Organic Letters

Letter

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

pubs.acs.org/OrgLett

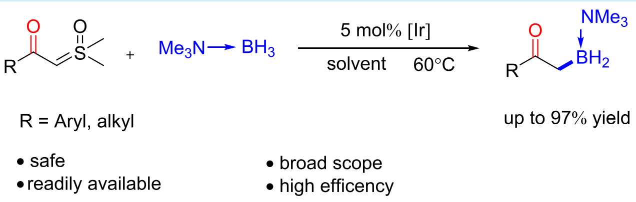
Iridium-Catalyzed B−H Bond Insertion Reactions Using Sulfoxonium Ylides as Carbene Precursors toward *α*-Boryl Carbonyls

Jianglian Li,[†] Hua He,[†] Mengyi Huang, Yuncan Chen, Yi Luo, Kaichuan Yan, Qiantao Wang,* and Yong Wu*

Key Laboratory of Drug-Targeting and Drug Delivery System of the Education Ministry, Sichuan Engineering Laboratory for Plant-Sourced Drug and Sichuan Research Center for Drug Precision Industrial Technology, West China School of Pharmacy, Sichuan University, Chengdu 610041, P. R. China

Supporting Information

ABSTRACT: An iridium-catalyzed B−H bond insertion reaction between borane adducts and sulfoxonium ylides to afford *α*-boryl carbonyls has been developed. The starting materials are safe and readily available. In addition, analogues of sulfoxonium ylides, such as sulfonium salts and sulfonium ylides could also be amenable to the reaction.



Organoboron compounds have a wide range of applications in pharmaceuticals, materials chemistry, organic synthesis, and other fields.[1] Several powerful methodologies for the construction of C−B bonds have been reported.[2] Among them, *α*-boryl carbonyl species have recently been regarded as a class of important molecular entities in organic synthesis due to their exhibited kinetic amphoterism.[3] However, reliable methods for the synthesis of stable and isolable *α*-boryl carbonyls are scarce and suffer from low yields,[4] harsh conditions, and multistep reaction properties.[5] The development of efficient, straightforward synthesis of *α*-boryl carbonyls remains to be desirable. Recently, transition-metal-catalyzed B−H insertion reaction of *α*-diazo carbonyl compounds with borane adducts were reported as an effective alternative for the synthesis of *α*-boryl carbonyls (Scheme 1a).[6] However, diazo compounds are toxic, unstable, and potentially explosive. Thereafter, Zhou's group developed an efficient method that utilized gold-catalyzed oxidative coupling reaction between the terminal alkynes and borane adducts (Scheme 1b).[7] This, however, has a limited practicality because of low atomic utilization and commercially unavailable catalyst. Most recently, the group of Curran described a fundamentally new approach to making *α*-NHC-boryl ketones from NHC-boranes and alkenyl triflates. In this procedure, although no catalyst nor the traditional high energy initiator were needed, its isolated yields were typically low to moderate (Scheme 1c).[8]

Since sulfoxonium ylides were proven to be the alternative metallocarbene surrogates to diazo compounds,[9] many reactions, such as insertions[10] and C−H activations,[11] have been reported by different groups because sulfoxonium ylides are safe, stable, and easily accessible (obtained from the corresponding carboxylic acid).[12] Inspired by recent reports on the transition-metal-catalyzed B−H bond insertion of carbenes[6,13] and our previous works of sulfoxonium ylides,[11d,e] we envisaged the possibility of transition-metal-catalyzed B−H bond insertion using sulfoxonium ylides as carbene precursors to constitute a new route to *α*-boryl carbonyls (Scheme 1d). To our best knowledge, no report on the B−H insertion of sulfoxonium ylides has been reported yet.

