OL Organic Letters

pubs.acs.org/OrgLett Letter

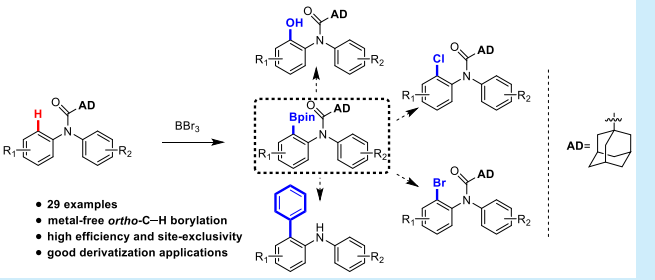
# C−H Borylation of Diphenylamines through Adamantane-1-carbonyl Auxiliary by $BBr_3$

Gaorong Wu, Xiaopan Fu, Yangyang Wang, Kezuan Deng, Lili Zhang, Tao Ma,* and Yafei Ji*

Cite This: https://dx.doi.org/10.1021/acs.orglett.0c02552 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

**ABSTRACT:** A method for *ortho*-C−H borylation of diphenylamines using $BBr_3$ as the boron source has been reported. The noncatalytic adamantane-1-carbonyl directed reaction exhibited site exclusivity and good functional group tolerance. Generally, the borylation occurred at the more electron-rich aromatic ring and the borylated products could be converted to various useful intermediates. Besides, the derived arylation and removal of auxiliary of the product could be achieved in a one-pot fashion.






As a highly important class of chemicals, diphenylamines are frequently found among drugs, dyes, agrochemicals, explosive stabilizers, and radical trapping antioxidants, such as diclofenac sodium, mefenamic acid, and clausine E (Figure 1).[1]

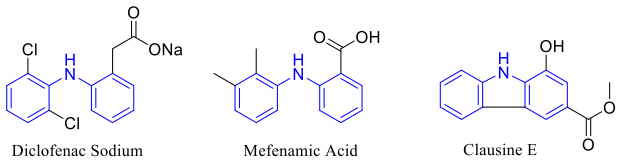
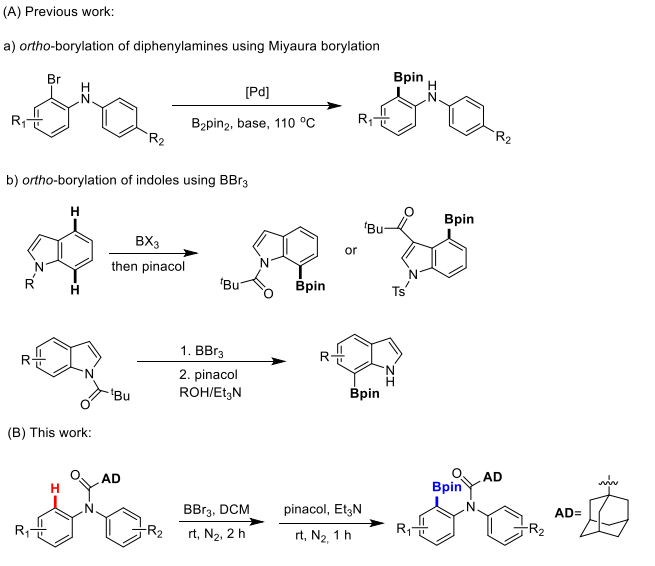



**Figure 1.** Bioactive molecules of diphenylamine.

Arylboronates are useful synthetic intermediates in modern organic synthesis due to the fact that the C−B bond can be converted into different functionalities such as C−C, C−N, C−O, and C−X (X = halogens) bonds.[2] In recent years, tremendous progress has been made in C−H borylation reactions, but few synthetic methods for *ortho*-borylation of diphenylamines have been developed.[3] Prevalent methods mainly involved transition-metal-catalyzed Miyaura borylation (Scheme 1Aa) and Buchwald−Hartwig amination.[4] These reactions mostly rely on metal catalysts and harsh conditions.[4] In addition, the difficulty in removal of toxic trace metals in pharmaceutical products will limit its application.[5] Thus, it is highly desirable to develop a reliable access for *ortho*-borylation of diphenylamines under mild, convenient, and eco-friendly conditions.

