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Relative Rates of Alkylation for B-Substituted Triarylphosphines: An ortho-Boron Group Enhances Reactivity on Phosphorus.

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Relative Rates of Alkylation for B-Substituted Triarylphosphines: An *ortho*-Boron Group Enhances Reactivity on Phosphorus.

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Advancements in main-group catalysis are contingent on our ability to quantify effects that enhance reactivity in these systems. Herein we report the rates of alkylation for several substituted phosphines. We report that by incorporating a single pinacolato(boron) group in the *ortho*- position on triphenylphosphine, the rate of substitution with benzyl bromide is approximately 4.7 times faster than the parent compound as measured by intial rates. The corresponding meta- and *para*-isomers are only 1.3 and 1.5 times as fast, respectively. Using X-ray crystallographic data and quantum chemical calculations, we propose this rate acceleration occurs from an O to P electrostatic interaction which stabilizes the transtion state.

Transition-metal catalysis has had a tremendous impact on society and now is an indispensable tool in chemistry.[1] These reactions have been optimized extensively due to the multitude of tunable reaction parameters available; however, the remaining limitations with this technology, such as functional group compatibility, cost, toxicity, and sustainability are often directly related to the unchanging component of these reactions: the transition-metal itself. Consequently, the past decade has witnessed a dramatic increase in studies using main group[2] elements to enable new bond forming reactions that are difficult to achieve using their transition-metal counterparts.[3] Reactions based on P are especially promising because of phosphorus' ability to undergo P(III)/P(V) redox cycling, a critical property needed to mimic transition-metal cross-coupling reactions.

Exciting stoichiometric[4] and catalytic reactions[5,6] using P(III) have been developed, however several challenges with this platform make cross-coupling difficult. Specifically, the ability of phosphorus to activate more inert bonds (e.g., aryl halides and heteroaryl halides) is hampered by the inability of phosphorus to associate with the π-system of these compounds for directed oxidative addition. Rather, such P(V) compounds are generated using the inherent nucleophilicity of P(III) to add to activated heteroaryl rings. Indeed, the direct oxidative addition of aryl halides to P(III) centres is seldom observed but would be uniquely enabling to achieve a catalytic P(III)–P(V) cross-coupling reaction.[5b] Thus, detailed mechanistic understanding of the factors that influence phosphorus reactivity and redox cycling are needed to enhance the reactivity on P(III).

As a part of a research program aimed at stabilizing carbenes using main group catalysts,[7] we became interested in quantifying potential cooperative effects between main group elements in intramolecular systems. The rationale for studying these effects was to improve reaction rates and turnover on main group elements, specifically P(III). In that regard, we hypothesized that an *ortho*-Bpin group could enhance the rate of substitution reactions by interacting with phosphorus. Our hypothesis seemed reasonable given boron-phosphorus synergy has been exploited in frustrated Lewis acid base pair (FLP) catalysis for some time, where together these elements enable transformations that neither can accomplish alone.[8] Indeed, phosphine/boranes have been used to trap CO_2[9] and difluorocarbene,[10] among other transformations. To this end, we used S_N2 substitution reactions as a metric to quantify the effects an *ortho*-Bpin group could have on a proximal phosphorus atom (Figure 1).[11]

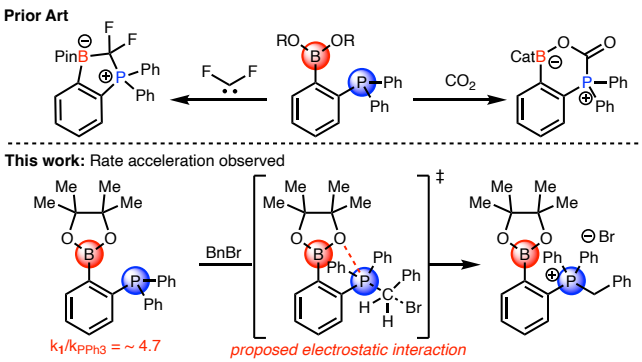

Figure 1: Prior art in small molecule activation with phosphine/boranes and summary of results in this study.

