HETEROCYCLES, Vol. 103, No. 2, 2021, pp. 670 - 677. © 2021 The Japan Institute of Heterocyclic Chemistry
Received, 16th November, 2020, Accepted, 7th December, 2021, Published online, 24th December, 2020
DOI: 10.3987/COM-20-S(K)45

GENERATION OF MONOARYL-λ^3-IODANES FROM ARYLBORON COMPOUNDS THROUGH *IPSO*-SUBSTITUTION

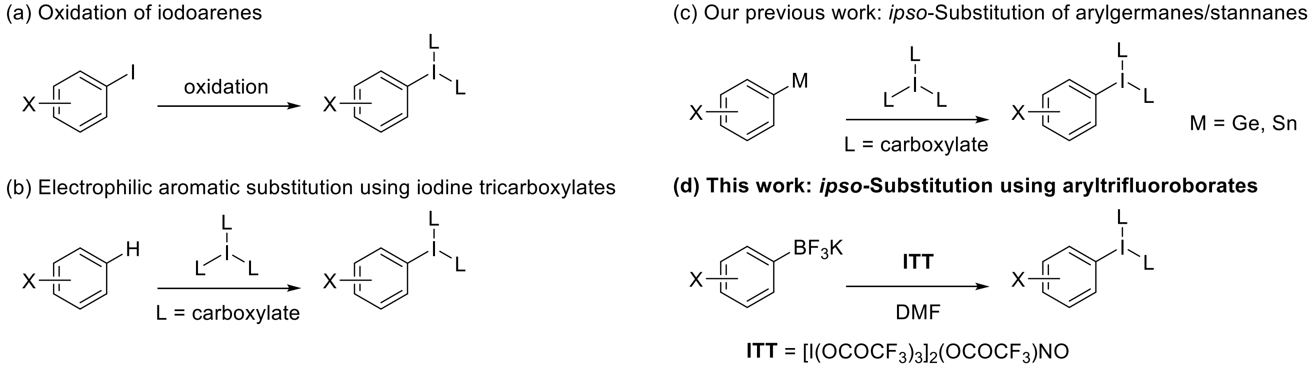
Ayako Nakano,[†] Yukino Okabe,[†] Keitaro Matsuoka,[†] Narumi Komami,[†] Keito Watanabe,[†] Masahiro Kojima,[†] Tatsuhiko Yoshino,[†]* and Shigeki Matsunaga[†,‡]*

[†]Faculty of Pharmaceutical Sciences, Hokkaido University, Kita-ku, Sapporo 060-0812, Japan. [‡]Global Station for Biosurfaces and Drug Discovery, Hokkaido University, Sapporo 060-0812, Japan. E-mail: tyoshino@pharm.hokudai.ac.jp, smatsuna@pharm.hokudai.ac.jp

Dedicated to Professor Yasuyuki Kita on the occasion of his 77th birthday

Abstract – Monoaryl-λ^3-iodanes serve as versatile oxidants and arylating reagents in organic synthesis. In addition to the oxidation of iodoarenes, electrophilic aromatic substitution reactions using iodine tricarboxylates have been used for the synthesis of monoaryl-λ^3-iodanes. Here, we report that *ipso*-substitution reactions of aryltrifluoroborates with iodine tris(trifluoroacetate) in DMF or DMA smoothly produced monoaryl-λ^3-iodanes, which were readily converted to aryliodonium ylides. We also demonstrated that sequential C–H borylation and the *ipso*-substitution efficiently introduced the I(III) group under steric control.