C−H borylation using strong Lewis acids such as $BX_3$ (X = F, Cl, Br) or $B(C_6F_5)_3$ has attracted more attention to synthesize organoboranes.[6] In 2019, Shi,[7] Ingleson[8] and their co-workers reported pivaloyl group directed *ortho*-borylation of indoles and anilines by just using $BBr_3$ (Scheme 1Ab). It offered an outstanding strategy for generating boron species

**Scheme 1. Borylation of Diphenylamines and Indoles**




with simple, mild, and efficient conditions. More recently, Iashin et al.[6k] achieved the C−H borylation of *N*-heteroarenes by $BF_3$, and the direct intramolecular aminoboration of allenes with $BCl_3$ was disclosed by Yang's group.[6l] The above-

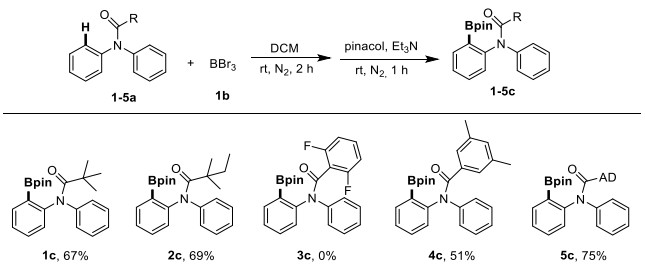
**Received:** July 31, 2020

mentioned reports all demonstrate that borylation using $BX_3$ is an effective measure to form C−B bonds in organic materials.

Inspired by the above achievements, we hope to develop a new and more bioactive directing group in this simple system, providing a general method for the preparation of diphenylamine borates that could be used as viable substrates in subsequent derivatization applications. Thus, we reported a method for C−H borylation of diphenylamines through an adamantane-1-carbonyl auxiliary by $BBr_3$ (Scheme 1B). The reaction exhibited site exclusivity and good functional group tolerance. The obtained diphenylamine boronic esters were shown to engage in C−X (X = C, O, Cl, Br) bond formation, providing a reliable access to obtain diphenylamine derivatives. Besides, we achieved the derived arylation and removal of auxiliary of the product in a one-pot fashion.

Our initial study aimed at evaluating the different types of acyl DGs (directing groups) for the borylation. The reaction was carried out in the presence of substrates **1**−**5a** (0.2 mmol) and **1b** (0.22 mL, 1.1 equiv) in dried DCM (1.5 mL) for 2 h at room temperature under a $N_2$ atmosphere, and then pinacol (1.1 equiv) and $Et_3N$ (5.0 equiv) were added for 1 h (Scheme 2). To our delight, **1c** and **2c** were obtained in 67% and 69%

**Scheme 2. Screening of Directing Groups**[a,b]



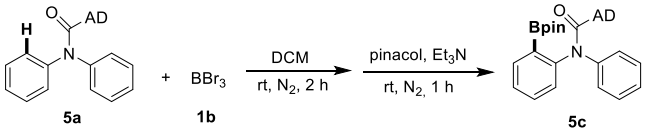

[a]Reaction conditions: **1**−**5a** (0.2 mmol), **1b** (0.22 mL, 1 M in DCM), DCM (1.5 mL), $N_2$, 2 h; then pinacol (0.22 mmol, dissolved in 1 mL of dry DCM), $Et_3N$ (1.0 mmol), rt, $N_2$, 1 h. [b]Isolated yields.

yields. However, there was no change in the $^1H$ NMR spectra before and after addition of $BBr_3$ of **3a**, indicating no adduct formation, probably because of the strong electron-withdrawing nature of the two fluorine atoms. When the aryl was replaced with 3,5-dimethyl, the desired compound **4c** was obtained in 51% yield. In addition, the adamantane-1-carbonyl DG delivered a better yield of the target compound **5c** of 75%. Although the isolated yields among **5c**, **1c**, and **2c** were slightly different, the adamantane moiety was commonly observed in drugs and its derivates possessed multiple biological activities such as antiviral, antidiabetic, antiparkinsonian, anticancer, and antimycobacterial.[9] Thus, adamantane-1-carbonyl was selected as the optimal directing group for further surveys.