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We began these studies by synthesizing a variety of functionalized triarylphosphines to measure their rates of reaction with alkyl halides (Figure 2).[12] We synthesized the *ortho*-borylphosphine **1**,[13] *meta*-borylphosphine **2**,[14] and *para*-borylphosphine **3**.[15] We envisioned the relative rates of reaction of phosphines **1**–**3** would shed light on the effect of the position of the Bpin on the ring. At the outset of these studies, we were unsure whether phosphine **1**, containing the inductively donating *ortho*-Bpin group,[16] would be slower than its meta- and *para*- isomers because S_N2 reactions are sensitive to the steric environment around the reaction centre.[17] Additionally, we surveyed a variety of electronically and sterically distinct groups *ortho*- to the phosphorus atom as controls. Compounds **4** and **6** containing, a 1,3-dioxolane and *ortho*- phenyl group, respectively, were used to test the effects of sterics around the P-atom. Compounds containing an *ortho*-cyano (**5**), *ortho*-bromo (**7**), and *ortho*-methoxy (**8**) groups were used to probe the effect of resonance donating or withdrawing groups on the P-atom.

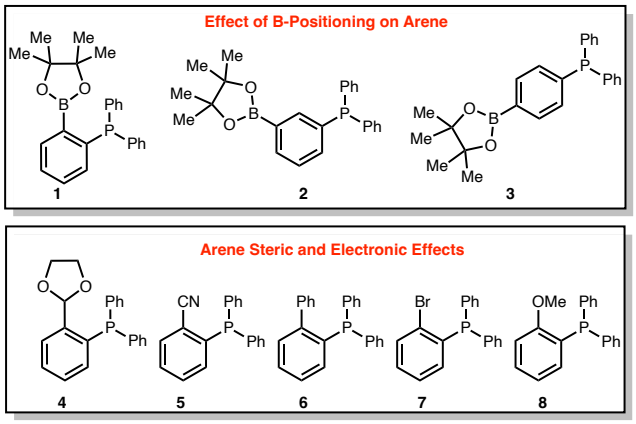

Figure 2: Phosphine compounds used in this study.

With phosphines in hand, we studied their rates of reaction with benzyl bromide by monitoring the formation of the corresponding phosphonium bromide salt using ^{1}H NMR (see Supporting Information for details). Upon reacting borylated phosphines **1**–**3** (7.0 mmol) with benzyl bromide (1.0 equiv) in $CDCl_3$ at 23 °C, we observed the following trends (Figure 3). Each of the borylated phosphines tested reacted faster than PPh_3. Using the slope of the concentration vs time curve at early time points (up to 500 s) revealed that the *para*- and *meta*-substituted Bpin phosphines were only moderately faster than PPh_3 (1.3 and 1.5 times as fast, respectively). Surprisingly, we found the *ortho*-Bpin compound **1** to be the fastest of the substituted derivatives, which reacted 4.7 times faster than PPh_3 despite the proximity of the Bpin group to the reacting P atom.

Next, we measured the rates of reaction of various *ortho*-functionalized phosphines with differing electronic and steric parameters and compared them to borylated phosphine **1**. Electron-withdrawing groups, as expected, significantly slowed the rate of reaction on the P atom. *ortho*-Bromo compound **7** reacted 4.9 times slower (k_{PPh3}/k_7 = 0.21) than triphenylphosphine. The rate of reaction for *ortho*-CN phosphine **5** was too slow to measure at 23 ºC, providing less than 1% yield of the corresponding phosphonium ion after 70 minutes. Dioxolane compound **4** reacted 2.3 times faster than Br-phosphine **7**, but slower than triphenyl phosphine (k_{PPh3}/k_4 = 0.47). We attribute this difference in rate to the size and inductive withdrawing nature of the acetal group. Interestingly, the *ortho*-phenyl compound reacted slightly faster than PPh_3, despite the increased steric demand of the phenyl group, relative to a hydrogen atom (k_{PPh3}/k_6 = 0.94). As expected, a strongly donating *ortho*-methoxy group reacted 7.2 times faster than PPh_3.