We initially studied reactions of sulfoxonium ylide **1a** with trimethylamine-borane **2a** in 1,2-dichloroethane (DCE) at 60 °C with $Rh(OAc)_2$ as catalyst, unfortunately, no desired product was detected (Table 1, entry 1). None of CuI, $Cu(OTf)_2$, and PPh_3AuCl as catalysts afforded the desired product (entries 2−4). To our delight, desired *α*-boryl ketone **3aa** was obtained in 46% yield using $[Ir(COD)Cl]_2$ as catalyst (entry 5), and the relatively low yield should be due to decomposition of **1a**. In our past research on sulfoxonium ylides, we found that this catalyst led to the decomposition of sulfoxonium ylide into ketone **4aa**. At the same time, we also observed that copper salts inhibited the decomposition slightly. To increase the conversion, we investigated several copper salts and other additives, CuF_2 gave the best result (entries 6−11). Further exploration of the solvents indicated that using chlorobenzene (PhCl) could improve the yield to 73% (entries 12−15). Subsequently, increasing the amount of **2a** to 4.0 equiv gave a higher yield (entry 16), and low concentrations could also promote the insertion process by inhibiting decomposition (entry 17). In addition, we conducted more detailed investigation of other reaction conditions, such as temperature, equivalent of catalyst and additive, atmosphere, concentration, and other borane adducts, but they did not give better results (see additional details in the Supporting Information).

With the optimal reaction conditions in hand, we next evaluated the scope of the insertion reaction using different sulfoxonium ylides (Scheme 2). The reaction tolerated a

Received: September 26, 2019

DOI: 10.1021/acs.orglett.9b03410
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 1. Synthesis of α-Boryl Carbonyl Compounds

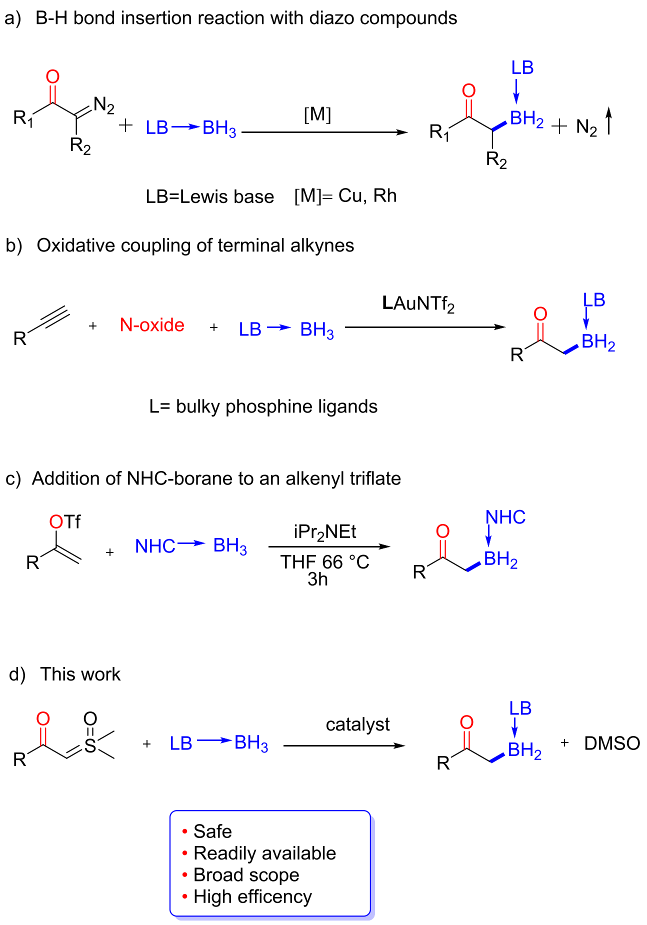
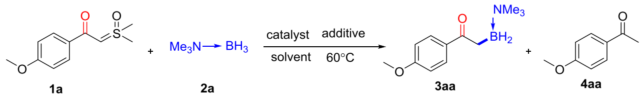


Table 1. Optimization of the Reaction Conditions[a]