Having identified the optimal DG, we further evaluated the parameters to optimize reaction conditions. The results were summarized in Table 1. Upon increasing **1b** to 2.2 equiv, the desired product **5c** was obtained in up to 80% yield (entries 1 and 2). However, further increasing **1b** did not lead to a higher yield (entry 3). In contrast to our initial solvent choice of DCM, DCE and TCM diminished the yield (entries 4 and 5) and ACN led to no desired compound (entry 6). Thus, entry 2 was established as the standard reaction conditions.

With the established reaction conditions, the scope of diphenylamines was examined as shown in Scheme 3. Both electron-rich and electron-deficient aromatics were tolerated

**Table 1. Optimization of the Reaction Conditions**[a]



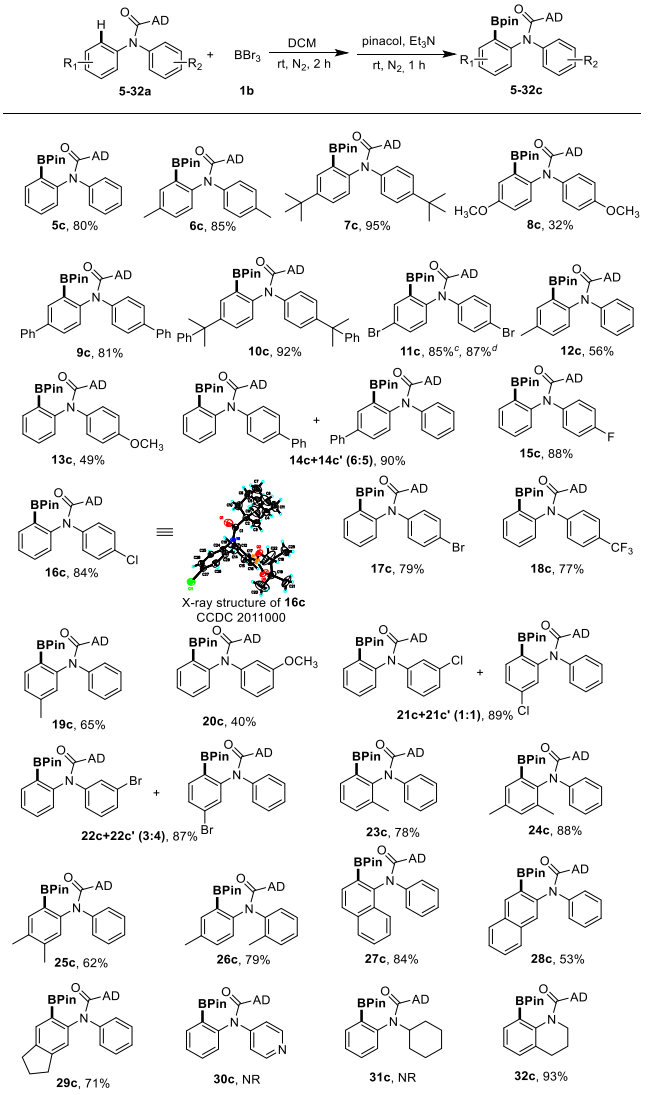

| Entry | Mainly deviation from the "primary conditions" | Yield[b] |
|---|---|---|
| 1 | None | 75% |
| 2 | **1b (2.2 equiv)** | **80%** |
| 3 | **1b** (3.3 equiv) | 78% |
| 4 | DCE[c] instead of DCM[d] | 73% |
| 5 | TCM[e] instead of DCM | 72% |
| 6 | ACN[f] instead of DCM | 0% |