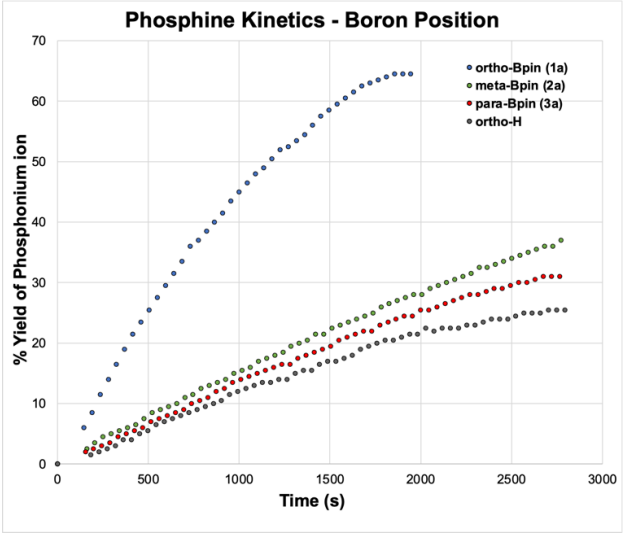

Figure 3: Rates of phosphonium ion formation using Bpin substituted phosphines. Phosphines **1**–**3** (7.0 mmol), benzyl bromide (1.0 equiv) in $CDCl_3$ at 23 °C. Yields are based on ^{1}H NMR integrations relative to mesitylene as an internal standard.

The results obtained indicate the significant impact an *ortho*-pinacolato(boron) group has on phosphine nucleophilicity, which can be rationalized by the inductive effect of B and conformational changes. Recent studies suggest the size of the Bpin group is small (A value = 0.34),[18] so the relative size of the Bpin group may have little ability to block the P-centre. Instead, this group may promote a "gearing" effect of the phenyl rings, placing the P-lone pair in a more favourable conformation for substitution.[19]

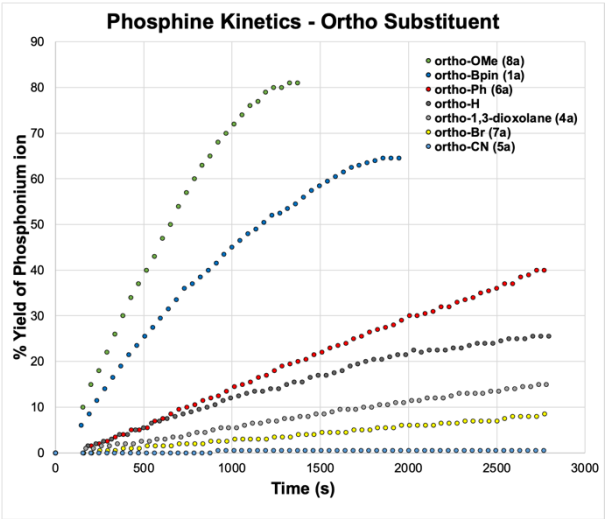

Figure 4: Rates of phosphonium ion formation using different ortho-substituted phosphines. Phosphines **1** and **4**–**8** (7.0 mmol), benzyl bromide (1.0 equiv) in $CDCl_3$ at 23

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°C. Yields are based on ^{1}H NMR integrations relative to mesitylene as an internal standard.

To further probe this effect, we grew single crystals of phosphonium salt **1a** and analysed its conformation in the solid state. The X-ray crystallographic data depicted in Figure 5 revealed several important features. First, there is no association of Br with the phosphonium ion centre or the Bpin group, which stands in direct contrast to similar fluoro phosphonium compounds that are known to coordinate fluoride ions with high affinities.[20] Second, each of the C–P bond distances for phosphonium **1a** were elongated compared to the parent phosphonium ion (benzyltriphenylphosphonium bromide).[21] For example, the C(benzylic)–P bond distance in **1a** is 1.822(5) Å while that of the parent compound is 1.803(3) Å. The C(aromatic)–P bond distances for phosphonium ion **1a** are 1.815(5) Å, 1.803(4) Å, and 1.795(4) Å, while for benzyltriphenylphosphonium bromide the C(aromatic)–P bond distances are 1.803(3) Å, 1.794(4) Å and 1.790(4) Å. The observed bond lengthening in **1a** suggests a donor-acceptor interaction. We noted the O to P distance in **1a** was 3.217(3) Å. This distance was remarkably similar to that reported by Tang and co-workers for *ortho*-methylmethoxy triphenylphosphonium bromide (3.218(3) Å) and also suggests an electrostatic interaction between the oxygen lone pair and the phosphorus atom.[22] This electrostatic interaction would be absent in the *meta*- and *para*- isomers **2** and **3**, so the increased rate of reaction (relative to PPh_3) is solely due to inductive effects. Similar *ortho*- interactions have been proposed to explain the increased rate of alkylation of *ortho*-anisylphosphines.[12b,23]