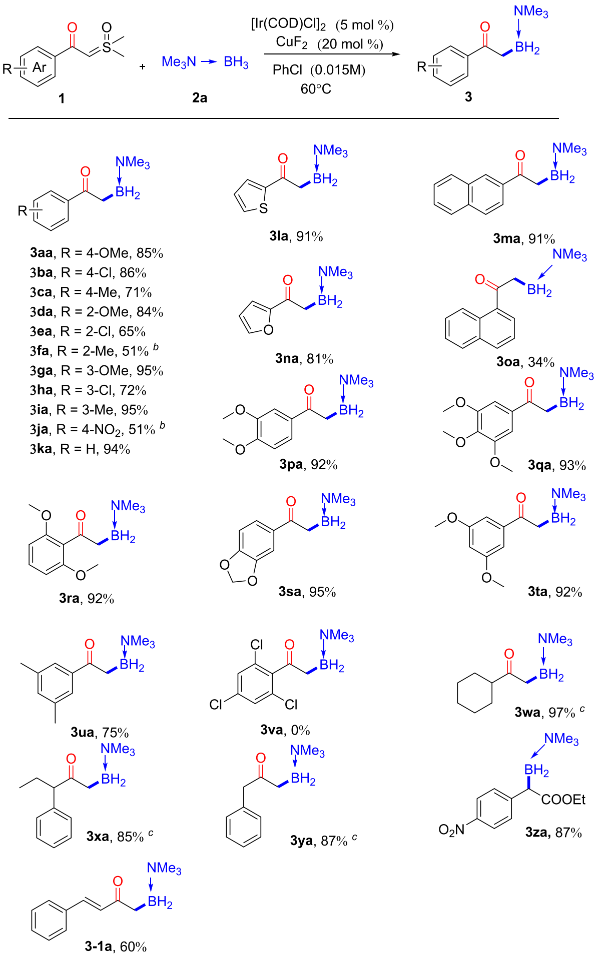


1a 2a 3aa 4aa

entry	catalyst	additive	solvent	3aa (%)[b]	4aa (%)[b]
1	$Rh(OAc)_2$		DCE	ND[c]	ND[c]
2	CuI		DCE	ND	ND
3	PPh_3AuCl		DCE	ND	ND
4	$Cu(OTf)_2$		DCE	ND	ND
5	$[Ir(COD)Cl]_2$		DCE	46	<10
6	$[Ir(COD)Cl]_2$	CuCN	DCE	53	<10
7	$[Ir(COD)Cl]_2$	$Cu(OAc)_2$	DCE	34	<10
8	$[Ir(COD)Cl]_2$	CuF_2	DCE	62	<5
9	$[Ir(COD)Cl]_2$	$ZnCl_2$	DCE	21	<10
10	$[Ir(COD)Cl]_2$	AgOAc	DCE	25	<10
11	$[Ir(COD)Cl]_2$	HOAc	DCE	ND	<10
12	$[Ir(COD)Cl]_2$	CuF_2	DCM	51	<5
13	$[Ir(COD)Cl]_2$	CuF_2	PhCl	73	ND
14	$[Ir(COD)Cl]_2$	CuF_2	H_2O	<5	<10
15	$[Ir(COD)Cl]_2$	CuF_2	DMSO	<10	<10
16[d]	$[Ir(COD)Cl]_2$	CuF_2	PhCl	80	ND
17[e]	$[Ir(COD)Cl]_2$	CuF_2	PhCl	85	ND

[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.3 mmol), catalyst (5 mol %), and additive (20 mol %) in 3 mL of solvent for 3 h at 60 °C under air. COD = 1,5-cyclooctadiene. [b] Isolated yield. [c] ND = not detected. [d] 4.0 equiv of **2a** was used. [e] 10 mL of solvent was used.

Scheme 2. Scope of Sulfoxonium Ylide[a]

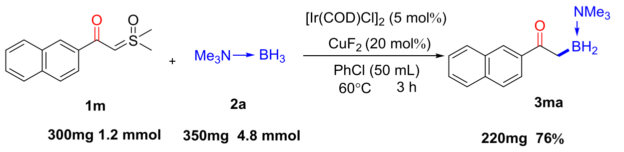


[a] Reaction conditions: **1a** (0.15 mmol), **2a** (0.6 mmol), $[Ir(COD)Cl]_2$ (5 mol %) and CuF_2 (20 mol %) in 10 mL of PhCl for 3 h at 60 °C under air. Isolated yield by chromatography on silica gel. [b] 24 h at 60 °C under air. [c] $[Ir(COD)Cl]_2$ (20 mol %) and CuF_2 (2.0 equiv).