[a]Reaction conditions: **5a** (0.20 mmol), **1b** (0.44 mL, 1 M in DCM), DCM (1.5 mL), $N_2$, 2 h; then pinacol (0.44 mmol, dissolved in 1 mL of dry DCM), $Et_3N$ (1.0 mmol), rt, $N_2$, 1 h. [b]Isolated yields. [c]DCE = 1,2-dichloroethane. [d]DCM = dichloromethane. [e]TCM = Trichloromethane. [f]ACN = acetonitrile.

with this procedure, producing the target compounds in 32−95% yield (**5c**−**29c**). In general, the diphenylamines under optimized reaction conditions gave the corresponding products with excellent site selectivity. All the borylations occurred at the *ortho*-position of diphenylamines, and most of them were substituted on the more electron-rich aromatic ring. It might due to the fact that the electron-donating group increases the electron cloud density of the aromatic ring, which was conducive to the electrophilic reaction.[10] However, the opposite results of **13c** and **20c** were obtained because methoxy was deactivating toward SEAr when it was in the *meta* position. Furthermore, the coordination of $BBr_3$ to the MeO rings was presumably deactivating the MeO substituted aromatic rings with excess $BBr_3$. *para*-Symmetrical substrates afforded the borylated products (**6c**, **7c**, **9c**−**11c**) with good yields; especially, the yield of **7c** was up to 95%. But **8c** was obtained in only 32% yield, probably because ether cleavage was a competing reaction.[11] Of note, **11c** was obtained in 85% yield with 5.0 equiv of $BBr_3$ for 2 h while the yield was slightly increased with 2.2 equiv of $BBr_3$ for 12 h, suggesting the borylation may be slow with the more deactivated system. In addition, *para*-asymmetrical diphenylamines bearing Me (**12c**), F (**15c**), Cl (**16c**), Br (**17c**), and $CF_3$ (**18c**) substituents could also be borylated with excellent yields. The structure of product **16c** was confirmed by X-ray analysis. Of note, *para*-phenyl-substituted substrate **14a** gave a pair of isomers (6:5) in high yield (see the Supporting Information). Likely, *meta*-Cl- and Br-substituted substrates **21a** and **22a** also produced isomers with 89% (1:1) and 87% (3:4) yields (see the SI). *ortho*-Me Substrate provided highest yield of the corresponding product (**23c**), while *para*-Me (**12c**) lowest. Besides, the yield of the *ortho*- and *para*-dimethyl borylated product (**24c**) was higher than that *meta*- and *para*-dimethyl product (**25c**). Interestingly, when the diphenylamine **26a** bearing two methyl groups at different aromatic rings (*ortho*- and *para*-) was treated in the system, the borylation occurred at the aromatic ring with *para*-methyl. A good yield was obtained with *N*-1-naphthylaniline (**27a**), but the yield of **28c** was decreased and the other six membered boracycle derived isomer was not observed, suggesting the deprotonation may be slow.[12] Moreover, indan-5-yl substituted **29a** gave the borylated products in 71% yield. The 4-(phenylamino)pyridine (**30a**) and *N*-cyclohexylaniline (**31a**) substrates were not suitable for