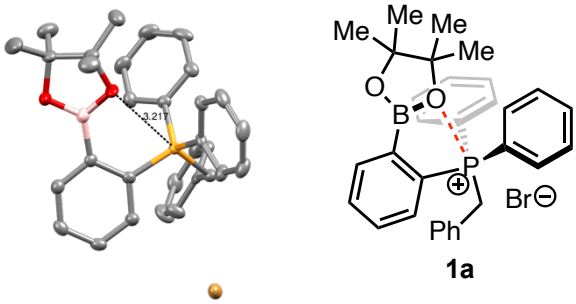

Figure 5: X-ray crystallographic data for phosphonium salt **1a** shows O–P interaction (green dotted line) of 3.217 Å. Red = oxygen, pink = boron, grey = carbon, white = hydrogen, orange = phosphorus, brown = bromine. Thermal ellipsoids represent 50% probability level.

Finally, we studied the substitution reaction for **1** and PPh_3 with BnBr as the electrophile using quantum chemical calculations. We located the transition states for the substitution reaction of **1** and PPh_3 with BnBr using the B3LYP level of theory and 6-311G(d) basis set for B, C, and using diffuse functions on O and P.[24–28] Consistent with experiment, we found that the barrier for the substitution reaction with borylated phosphine **1** was lower (18.2 kcal/mol) than the corresponding transition state using PPh_3 (19.8 kcal/mol). To understand the origins of this effect, we applied an energetic decomposition analysis approach to the transition states of these reactions.[29–31] Upon decomposing the transition state energies into kinetic, exchange-correlation, electrostatic (E_e), steric (E_s), and quantum (E_q) effect components, we found the electrostatic interaction in the transition state was the dominant factor contributing to this difference in reactivity (ΔE_e = 7.54 kcal/mol). Interestingly, we found steric factors also contributed to the higher reaction rate of borylated phosphine **1** (ΔE_e = 2.49 kcal/mol).[32] Since Bpin itself is much larger than an H atom, the steric energy difference lends support to the idea that an *ortho*-Bpin group places the P atom lone pair in a more favourable conformation[19] to react with the incoming electrophile, while also stabilizing the transition state through the proposed electrostatic interaction. In contrast, we believe the larger steric bulk of the 1,3-dioxolane group in **4** amplifies unfavourable steric interactions in the transition state at the expense of beneficial O–P electrostatic stabilization.[22]

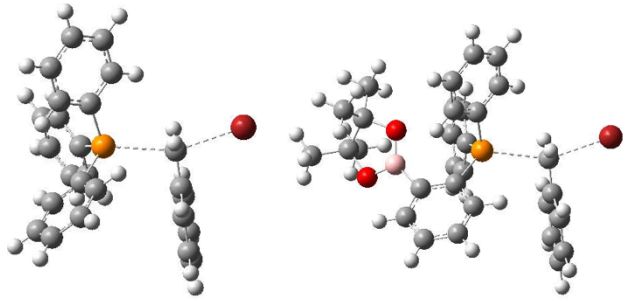

Figure 6: Calculated transitions states for phosphonium ion formation using (a) PPh_3 and (b) **1** in substitution reactions with BnBr. Red = oxygen, pink = boron, grey = carbon, white = hydrogen, orange = phosphorus, dark red = bromine.

In conclusion, we have measured the rate of substitution some mono-substituted triarylphosphines and found that an *ortho*-Bpin group increases the rate of reaction with alkyl halides. When considered with the X-ray crystallographic data collected, it appears that the nature of the increased rate of reaction for these systems can be attributed in part to an electrostatic stabilization of the resultant phosphonium ion (ΔE_e = 7.54 kcal/mol). Energy decomposition analysis using quantum chemical calculations supports the claim that the oxygen atom within the boronic ester group provides electrostatic stabilization within the transition state. Steric hindrance also contributes positively to this increased reaction rate (ΔE_e = 2.49 kcal/mol) by placing the P atom in a favourable conformation for substitution. Our future studies are aimed at identifying substitution patterns on B and P which substantially increase the rate of reactivity with alkyl and heteroaryl halides.