variety of functional groups. Electron-donating and -withdrawing groups, such as methoxy, methyl, and chloro at the ortho, meta, and para positions of the phenyl ring proceeded smoothly, giving the corresponding products in moderate to excellent yields (**3aa**−**3ia**). By comparing the yields of substrates with the same group at different positions, we found that ortho-substituted substrates exhibited slightly reduced efficiency in this transformation, perhaps because of the steric hindrance. At the same time, possibly due to the strong inductive effect of electron-withdrawing groups, nitro-substituted at the para position only afforded moderate yield (**3ja**). Notably, nonsubstituted (hetero) aromatic α-boryl carbonyls were obtained in good to excellent yields (**3ka**−**3na**), but 1-naphthalene was exception, affording a moderate yield of **3oa**. To further evaluate the scope of this process, several polysubstituted substrates were also studied, substrates with at least two electron-donating groups on the benzene ring were fully compatible (**3pa**−**3ua**). Unfortunately, if there are too many electron-withdrawing groups on the benzene ring, the reaction could not proceed (**3va**). Next, we turned our attention to aliphatic sulfoxonium ylides. First, **1w** were treated with **2a** under standard conditions, no desired product was obtained. When we increase the amount of catalyst to 0.2 equiv and the equivalent of copper salt to 2.0 equiv, **3wa** was delivered in 97% yield. In addition, substrates with benzyl group were also compatible (**3xa**, **3ya**). The effect of substitution at the ylide carbon atom was investigated with the compound **1z** under standard conditions (**3za**). Because of the existence of chiral carbon in **1z**, theoretically, enantioselectivity can be achieved by using chiral iridium catalysts. Moreover, this method is also suitable for substrates with alkenyl group (**3-1a**).

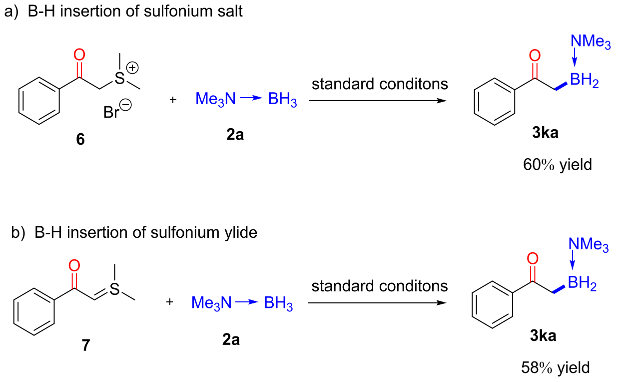
To investigate the efficiency and further practicality of this transformation, a 10-fold scale-up of the reaction using **1m** and **2a** in 50 mL of PhCl was then examined. The desired product **3ma** was isolated in 76% yield (Scheme 3). The slight decrease in yield might be attributed to that the decomposition of sulfoxonium ylide was increased with the increasing concentration.

Scheme 3. 10-Fold Scale-Up Reaction



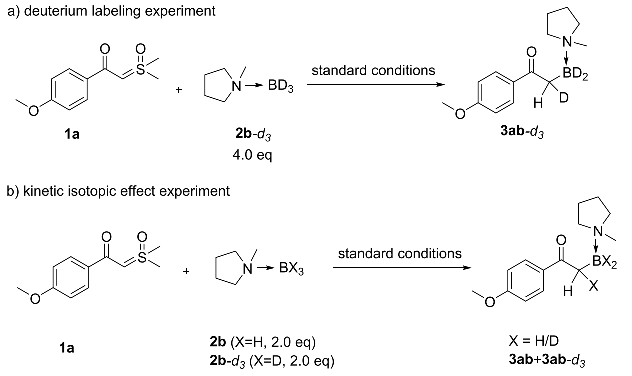
Afterward, we envisioned that, in analogy with sulfoxonium ylides, sulfonium salts, and sulfonium ylides could also be amenable to the reaction. Among them, B−H insertion reactions of sulfonium salts with B_2pin_2 has been reported.[14] When sulfonium salt **6** was used, **3ka** was isolated in 60% yield (Scheme 4a). Delightedly, when sulfoxonium ylides were replaced by sulfonium ylide **7**, corresponding product was also obtained in 58% yield (Scheme 4b). To our knowledge, to date there is only one report on X−H (X = C, Si, O, S, N) insertion reactions of sulfonium ylide derived carbenoids.[15]