Monoaryl-λ^3-iodanes ($ArIL_2$) are widely used versatile reagents in organic synthesis that exhibit mild and unique reactivity. These compounds are predominantly used as oxidants for various transformations, wherein iodoarenes (ArI) are eliminated as byproducts. On the other hand, $ArIL_2$ have been increasingly employed as arylating reagents to enable the facile introduction of the aryl moiety into the reaction products.[1] In this context, iodonio-Claisen rearrangement reactions are unique and attractive ways to use $ArIL_2$ as arylating reagents,[2,3] leading to the introduction of a 2-iodoaryl group into a conjugate carbon nucleophile without cleavage of the aryl-iodine bond. Furthermore, iodonium ylides that bear a spirocyclic scaffold are readily prepared from $ArIL_2$ and serve as precursors for ^{18}F positron emission tomography (PET) probes.[4,5] To further expand the applications of $ArIL_2$ in such arylating reactions, the development of efficient synthetic routes of $ArIL_2$ that contain multiple functional groups is essential. Although the oxidation of aryl iodides represents a straightforward and well-documented way to synthesize $ArIL_2$ (**Scheme 1a**),[6-13] the functional group compatibility is of great concern when the substrates contain oxidizable functional groups. To circumvent this problem, a direct introduction of the IL_2 fragment into aromatic rings using iodine tricarboxylates without the oxidation step has been investigated in several studies. Electrophilic aromatic substitution reactions using $[I(OCOCF_3)_3]_2(OCOCF_3)NO$ (ITT) was reported by Maletina in 1974,[14] followed by Kurosawa in 1987,[15] and Wirth in 2018 (**Scheme 1b**).[16] In these reactions, the IL_2 fragment is generally introduced at the most nucleophilic position of the substrate. To enable the synthesis of a wider range of $ArIL_2$ regardless of the electronic nature of the substrate, we have focused on *ipso*-substitution reactions of arylgermanes and (hetero)arylstannanes with iodine tricarboxylates $I(OCOCR_3)_3$ (R = H, F) (**Scheme 1c**).[17] These *ipso*-substitution reactions proceed under very mild reaction conditions and exhibit good chemo- and site-selectivity to afford multi-functionalized products. Compared to arylgermanes and arylstannanes, arylboron derivatives are much more attractive aryl sources due to their low cost and toxicity, which prompted us to also investigate their *ipso*-substitution reactions[18] with iodine tricarboxylates. Herein, we report that aryltrifluoroborates[19] smoothly react with ITT to afford the corresponding $ArIL_2$ using DMF or DMA as the solvent (**Scheme 1d**). Even though Wirth has reported that ITT reacts with $B(C_6F_5)_3$ to provide $C_6F_5I(OCOCF_3)_2$ and $(C_6F_5)_2IOCOCF_3$,[16a] the reaction scope and synthetic utility have not been elucidated.


(a) Oxidation of iodoarenes

(b) Electrophilic aromatic substitution using iodine tricarboxylates

(c) Our previous work: *ipso*-Substitution of arylgermanes/stannanes

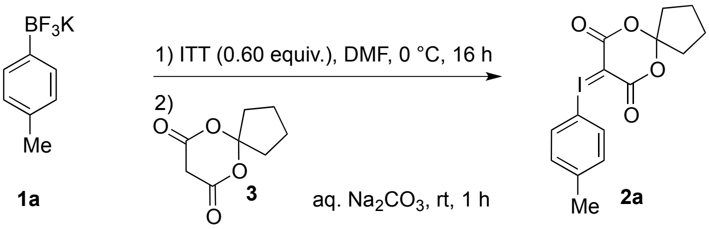
(d) This work: *ipso*-Substitution using aryltrifluoroborates

ITT = $[I(OCOCF_3)_3]_2(OCOCF_3)NO$

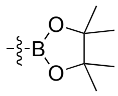
Scheme 1. Synthesis of monoaryl-λ^3-iodanes