https://dx.doi.org/10.1021/acs.orglett.0c02552
Org. Lett. XXXX, XXX, XXX−XXX

**Scheme 3. Substrate Scope of Diphenylamines**[a,b]



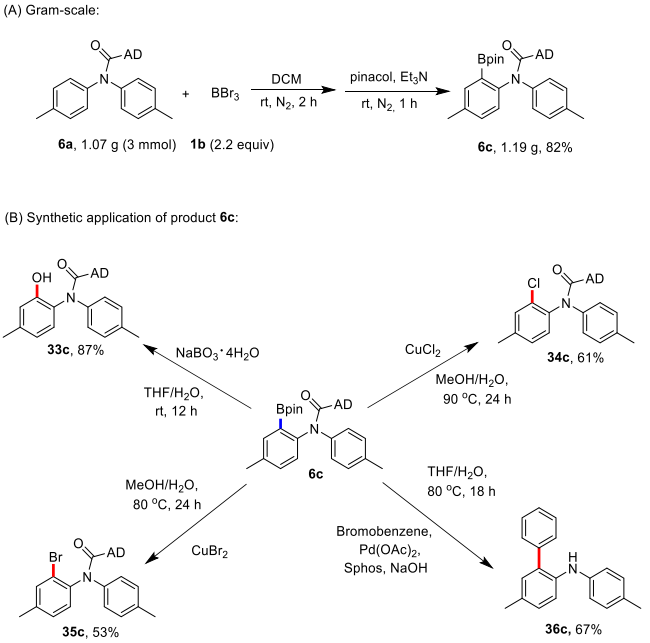

[a]Reaction conditions: **5**−**32a** (0.20 mmol), **1b** (0.44 mL, 1 M in DCM), DCM (1.5 mL), $N_2$, 2 h; then pinacol (0.44 mmol, dissolved in 1 mL of dry DCM), $Et_3N$ (1.0 mmol), rt, $N_2$, 1 h. [b]Isolated yields. [c]Using $BBr_3$ (5 equiv, 1.0 mL, 1 M in DCM). [d]Using $BBr_3$ (0.44 mL, 1 M in DCM), 12 h.

the reaction. However, the tetrahydroquinoline **32a** afford the borylated product in excellent yield.

The boryl groups could be transformed into a range of other functional groups. To certify the utility of the current borylation reaction, we performed the reaction on gram scale. The borylated product **6c** was provided in 82% yield. Then we converted **6c** to several useful intermediates as shown in Scheme 4. With excess $NaBO_3{\cdot}4H_2O$ in THF/$H_2O$ at room temperature, the hydroxylated product **33c** was afforded in 87% yield.[13] The C($sp^2$)−B bond of **6c** was transformed into the C−Cl bond with $CuCl_2$ in 61% yield.[14] Similarly, bromination of **6c** with $CuBr_2$ furnished **35c** in 53% yield.[15] Moreover, in a one-pot fashion we realized the arylation of **6c** by Suzuki−Miyaura reaction with bromobenzene and the removal of the directing group, which provided **36c** in 67% yield.[16]

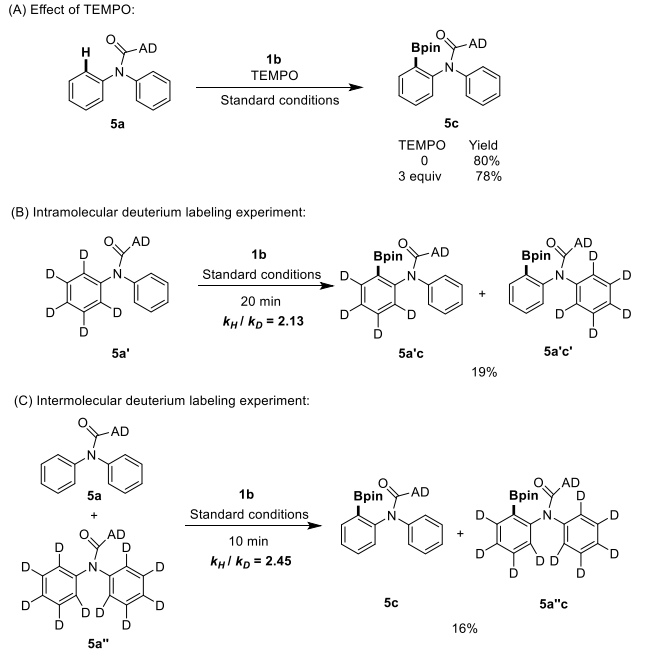
To obtain mechanistic insight into the reaction, a control experiment was performed. When 3.0 equiv of TEMPO, a