Scheme 4. B−H Bond Insertion of Analogues of Sulfoxonium Ylides

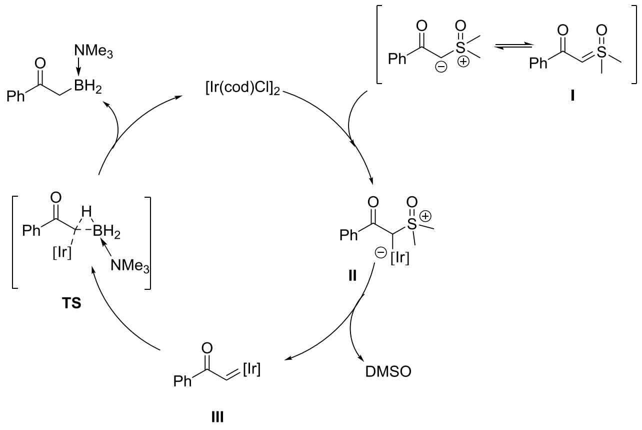


In order to clarify the mechanism of this present process, we carried out a labeling experiment with **2b**-d_3 and observed a kinetic isotope effect ($k_H/k_D = 3.35$), the result indicated that cleavage of the B−H bond is probably involved in the turnover-limiting step (Scheme 5).

Scheme 5. Control Experiments



Scheme 6. Proposed B−H Insertion Mechanism



Based on our preliminary studies and previous literature values,[12] we propose the following reaction mechanism (Scheme 6). Initially, sulfoxonium ylide reacts with Ir species and extrudes DMSO to generate the iridium carbene complex **III**, which was inserted into the B−H bond of the borane adduct to affford the product also regenerates the catalyst via a concerted transition state.

In summary, we have described a protocol for iridium-catalyzed B−H bond insertion reactions of borane adducts and sulfoxonium ylides. With this reaction, various α-boryl ketones were synthesized in good to excellent yields from safe and readily accessible starting materials. Analogues of sulfoxonium ylides, sulfonium salts are also applicable to this procedure. We firmly believe that this successful use of sulfur (sulfonium and sulfoxonium) ylides as carbene precursors in B−H bond insertion reactions could open up a new route to organoboron compounds.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03410.

Experimental procedures and spectroscopic data for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: qiantao_wang@hotmail.com.
*E-mail: wyong@scu.edu.cn.
ORCID
Yong Wu: 0000-0003-0719-4963

Author Contributions

[†]J.L. and H.H. contributed equally.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful for the support from the National Natural Science Foundation of China (NSFC) (Grant Number 81602954, 81573286, 81373259, and 81773577) and Sichuan Youth Science and Technology Program (Grant No. 2019YJ0036).

■ REFERENCES

(1) For selected reviews on organoboron compounds, see (a) Braunschweig, H.; Dewhurst, R. D.; Schneider, A. *Chem. Rev.* **2010**, *110*, 3924–57. (b) Brooks, W. L.; Sumerlin, B. S. *Chem. Rev.* **2016**, *116*, 1375–97. (c) Cherney, A. H.; Kadunce, N. T.; Reisman, S. E. *Chem. Rev.* **2015**, *115*, 9587–652. (d) Dembitsky, V. M.; Al Quntar, A. A.; Srebnik, M. *Chem. Rev.* **2011**, *111*, 209–37. (e) Jakle, F. *Chem. Rev.* **2010**, *110*, 3985–4022. (f) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–92. (g) Leonori, D.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082–96. (h) Liu, S. Y.; Stephan, D. W. *Chem. Soc. Rev.* **2019**, *48*, 3434–3435. (i) Ollivier, C.; Renaud, P. *Chem. Rev.* **2001**, *101*, 3415–3434. (j) Ramachandran, P. V.; Brown, H. C. Recent Advances in Borane Chemistry. In *Organoboranes for Syntheses*; ACS Symposium Series, Vol. *783*; American Chemical Society: Washington, DC, 2001; pp 1–15. (k) Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev.* **2011**, *111*, 1417–1492. (l) Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F.-G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G. *Chem. Rev.* **1998**, *98*, 1515–1562.