After intensive screening of the reaction conditions, we found that aryltrifluoroborate **1a** reacted with ITT in DMF at 0 °C (Table 1, entry 1). The direct treatment of the reaction mixture with an aqueous basic solution of Meldrum's acid derivative **3** afforded iodonium ylide **2a** in good yield (80% ^{1}H NMR yield; 74% isolated yield). When boronic acid or boronic acid esters (**4a**–**6a**) were used as substrates, **2a** was obtained only in lower yields possibly due to inferior nucleophilicity (entries 2–4).[20] MIDA ester **7a**[21] (entry 5) and triolborate **8a**[22] (entry 6) did not afford **2a**, indicating that the *ipso*-substitution reaction could be sensitive to steric hindrance. Thus, the high nucleophilicity and low steric hindrance of trifluoroborate **1a** could be crucial for the high reactivity.[20] The choice of the reaction solvent was also important (entries 7–9). The reaction in DCM, which was used in our previous study,[17] did not provide **2a** (entry 7), while **2a** was obtained in moderate yield in EtCN (entry 8, 41%). The use of DMA led to a yield similar to that in DMF (entry 9, 77%). At this point, we think that the good solubility of trifluoroborate salt **1a** in polar solvents contributes significantly to the good reactivity.

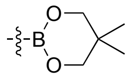
Table 1. Investigation of the reaction conditions for the *ipso*-substitution reactions of arylboron compounds with ITT[a]



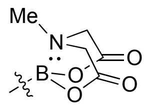
Entry	Deviation from the standard conditions	Yield[b] [%]
1	None	80(74)[c]
2	Ar-Bpin (**4a**) instead of **1a**	12
3	Ar-Bnep (**5a**) instead of **1a**	20
4	Ar-B(OH)$_2$ (**6a**) instead of **1a**	32
5	Ar-BMIDA (**7a**) instead of **1a**	0
6	Ar-triolborate (**8a**) instead of **1a**	0
7	DCM instead of DMF	0
8	EtCN instead of DMF	41
9	DMA instead of DMF	77



