J. C.; Arrayas, R. G.; Buezo, N. D.; Garrido, J. L.; Alonso, I.; Adrio, J. Phosphorus Sulfur Silicon Relat. *Phosphorus, Sulfur Silicon Relat. Elem.* **1999**, *153*, 259−273.

(2) (a) Reutrakul, V.; Jarussophon, S.; Pohmakotr, M.; Chaiyasut, Y.; U-Thet, S.; Tuchinda, P. *Tetrahedron Lett.* **2002**, *43*, 2285−2288. (b) Jang, W. B.; Jeon, H. J.; Oh, D. Y. *Synth. Commun.* **1998**, *28*, 1253−1256. (c) Doomes, E.; Clarke, U.; Neitzel, J. J. *J. Org. Chem.* **1987**, *52*, 1540−1543. (d) Ager, D. J. *J. Chem. Soc., Chem. Commun.* **1984**, 486−488.

(3) (a) Yan, Q.; Xiao, G.; Wang, Y.; Zi, G.; Zhang, Z.; Hou, G. *J. Am. Chem. Soc.* **2019**, *141*, 1749−1756. (b) Lee, J. W.; Lee, C. W.; Jung, J. H.; Oh, D. Y. *Synth. Commun.* **2000**, *30*, 279−283.

(4) (a) Shelke, G. M.; Rao, V. K.; Pericherla, K.; Kumar, A. *Synlett* **2014**, *25*, 2345−2349. (b) Wei, W.; Li, J.; Yang, D.; Wen, J.; Jiao, Y.; You, J.; Wang, H. *Org. Biomol. Chem.* **2014**, *12*, 1861−1864.

(5) Mao, R.; Yuan, Z.; Zhang, R.; Ding, Y.; Fan, X.; Wu, J. *Org. Chem. Front.* **2016**, *3*, 1498−1502.

(6) (a) Zhang, W.; Wu, H.; Liu, Z.; Zhong, P.; Zhang, L.; Huang, X.; Cheng, J. *Chem. Commun.* **2006**, 4826−4828. (b) Jiang, Y.; Kuang, C.; Yang, Q. *Synlett* **2009**, *2009*, 3163−3166. (c) Lin, Z.; Yu, D.; Sum, Y. N.; Zhang, Y. *ChemSusChem* **2012**, *5*, 625−628. (d) Yu, D.; Sum, Y. N.; Ean, A. C. C.; Chin, M. P.; Zhang, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 5125−5128. (e) Sum, Y. N.; Yu, D.; Zhang, Y. *Green Chem.* **2013**, *15*, 2718−2721. (f) Hosseini, A.; Seidel, D.; Miska, A.; Schreiner, P. R. *Org. Lett.* **2015**, *17*, 2808−2811. (g) Kaewchangwat, N.; Sukato, R.; Vchirawongkwin, V.; Vilaivan, T.; Sukwattanasinitt, M.; Wacharasindhu, S. *Green Chem.* **2015**, *17*, 460−465. (h) Rodygin, K. S.; Ananikov, V. P. *Green Chem.* **2016**, *18*, 482−486. (i) Rodygin, K. S.; Werner, G.; Kucherov, F. A.; Ananikov, V. P. *Chem. - Asian J.* **2016**, *11*, 965−976. (j) Teong, S. P.; Yu, D.; Sum, Y. N.; Zhang, Y. *Green Chem.* **2016**, *18*, 3499−3502. (k) Rattanangkool, E.; Vilaivan, T.; Sukwattanasinitt, M.; Wacharasindhu, S. *Eur. J. Org. Chem.* **2016**, *2016*, 4347−4353. (l) Yu, Y.; Huang, W.; Chen, Y.; Gao, B.; Wu, W.; Jiang, H. *Green Chem.* **2016**, *18*, 6445−6449. (m) Yu, Y.; Chen, Y.; Huang, W.; Wu, W.; Jiang, H. *J. Org. Chem.* **2017**, *82*, 9479−9486. (n) Samzadeh-Kermani, A. *Synlett* **2017**, *28*, 2126−2130. (o) Turberg, M.; Ardila-Fierro, K. J.; Bolm, C.; Hernandez, J. G. *Angew. Chem., Int. Ed.* **2018**, *57*, 10718−10722. (p) Voronin, V. V.; Ledovskaya, M. S.; Gordeev, E. G.; Rodygin, K. S.; Ananikov, V. P. *J. Org. Chem.* **2018**, *83*, 3819−3828. (q) Van Beek, W. E.; Gadde, K.; Tehrani, K. A. *Chem. - Eur. J.* **2018**, *24*, 16645−16651. (r) Ledovskaya, M. S.; Rodygin, K. S.; Ananikov, V. P. *Org. Chem. Front.* **2018**, *5*, 226−231. (s) Rodygin, K. S.; Vikenteva, Y. A.; Ananikov, V. P. *ChemSusChem* **2019**, *12*, 1483−1516. (t) Hosseini, A.; Schreiner, P. R. *Org. Lett.* **2019**, *21*, 3746−3749.