(2) For selected reviews on the synthesis of organoboron compounds: (a) Brown, H. C. *Science* **1980**, *210*, 485–492. (b) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320–2354. (c) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992–2002. (d) Ishiyama, T.; Murata, M.; Miyaura, N. *J. Org. Chem.* **1995**, *60*, 7508–7510. (e) Mkhalid, I. A.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890–931. (f) Burgess, K.; Ohlmeyer, M. J. *Chem. Rev.* **1991**, *91*, 1179–1191. (g) Ros, A.; Fernandez, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229–3243.

(3) For selected reviews on α-boryl carbonyls: (a) He, Z.; Zajdlik, A.; Yudin, A. K. *Acc. Chem. Res.* **2014**, *47*, 1029–1040. (b) He, Z.; Zajdlik, A.; Yudin, A. K. *Dalton. Trans.* **2014**, *43*, 11434–11451.

(4) Kobayashi, M.; Sanda, F.; Endo, T. *Macromolecules* **2002**, *35*, 346–348.

(5) (a) Ansorge, A.; Brauer, D.J.; Burger, H.; Hagen, T.; Pawelke, G. *J. Organomet. Chem.* **1993**, *444*, 5–14. (b) He, Z.; Yudin, A. K. *J. Am. Chem. Soc.* **2011**, *133*, 13770–13773. (c) Li, J.; Burke, M. D. *J. Am. Chem. Soc.* **2011**, *133*, 13774–13777. (d) Lv, W.-X.; Zeng, Y.-F.; Li, Q.; Chen, Y.; Tan, D.-H.; Yang, L.; Wang, H. *Angew. Chem., Int. Ed.* **2016**, *55*, 10069–10073.

(6) (a) Allen, T. H.; Kawamoto, T.; Gardner, S.; Geib, S. J.; Curran, D. P. *Org. Lett.* **2017**, *19*, 3680–3683. (b) Chen, D.; Zhang, X.; Qi, W.-Y.; Xu, B.; Xu, M.-H. *J. Am. Chem. Soc.* **2015**, *137*, 5268–5271. (c) Cheng, Q.-Q.; Zhu, S.-F.; Zhang, Y.-Z.; Xie, X.-L.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2013**, *135*, 14094–14097. (d) Huang, X.; Garcia-Borras, M.; Miao, K.; Kan, S. B. J.; Zutshi, A.; Houk, K. N.; Arnold, F. H. *ACS Cent. Sci.* **2019**, *5*, 270–276. (e) Kan, S. B. J.; Huang, X.; Gumulya, Y.; Chen, K.; Arnold, F. H. *Nature* **2017**, *552*, 132–136. (f) Li, X.; Curran, D. P. *J. Am. Chem. Soc.* **2013**, *135*, 12076–12081. (g) Cheng, Q.; Xu, H.; Zhu, S.; Zhou, Q. *Huaxue Xuebao* **2015**, *73*, 326–329. (h) Yang, J.; Li, Z.; Zhu, S. *Chin. J. Org. Chem.* **2017**, *37*, 2481–2497.

(7) Yang, J.-M.; Zhao, Y.-T.; Li, Z.-Q.; Gu, X.-S.; Zhu, S.-F.; Zhou, Q.-L. *ACS Catal.* **2018**, *8*, 7351–7355.

(8) Dai, W.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2019**, *141*, 12355.