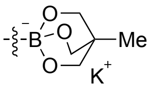
Bpin, **4a**



Bnep, **5a**



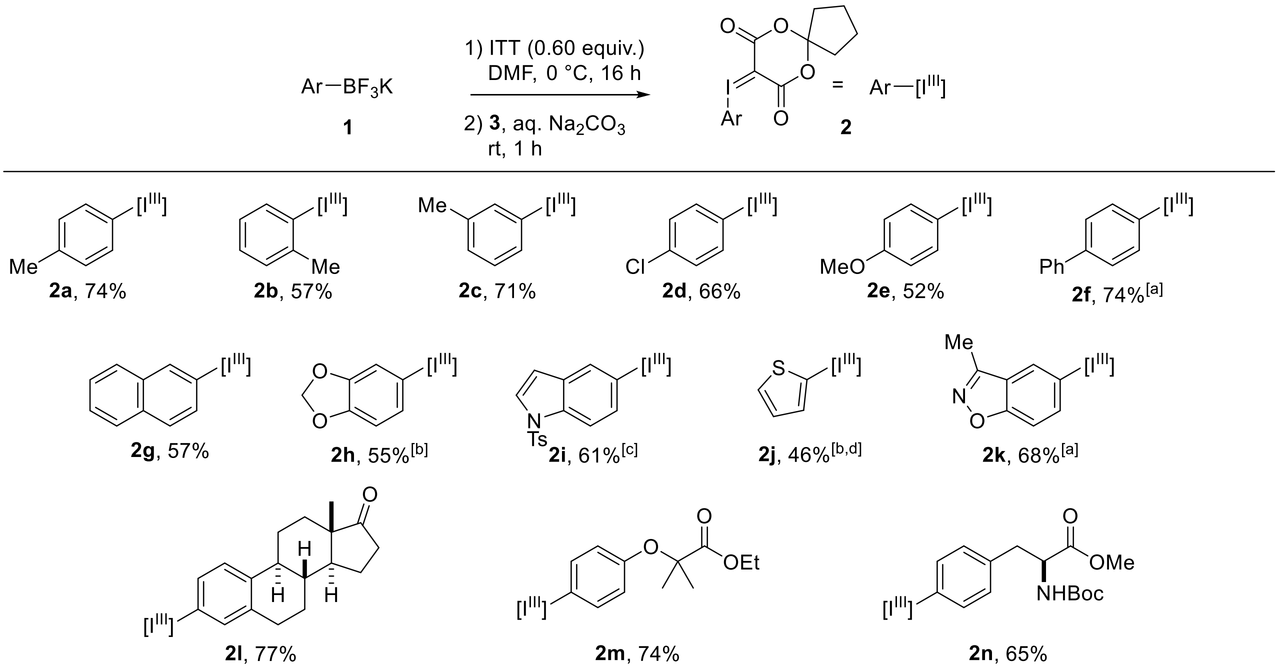
BMIDA, **7a**



triolborate, **8a**

[a] Reaction conditions: 1) **1a** (0.10 mmol), ITT (0.06 mmol) in DMF (1.0 mL) for 16 h at 0 °C; 2) **3** (0.20 mmol), aq. Na$_2$CO$_3$ (15% w/v, 1.0 mL) for 1 h at room temperature. [b] Determined by ^{1}H NMR analysis of the crude mixture using 1,1,2,2-tetrachloroethane as the internal standard. [c] Isolated yield on a 0.30 mmol scale. DMF = *N*,*N*-dimethylformamide. DCM = dichloromethane. DMA = *N*,*N*-dimethylacetamide. EtCN = propionitrile.

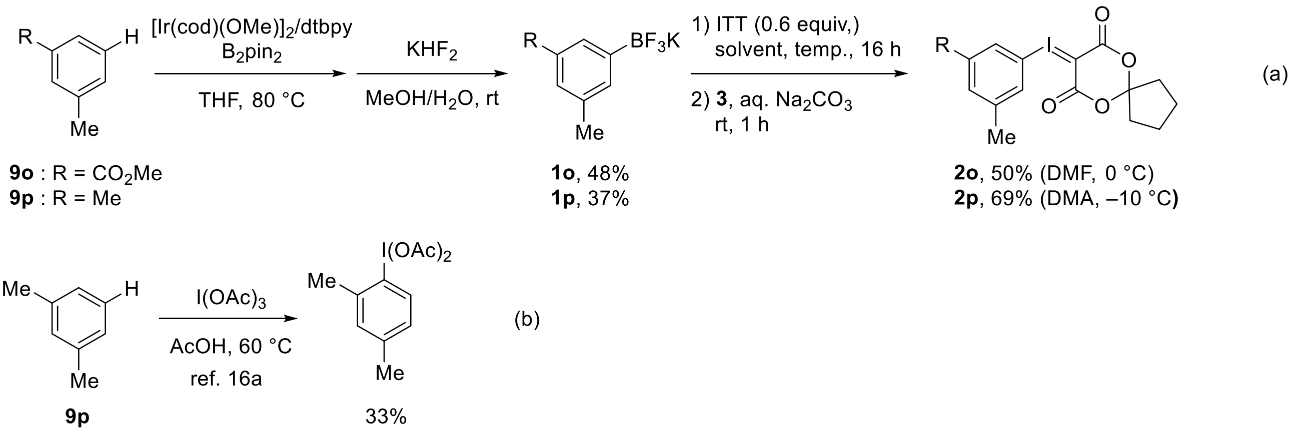
Subsequently, we applied the optimized conditions (Table 1, entry 1) to aryltrifluoroborates **1** that contain various functional groups, and the results are summarized in **Scheme 2**. In all cases, the generated monoaryl-λ^3-iodane (ArIL$_2$) was converted to the corresponding iodonium ylide **2** and isolated by chromatographic purification or recrystallization. Electron-rich as well as electron-deficient aryltrifluoroborates smoothly underwent the site-selective *ipso*-substitution and afforded the corresponding ylides in a moderate to good yield (**2a**–**2g**). When we used an electron-rich aryltrifluoroborate such as **2m**, a small amount of the corresponding diaryliodonium salt was observed in the NMR analysis of the crude mixture. Regardless of the substitution pattern, the formation of the C–I(III) bond proceeded at the *ipso*-position relative to the borate group. Then, we investigated heterocyclic substrates (**1h**–**1k**), including an oxidizable indole derivative (**1i**). Although the standard reaction conditions afforded lower yields, probably on account of some side reactions, the corresponding iodonium ylides (**2h**–**2k**) were obtained in moderate yields by decreasing the reaction temperature and/or the amount of ITT. Furthermore, aryltrifluoroborates derived from estrone (**1l**), a fibrate-like structure (**1m**), and tyrosine (**1n**) provided iodonium ylides **2l**–**2n** in 65–77% yield, validating the applicability of our protocol for the synthesis of functionalized, biologically active molecules.