**Scheme 4. Gram-Scale Reaction and Synthetic Application of Product 6c**




radical quencher, were added under the standard reaction conditions, it was found that TEMPO had negligible effect on the yield of **5c**, which did not evidence a radical pathway (Scheme 5A). Subsequently, we conducted the intra- and

**Scheme 5. Effect of TEMPO and Intra-/Intermolecular Deuterium Labeling Experiments**




intermolecular competition experiments with deuterium-labeled diphenylamine to further investigate the mechanism. The intramolecular competition reaction of **5a′** ($D_5$) under the standard conditions for 20 min gave a KIE value of 2.13 by $^1H$ NMR spectroscopic analysis (see the SI) (Scheme 5B). On the other hand, the intermolecular competition reaction between

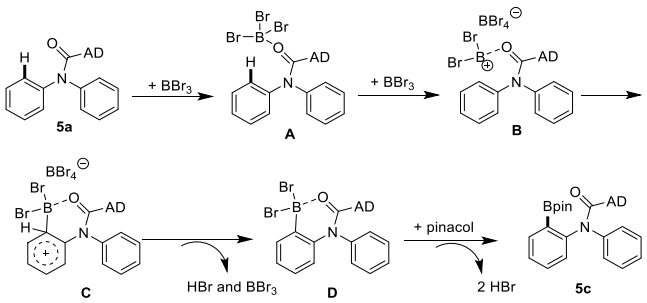


https://dx.doi.org/10.1021/acs.orglett.0c02552
Org. Lett. XXXX, XXX, XXX−XXX

**5a** (undeuterated) and **5a′′** ($D_{10}$) under the standard conditions for 10 min gave a KIE value of 2.45 (see the SI) (Scheme 5C). These results were consistent with the calculations by Houk on the electrophilic borylation of aniline, indicating that C($sp^2$)−H bond cleavage was the rate-determining step.[7,17]

Based upon the mechanistic experimental results and relevant literature reports, a possible mechanism for this reaction is depicted in Scheme 6.[6c,i,k,l,7,8] First, complex **A**,

**Scheme 6. Proposed Mechanism**




consisting of substrate and $BBr_3$, was formed upon the addition of $BBr_3$. With another $BBr_3$, the Br transferred from **A** to generate a borenium cation **B**. Then the borenium cation undergoes electrophilic reaction, attacking the *ortho*-carbon of diphenylamine, and the deprotonation by $BBr_4^-$ formed a six-membered cyclic **C**. Subsequently, intermediate **D** was generated. Finally, with pinacol, the B−Br bonds and B−O bond of the acyl cleavage event provided the desired compound **5c**.

In summary, we have developed a method for C−H borylation of diphenylamines using $BBr_3$ as the boron source with an adamantane-1-carbonyl auxiliary. This method shows good functional group tolerance, high efficiency, and site exclusivity. In view of the widespread application of diphenylamine, it may serve as a significant tool to construct structurally diversified diphenylamine derivatives for the screening of potential pharmaceuticals in the future.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02552.

Experimental procedures and spectral data (PDF)

### Accession Codes

CCDC 2011000 contains 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 Authors

**Tao Ma** − *School of Chinese Materia Medica, Beijing University of Chinese Medicine, Beijing 102488, P. R. China;* orcid.org/0000-0001-9856-2631; Email: mosesmatao@163.com

**Yafei Ji** − *Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education; School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China;* orcid.org/0000-0002-3562-6703; Email: jyf@ecust.edu.cn

### Authors

**Gaorong Wu** − *Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education; School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China*

**Xiaopan Fu** − *Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education; School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China*

**Yangyang Wang** − *Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education; School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China*

**Kezuan Deng** − *Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education; School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China*

**Lili Zhang** − *Engineering Research Centre of Pharmaceutical Process Chemistry, Ministry of Education; School of Pharmacy, East China University of Science and Technology, Shanghai 200237, P. R. China*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c02552


### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

We gratefully thank the National Natural Science Foundation of China (Project No. 21676088) for financial support.