Author Contributions

Joseph P. Mancinelli: investigation, data curation. **Shubin Liu**: formal analysis, visualization. **Sidney M. Wilkerson Hill**: Conceptualization, supervision, writing-original draft, writing-reviewing and editing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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CCDC 2155960 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.

References

1 A. de Meijere, S. Bräse, and Martin Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More Vol. 1-3,* Wiley-VCH 2014.
2 P. P. Power, *Nature*, 2010, **463**, 171–177.
3 H. W. Moon and J. Cornella *ACS Catal.*, 2022, **12**, 1382–1393.
4 M. C. Hilton, R. D. Dolewski, A. McNally *J. Am. Chem. Soc.*, 2016, **138**, 13806.; b) X. Zhang, A. McNally, *Angew. Chem., Int. Ed.* 2017, **56**, 9833.; c) R. D. Dolewski, M. C. Hilton, A. McNally *Synlett*, 2018, **29**, 8.; d) R. G. Anderson, B. M. Jett, A. McNally, *Tetrahedron,* 2018, **74**, 3129.; e) J. L. Koniarczyk, D. Hesk, A. Overgard, I. W. Davies, A. McNally *J. Am. Chem. Soc*. 2018, **140** 1990.; f) C. Patel, M. Mohnike, M. C. Hilton, A. McNally, *Org. Lett*., 2018, **20**, 2607.; g) R. D. Dolewski, P. J. Fricke, A. McNally, *J. Am. Chem. Soc*., 2018, **140**, 8020.; h) R. G. Anderson, B. M. Jett, A. McNally*, Angew. Chem., Int. Ed*. 2018 **57**, 12514.; i) M. C. Hilton, X. Zhang, B. T. Boyle, J. V. Alegre-Requena, R. S. Paton, A. McNally, *Science,* 2018, **362,** 799.; j) X. Zhang, A. McNally, *ACS Catal.,* 2019, **9**, 4862.; k) J. L. Koniarczyk, J. W. Greenwood, J. V. Alegre-Requena, R. S. Paton, A. McNally, *Angew. Chem., Int. Ed*., 2019, **58**, 14882.; l) B. T. Boyle, M. C. Hilton, A. McNally, *J. Am. Chem. Soc*., 2019, *141*, 15441.; m) J. N. Levy, J. V. Alegre-Requena, R. Liu, R. S. Paton, A. McNally, *J. Am. Chem. Soc*., 2020, **142**, 11295.; n) B. T. Boyle, J. L. Koniarczyk, A. McNally, *Synlett*, 2021, **32**, 215.; o) J. W. Greenwood, B. T. Boyle, A. McNally, *Chem. Sci.,* 2021, **12**, 10538.; p) X. Zhang, K. G. Nottingham, C. Patel, J. V. Alegre-Requena, J. N. Levy, R. S. Paton, A. McNally, *Nature*, 2021, **594**, 217.; q) P. J. Fricke, R. D.; Doleski, A. McNally, *Angew. Chem., Int. Ed.,* 2021, **60**, 1.
5 a) For reviews, see: C. Xie, A. J. Smaligo, X.-R. Song, O. Kwon, *ACS Central Sci*., 2021, **7**, 536.; b) H. Guo, Y. C. Fan, Z. Sun, Y. Wu, O. Kwon., *Chem. Rev.,* 2018, **20**, 10049. b) J. M. Bayne, D. W. Stephan, *Chem. Soc. Rev*., 2016, **45**, 765.
6 a) J. M. Lipshultz, A. T. Radosevich, *J. Am. Chem. Soc*. 2021, **143**, 14487. b) S. Lim, A. T. Radosevich *J. Am. Chem. Soc.* 2020, *142*, 16188.
7 J. P. Mancinelli, S. M. Wilkerson-Hill, *ACS Catal.*, 2020, **10**, 11171.
8 a) G. Erker, D. W. Stephan, Eds. Frustrated Lewis Pairs II, Expanding the Scope. Springer, Berlin, 2013; b) G. Erker, D. W. Stephan, Eds. Frustrated Lewis Pairs I, Uncovering and Understanding. Springer, Berlin, 2013; c) J. C. Slootweg, A. R. Jupp, Eds. Frustrated Lewis Pairs. Cham, Switzerland. Springer, 2021.