Reaction conditions: 1) **1** (0.30 mmol), ITT (0.18 mmol) in DMF (3.0 mL) for 16 h at 0 °C; 2) **3** (0.60 mmol), aq. Na_2CO_3 (15% w/v, 3 mL) for 1 h at room temperature. [a] –20 °C. [b] ITT (0.16 mmol). [c] –10 °C. [d] –40 °C.

Scheme 2. Substrate scope of the *ipso*-substitution reactions of aryltrifluoroborates **1** with ITT

In order to further demonstrate the utility of the developed protocol, we synthesized iodonium ylides via sequential C–H borylation and *ipso*-substitution reactions using ITT (**Scheme 3**). The iridium-catalyzed C–H borylation of aromatic compounds is a well-established method for the introduction of boron-based functional groups at the sterically most accessible position.[23] Thus, the integration of the C–H borylation and the *ipso*-substitution protocol could potentially allow us to introduce the I(III) moiety under steric rather than electronic control. Therefore, we subjected 1,3-disubstituted benzenes (**9o**, **9p**) to the reported conditions for Ir-catalyzed C–H borylation using B_2pin_2.[24] The obtained arylboronates were then directly converted into the corresponding aryltrifluoroborates (**1o**, **1p**). In the end, treatment of **1o** and **1p** with ITT followed by Meldrum's acid derivative **3** provided iodonium ylides **2o** and **2p** in 50% and 69% yield, respectively (Scheme 3a). Wirth and co-workers reported a direct electrophilic aromatic substitution reaction of *m*-xylene **9p** with $I(OAc)_3$ to give an $ArI(OAc)_2$, but the site-selectivity was dominated by the electronic factor (Scheme 3b).[16a] Thus, the C–H borylation/*ipso*-substitution protocol exhibits the site-selectivity complementary to the direct substitution reaction.



Scheme 3. Sequential C–H borylation and *ipso*-substitution reactions for the synthesis of iodonium ylides

In summary, we have demonstrated that *ipso*-substitution reactions of aryltrifluoroborates **1** with $[I^{III}(OCOCF_3)_3]_2(OCOCF_3)NO$ (ITT) in DMF or DMA provided monoaryl–λ^3-iodanes, which could be readily converted to iodonium ylides **2**. In addition, a sequential C–H borylation and *ipso*-substitution protocol enables the introduction of the I(III) moiety under steric rather than electronic control. The present method would enable facile access to monoaryl–λ^3-iodanes and iodonium ylides and facilitate the development of arylation reactions and other chemical reactions using such hypervalent iodine reagents in organic synthesis.

ACKNOWLEDGEMENTS

This work was supported in part by JSPS KAKENHI Grant Number 19K22177. We thank the Open Facility, Global Facility Center, Creative Research Institution, Hokkaido University for the high-resolution mass spectrometry analysis.

SUPPORTING INFORMATION

Supplementary data (synthesis of trifluoroborates, experimental procedures, characterization data, and ^{1}H, ^{13}C, and ^{19}F NMR spectra) associated with this article can be found, in the online version, at URL: https://www.heterocycles.jp/newlibrary/downloads/PDFsi/26896/103/2