(7) (a) Fu, R.; Li, Z. *Org. Lett.* **2018**, *20*, 2342−2345. (b) Song, G.; Li, Z. *Eur. J. Org. Chem.* **2018**, *2018*, 1326−1332. (c) Fu, R.; Li, Z. *Eur. J. Org. Chem.* **2017**, *2017*, 6648−6651. (d) Fu, R.; Li, Z. *J. Chem. Res.* **2017**, *41*, 341−345. (e) Li, Z.; He, L.; Fu, R.; Song, G.; Song, W.; Xie, D.; Yang, J. *Tetrahedron* **2016**, *72*, 4321−4328. (f) Gao, L.; Li, Z. *Synlett* **2019**, *30*, 1580−1584. (g) Lu, H.; Li, Z. *Adv. Synth. Catal.* **2019**, *361*, 4474−4482. (h) Gao, L.; Li, Z. *Org. Chem. Front.* **2020**, *7*, 702−708.

(8) (a) Wang, L.; Yue, H.; Yang, D.; Cui, H.; Zhu, M.; Wang, J.; Wei, W.; Wang, H. *J. Org. Chem.* **2017**, *82*, 6857−6864. (b) Ojha, D. P.; Prabhu, K. R. *Org. Lett.* **2015**, *17*, 18−21.

(9) (a) Hosseini, A.; Pilevar, A.; Hogan, E.; Mogwitz, B.; Schulze, A. S.; Schreiner, P. R. *Org. Biomol. Chem.* **2017**, *15*, 6800−6807. (b) Werner, G.; Rodygin, K. S.; Kostin, A. A.; Gordeev, E. G.; Kashin, A. S.; Ananikov, V. P. *Green Chem.* **2017**, *19*, 3032−3041.

(10) Bamford, W. R.; Stevens, T. S. *J. Chem. Soc.* **1952**, 4735−4740.

(11) (a) Hossain, M. L.; Ye, F.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2013**, *78*, 1236−1241. (b) Suárez, A.; Fu, G. C. *Angew. Chem.* **2004**, *116*, 3664−3666. (c) Hassink, M.; Liu, X.; Fox, J. M. *Org. Lett.* **2011**, *13*, 2388−2391.

(12) (a) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114−1117. (b) Ye, F.; Wang, C.; Ma, X.; Hossain, M. L.; Xia, Y.; Zhang, Y.; Wang, J. *J. Org. Chem.* **2015**, *80*, 647−652.
(13) (a) Taniguchi, N. *Synlett* **2012**, *23*, 1245−1249. (b) Taniguchi, N. *Tetrahedron* **2014**, *70*, 1984−1990. (c) Taniguchi, N. *Tetrahedron* **2018**, *74*, 1454−1460. (d) Liang, S.; Jiang, L.; Yi, W.; Wei, J. *Org. Lett.* **2018**, *20*, 7024−7028.

https://dx.doi.org/10.1021/acs.orglett.0c01915
Org. Lett. XXXX, XXX, XXX−XXX