## ■ REFERENCES


(1) (a) Suwanprasop, S.; Nhujak, T.; Roengsumran, S.; Petsom, A. *Ind. Eng. Chem. Res.* **2004**, *43*, 4973. (b) Kim, T. H.; Kwon, S. H.; Choi, J. H. B. *Kor. Chem. Soc.* **2019**, *40*, 1229. (c) Yücel, A.; Inal, E. K.; Akay, M. A. *Cent. Eur. J. Energy Mater.* **2011**, *8*, 183. (d) Haidasz, E. A.; Shah, R.; Pratt, D. A. *J. Am. Chem. Soc.* **2014**, *136*, 16643. (e) Parihar, J. A.; Dash, P.; Kudav, D. P. *J. Chem. Res.* **2004**, *2004*, 220. (f) Verma, V.; Ramamoorthi, M.; Morris, M. *JDR Clin. Trans. Res.* **2016**, *1*, 178. (g) Lyons, B. M.; Poppenga, R. H.; Thawley, V. J. *J. Am. Anim. Hosp. Assoc.* **2019**, *55*, e555-02. (h) Stip, E. *Can. J. Psychiat.* **2020**, 0706743720934997.

(2) (a) Miyaura, N. *Top. Curr. Chem.* **2002**, *219*, 11. (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633. (c) Leonori, D.; Aggarwal, V. K. *Acc. Chem. Res.* **2014**, *47*, 3174. (d) Leonori, D.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 1082. (e) Zweifel, G. T.; Brown, H. C. *Org. React.* **1963**, *13*, 22. (f) Brown, H. C. *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972. (g) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2011**, *133*, 16794. (h) Scott, H. K.; Aggarwal, V. K. *Chem. - Eur. J.* **2011**, *17*, 13124.

(3) (a) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev.* **2010**, *110*, 890. (b) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992.

(4) (a) Billingsley, K. L.; Barder, T. E.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 5359. (b) Morris, S. A.; Nguyen, T. H.; Zheng, N. *Adv. Synth. Catal.* **2015**, *357*, 2311.