REFERENCES

1. For general reviews on hypervalent iodine compounds, see: (a) V. V. Zhdankin, Hypervalent Iodine Chemistry: Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds, Wiley, New York, United States 2014; (b) T. Wirth, Hypervalent Iodine Chemistry *Top. Curr. Chem.*, Vol. 373, Springer, Berlin, Germany 2016; (c) M. Ochiai, *Chem. Rec.*, 2007, **7**, 12; (d) T. Dohi and Y. Kita, *Chem. Commun.*, 2009, 2073; (e) T. Dohi, M. Ito, N. Yamaoka, K. Morimoto, H. Fujioka, and Y. Kita, *Tetrahedron*, 2009, **65**, 10797.
2. W. W. Chen, A. B. Cuenca, and A. Shafir, *Angew. Chem. Int. Ed.*, 2020, **59**, 16294.
3. For early studies on reductive iodonio-Claisen rearrangement reactions, see: (a) K. S. Lee, D. Y. Kim, and D. Y. Oh, *Tetrahedron Lett.*, 1988, **29**, 667; (b) M. Ochiai, T. Ito, Y. Takaoka, and Y. Masaki, *J. Am. Chem. Soc.*, 1991, **113**, 1319. For related recent reports, see: (c) H. R. Khatri and J. Zhu, *Chem. Eur. J.*, 2012, **18**, 12232; (d) Z. Jia, E. Gálvez, R. M. Sebastián, R. Pleixats, Á. Álvarez-Larena, E. Martin, A. Vallribera, and A. Shafir, *Angew. Chem. Int. Ed.*, 2014, **53**, 11298; (e) M. Hori, J.-D. Guo, T. Yanagi, K. Nogi, T. Sasamori, and H. Yorimitsu, *Angew. Chem. Int. Ed.*, 2018, **57**, 4663; (f) J. Tian, F. Luo, C. Zhang, X. Huang, Y. Zhang, L. Zhang, L. Kong, X. Hu, Z.-X. Wang, and B. Peng, *Angew. Chem. Int. Ed.*, 2018, **57**, 9078; (g) Y. Wu, S. Bouvet, S. Izquierdo, and A. Shafir, *Angew. Chem. Int. Ed.*, 2019, **58**, 2617. For other examples, see ref. 2.
4. (a) N. Satyamurthy and J. R. Barrio, 2010, WO2010/117435 A2; (b) B. H. Rotstein, N. A. Stephenson, N. Vasdev, and S. H. Liang, *Nat. Commun.*, 2014, **5**, 4365; (c) L. Wang, O. Jacobson, D. Avdic, B. H. Rotstein, I. D. Weiss, L. Collier, X. Chen, N. Vasdev, and S. H. Liang, *Angew. Chem. Int. Ed.*, 2015, **54**, 12777; (d) B. H. Rotstein, L. Wang, R. Y. Liu, J. Patteson, E. E. Kwan, N. Vasdev, and S. H. Liang, *Chem. Sci.*, 2016, **7**, 4407; (e) J. E. Jakobsson, G. Grønnevik, and P. J. Riss, *Chem. Commun.*, 2017, **53**, 12906.
5. For a review on monoaryliodonium ylides in organic synthesis, see: M. S. Yusubov, A. Yoshimura, and V. V. Zhdankin, *ARKIVOC*, 2016, **i**, 342.
6. For oxidation reactions with peracetic acid, see: J. G. Sharefkin and H. Saltzman, *Org. Synth.*, 1963, **43**, 62.
7. For oxidation reactions with *m*CPBA, see: (a) E. A. Merritt, V. M. T. Carneiro, L. F. Silva Jr., and B. Olofsson, *J. Org. Chem.*, 2010, **75**, 7416; (b) M. Iinuma, K. Moriyama, and H. Togo, *Synlett*, 2012,

23, 2663 and references therein.