9 R. Declercq, G. Bouhadir, D. Bourissou, M.-A. Légaré, M.-A. Courtemanche, K. S. Nahi, N. Bouchard, F.-G. Fontaine and L. Maron., *ACS Catal.* 2015, **5**, 2513.
10 V. O. Smirnov, A. D. Volodin, A. A. Korlyukov, A. D. Dilman *Angew. Chem., Int. Ed.*, 2020, **59**, 12428.
11 W. A. Henderson Jr., S. A. Buckler, *J. Am. Chem. Soc.,* 1960, **82**, 5794.
12 a) J. F. Bunnett, J. D. Reinheimer *J. Am. Chem. Soc.* 1962, **84**, 3284.; b) W. E. McEwen, W.-I. Shiau, Y.-I. Yeh, D. N. Schulz, R. U. Pagilagan, J. B. Levey, C. Symmes, Jr., G. O. Nelson, I. Granoth *J. Am. Chem. Soc.* 1975, **97***,* 1787., c) W. E. McEwen, J. E. Fountain, D. N. Schulz, W.-I. Shiau *J. Org. Chem.* 1976, **41**, 1684.
13 K. Fukuda, N. Iwasawa, J. Takaya, *Angew. Chem., Int. Ed.,* 2019, **58**, 2850.
14 P. Lustenberger, F. Diederich, *Helv. Chim. Acta.* 2000, **83**, 2865.
15 N. Suzuki, S. Yoneyama, K. Shiba, T. Hasegawa, Y. Masuyama, *Inorg. Chim. Acta,* 2018, **471**, 355.
16 C. Hansch, A. Leo, R. W. Taft, *Chem. Rev.* 1991, **91**, 165.
17 E.V. Anslyn and D.A. Dougherty, *Modern Physical Organic Chemistry*, University Science Books, 2006.
18 a) V. Fasano, A. W. McFord, C. P. Butts, B. S. L. Collins, N. Fey, R. W. Alder, V. K. Aggarwal, *Angew. Chem., Int. Ed.,* 2020, **59**, 22403. b) V. Fasano, A. W. McFord, C. P. Butts, B. S. L. Collins, N. Fey, R. W. Alder, V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2021, **60**, 20087.
19 a) C. Roussel, A. Lidén, M. Chanon, J. Metzger, J. Sandström., *J. Am. Chem. Soc.,* 1976, ***98*,** 2847.; b) H. Iwamura.; K. Mislow, *Acc. Chem. Res.,* **1988**, 21, 175.
20 a) T. W. Hundall, Y.-M. Kim, M. W. P. Bebbington, D. Bourissou, F. G. Gabbï, *J. Am. Chem. Soc*. 2008, **130**, 10890. b) H. Zhao, L. A. Leamer, F. P. Gabbaï, *Dalton Trans*., 2013, **42**, 8164.
21 V. Sharutin *CSD Commun.* 2016, DOI: 10.5517/ccdc.csd.cc14hs7n
22 J.-B. Zhu, H. Chen, S. Liao, Y.-X. Li, Y. Tang. *Org. Chem. Front.,* 2014, **1**, 1035.
23 Interactions invoking the O-atoms in boronic ester derivatives have recently been used to rationalize the regioselective outcomes of aniline borylation reactions, see: J. R. Montero Bastidas, A. Chhabra, Y. Feng, T. J. Oleskey, M. R. Smith III, R. E. Maleczka, Jr., *ACS Catal*. 2022, **12**, 2694.
24 See the supporting information for details.
25 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, D. Williams-Young, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman, and D. J. Fox, Gaussian 16, Revision C.01, Gaussian, Inc., Wallingford CT, 2019.
26 A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098.
27 C. Lee, W. Yang, R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
28 R. Ditchfield, W. J. Hehre, J. A. Pople, *J. Chem. Phys.*, 1971, **54**, 724.
29 M. Cossi, N. Rega, G. Scalmani, and V. Barone, *J. Comp. Chem.*, 2003, **24,** 669.

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30 J. P. Foster, F. Weinhold, *J. Am. Chem. Soc.*, 1980, **102**, 7211.
31 S.B. Liu, *J. Chem. Phys*., 2007, **126,** 244103.
32 C. Rong, B. Wang, D. Zhao, S.B. Liu, *WIREs Comp. Mol. Sci.*, 2020, **10**, e1461.

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