(5) (a) Garrett, C. E.; Prasad, K. *Adv. Synth. Catal.* **2004**, *346*, 889. (b) Nair, D.; Scarpello, J.; White, L.; Freista dos Santos, L.; Vankelecom, I.; Livingston, A. *Tetrahedron Lett.* **2001**, *42*, 8219.
(6) (a) Focante, F.; Camurati, I.; Nanni, D.; Leardini, R.; Resconi, L. *Organometallics* **2004**, *23*, 5135. (b) Niu, L.; Yang, H.; Wang, R.; Fu, H. *Org. Lett.* **2012**, *14*, 2618. (c) De Vries, T. S.; Prokofjevs, A.; Vedejs, E. *Chem. Rev.* **2012**, *112*, 4246. (d) Bagutski, V.; Del Grosso, A.; Carrillo, J. A.; Cade, I. A.; Helm, M. D.; Lawson, J. R.; Singleton, P. J.; Solomon, S. A.; Marcelli, T.; Ingleson, M. J. *J. Am. Chem. Soc.* **2013**, *135*, 474. (e) Crossley, D. L.; Cade, I. A.; Clark, E. R.; Escande, A.; Humphries, M. J.; King, S. M.; VitoricaYrezabal, I.; Ingleson, M. J.; Turner, M. L. *Chem. Sci.* **2015**, *6*, 5144. (f) Yin, Q.; Klare, H. F. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 3712. (g) Liu, Y. L.; Kehr, G.; Daniliuc, C. G.; Erker, G. *Chem. - Eur. J.* **2017**, *23*, 12141. (h) Tanaka, S.; Saito, Y.; Yamamoto, T.; Hattori, T. *Org. Lett.* **2018**, *20*, 1828. (i) Tanaka, S.; Saito, Y.; Yamamoto, T.; Hattori, T. *Org. Lett.* **2018**, *20*, 1828. (j) Liu, K.; Lalancette, R. A.; Jäkle, F. *J. Am. Chem. Soc.* **2019**, *141*, 7453. (k) Iashin, V.; Berta, D.; Chernichenko, K. *Chem. - Eur. J.* **2020**, DOI: 10.1002/chem.202001436. (l) Yang, C.; Han, M.; Li, W.; Zhu, N.; Sun, Z.; Wang, J.; Yang, Z.; Li, Y. *Org. Lett.* **2020**, *22*, 5090. (m) Lv, J.; Zhao, B.; Yuan, Y.; Han, Y.; Shi, Z. *Nat. Commun.* **2020**, *11*, 1316.
(7) Lv, J.; Chen, X.; Xue, X.; Zhao, B.; Liang, Y.; Wang, M.; Jin, L.; Yuan, Y.; Han, Y.; Zhao, Y.; Lu, Y.; Zhao, J.; Sun, W.; Houk, K. N.; Shi, Z. *Nature* **2019**, *575*, 336.
(8) Iqbal, S. A.; Cid, J.; Procter, R. J.; Uzelac, M.; Yuan, K.; Ingleson, M. *Angew. Chem., Int. Ed.* **2019**, *58*, 15381.
(9) (a) Liu, J.; Obando, D.; Liao, V.; Lifa, T.; Codd, R. *Eur. J. Med. Chem.* **2011**, *46*, 1949. (b) Sacksteder, K. A.; Protopopova, M.; Barry, C. E.; Andries, K.; Nacy, C. A. *Future Microbiol.* **2012**, *7*, 823. (c) Göktaş, F.; Vanderlinden, E.; Naesens, L.; Cesur, N.; Cesur, Z. *Bioorg. Med. Chem.* **2012**, *20*, 7155. (d) Khaziev, R.; Shtyrlin, N.; Pavelyev, R. *Lett. Drug. Des. Discovery* **2019**, *16*, 1360. (e) Scherman, M. S.; North, E. J.; Jones, V.; Hess, T. N.; Grzegorzewicz, A. E.; Kasagami, T.; Kim, I. H.; Merzlikin, O.; Lenaerts, A. J.; Lee, R. E.; Jackson, M.; Morisseau, C.; McNeil, M. R. *Bioorg. Med. Chem.* **2012**, *20*, 3255.
(10) Oliveira, F. G.; Rodrigues, F. L.; de Oliveira, A. V. B. *Struct. Chem.* **2017**, *28*, 545.
(11) (a) Williard, P. G.; Fryhle, C. B. *Tetrahedron Lett.* **1980**, *21*, 3731. (b) Kosak, T. M.; Conrad, H. A.; Korich, A. L. *Eur. J. Org. Chem.* **2015**, *2015*, 7460. (c) Ryu, I.; Matsubara, H.; Yasuda, S. *J. Am. Chem. Soc.* **2002**, *124*, 12946. (d) Sumida, Y.; Harada, R.; Kato-Sumida, T. *Org. Lett.* **2014**, *16*, 6240.
(12) Iqbal, S. A.; Pahl, J.; Yuan, K.; Ingleson, M. *Chem. Soc. Rev.* **2020**, *49*, 4564.
(13) Zou, X.; Zhao, H.; Li, Y. *J. Am. Chem. Soc.* **2019**, *141*, 5334.
(14) Dai, H.; Yu, J. *J. Am. Chem. Soc.* **2012**, *134*, 134.
(15) Murphy, J. M.; Liao, X.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 15434.
(16) Meng, F.; McGrath, K. P.; Hoveyda, A. H. *Nature* **2014**, *513*, 367.
(17) Wang, J. B. *Concise Course of Physical Organic Chemistry*; Peking University Press: 2013.


https://dx.doi.org/10.1021/acs.orglett.0c02552
*Org. Lett.* XXXX, XXX, XXX−XXX