8. For oxidation reactions with $NaBO_3$, see: (a) A. Mckillop and D. Kemp, *Tetrahedron*, 1989, **45**, 3299; (b) H. Togo, T. Nabana, and K. Yamaguchi, *J. Org. Chem.*, 2000, **65**, 8391; (c) M. D. Hossain and T. Kitamura, *J. Org. Chem.*, 2005, **70**, 6984.
9. For oxidation reactions with Oxone, see: A. A. Zagulyaeva, M. S. Yusubov, and V. V. Zhdankin, *J. Org. Chem.*, 2010, **75**, 2119.
10. For oxidation reactions with Selectfluor, see: (a) C. Ye, B. Twamley, and J. M. Shreeve, *Org. Lett.*, 2005, **7**, 3961; (b) L. Qin, B. Hu, K. D. Neumann, E. J. Linstad, K. McCauley, J. Veness, J. J. Kempinger, and S. G. DiMagno, *Eur. J. Org. Chem.*, 2015, 5919.
11. For oxidation reactions with $NaClO \cdot 5H_2O$, see: A. Watanabe, K. Miyamoto, T. Okada, T. Asawa, and M. Uchiyama, *J. Org. Chem.*, 2018, **83**, 14262.
12. For formal oxidation reactions via transylidation, see: (a) M. Ochiai, N. Tada, T. Okada, A. Sota, and K. Miyamoto, *J. Am. Chem. Soc.*, 2008, **130**, 2118; (b) M. Ochiai, T. Okada, N. Tada, and A. Yoshimura, *Org. Lett.*, 2008, **10**, 1425.
13. For oxidation reactions with O_2/MeCHO, see: A. Maity, S.-M. Hyun, and D. C. Powers, *Nat. Chem.*, 2018, **10**, 200.
14. I. I. Maletina, V. V. Orda, and L. M. Yagupolskii, *Zh. Org. Khim.*, 1974, **10**, 294.
15. N. Fukuyama, H. Nishino, and K. Kurosawa, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 4363.
16. (a) T. Hokamp, L. Mollari, L. C. Wilkins, R. L. Melen, and T. Wirth, *Angew. Chem. Int. Ed.*, 2018, **57**, 8306; (b) T. Hokamp and T. Wirth, *J. Org. Chem.*, 2019, **84**, 8674.
17. (a) N. Komami, K. Matsuoka, A. Nakano, M. Kojima, T. Yoshino, and S. Matsunaga, *Chem. Eur. J.*, 2019, **25**, 1217; (b) K. Matsuoka, N. Komami, M. Kojima, T. Yoshino, and S. Matsunaga, *Asian J. Org. Chem.*, 2019, **8**, 1107.
18. *ipso*-Substitution reactions using organoboron compounds for the synthesis of iodonium salts were reported: (a) M. Ochiai, M. Toyonari, T. Nagaoka, D. W. Chen, and M. Kida, *Tetrahedron Lett.*, 1997, **38**, 6709; (b) Y. Masuda and A. Arase, *Bull. Chem. Soc. Jpn.*, 1978, **51**, 901; (c) M. Yoshida , K. Osafune, and S. Hara, *Synthesis*, 2007, 1542. See also ref. 10b.
19. S. Darses and J.-P. Genet, *Chem. Rev.*, 2008, **108**, 288.
20. G. Berionni, B. Maji, P. Knochel, and H. Mayr, *Chem. Sci.*, 2012, **3**, 878.
21. J. L. Anthony, S. Crillo, and M. D. Burke, *Acc. Chem. Res.*, 2015, **48**, 2297.
22. Y. Yamamoto, *Heterocycles*, 2012, **85**, 799.
23. For reviews on $C(sp^2)$–H borylation reactions, see: (a) T. Ishiyama and N. Miyaura, *Chem. Rec.*, 2004, **3**, 271; (b) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, and J. F. Hartwig, *Chem. Rev.*, 2010, **110**, 890; (c) L. Xu, G. Wang, S. Zhang, H. Wang, L. Wang, L. Liu, J. Jiao, and P.

Li, *Tetrahedron*, 2017, **73**, 7123.

24. (a) J. M. Murphy, X. Liao, and J. F. Hartwig, *J. Am. Chem. Soc.*, 2007, **129**, 15434; (b) J. M. Murphy, C. C. Tzschucke, and J. F. Hartwig, *Org. Lett.*, 2007, **9**, 757.