(9) Burtoloso, A. C. B.; Dias, R. M. P.; Leonarczyk, I. A. *Eur. J. Org. Chem.* **2013**, *2013*, 5005–5016.

(10) For selected reports on insertion reactions of sulfoxonium ylides: (a) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Vaughan, J. G. *J. Chem. Soc., Chem. Commun.* **1993**, 1434–1435. (b) Dias, R. M.; Burtoloso, A. C. *Org. Lett.* **2016**, *18*, 3034–3037. (c) Gallo, R. D. C.; Ahmad, A.; Metzker, G.; Burtoloso, A. C. B. *Chem. - Eur. J.* **2017**, *23*, 16980–16984. (d) Jiang, H.; Zhang, H.; Xiong, W.; Qi, C.; Wu, W.; Wang, L.; Cheng, R. *Org. Lett.* **2019**, *21*, 1125–1129. (e) Phelps, A. M.; Chan, V. S.; Napolitano, J. G.; Krabbe, S. W.; Schomaker, J. M.; Shekhar, S. *J. Org. Chem.* **2016**, *81*, 4158–4169. (f) Vaitla, J.; Bayer, A.; Hopmann, K. H. *Angew. Chem., Int. Ed.* **2017**, *56*, 4277–4281. (g) Mangion, I. K.; Nwamba, I. K.; Shevlin, M.; Huffman, M. A. *Org. Lett.* **2009**, *11*, 3566–3569.

(11) For selected reports on C-H activations of sulfoxonium ylides: (a) Barday, M.; Janot, C.; Halcovitch, N. R.; Muir, J.; Aissa, C. *Angew. Chem., Int. Ed.* **2017**, *56*, 13117–13121. (b) Hu, P.; Zhang, Y.; Xu, Y.; Yang, S.; Liu, B.; Li, X. *Org. Lett.* **2018**, *20*, 2160–2163. (c) Ji, S.; Yan, K.; Li, B.; Wang, B. *Org. Lett.* **2018**, *20*, 5981–5984. (d) Lai, R.; Wu, X.; Lv, S.; Zhang, C.; He, M.; Chen, Y.; Wang, Q.; Hai, L.; Wu, Y. *Chem. Commun.* **2019**, *55*, 4039–4042. (e) Luo, Y.; Guo, L.; Yu, X.; Ding, H.; Wang, H.; Wu, Y. *Eur. J. Org. Chem.* **2019**, *2019*, 3203–3207. (f) Wu, X.; Xiong, H.; Sun, S.; Cheng, J. *Org. Lett.* **2018**, *20*, 1396–1399. (g) Xu, Y.; Zheng, G.; Yang, X.; Li, X. *Chem. Commun.* **2018**, *54*, 670–673. (h) Xu, Y.; Zhou, X.; Zheng, G.; Li, X. *Org. Lett.* **2017**, *19*, 5256–5259.

(12) Bayer, A.; Vaitla, J. *Synthesis* **2019**, *51*, 612–628.

(13) (a) Allen, T. H.; Curran, D. P. J. *J. Org. Chem.* **2016**, *81*, 2094–2098. (b) Pang, Y.; He, Q.; Li, Z.-Q.; Yang, J.-M.; Yu, J.-H.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2018**, *140*, 10663–10668. (c) Yang, J.-M.; Li, Z.-Q.; Li, M.-L.; He, Q.; Zhu, S.-F.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2017**, *139*, 3784–3789.

(14) (a) Berger, F.; Plutschack, M. B.; Riegger, J.; Yu, W.; Speicher, S.; Ho, M.; Frank, N.; Ritter, T. *Nature* **2019**, *567*, 223–228. (b) Minami, H.; Otsuka, S.; Nogi, K.; Yorimitsu, H. *ACS Catal.* **2018**, *8*, 579–583.

(15) Kolattoor, J.; Sherman, M.; Jenks, W. *J. Photochem. Photobiol., A* **2018**, *365*, 208–212.

DOI: 10.1021/acs.orglett.9b03410
Org. Lett. XXXX, XXX, XXX−XXX