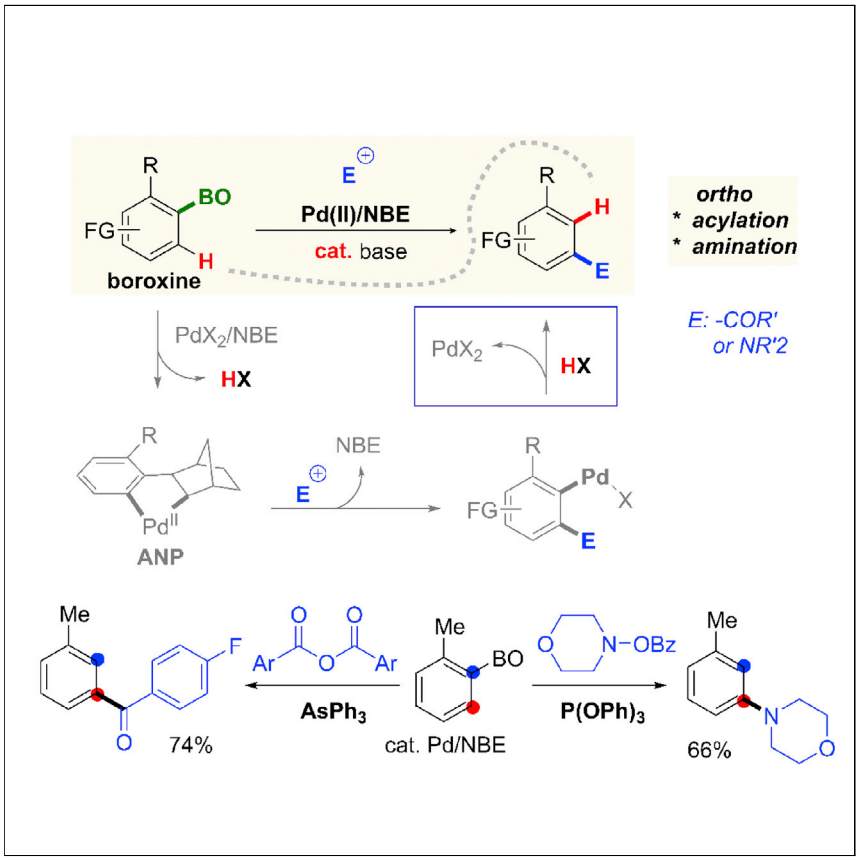
Chem

CellPress

Article

Redox-Neutral *ortho* Functionalization of Aryl Boroxines via Palladium/Norbornene Cooperative Catalysis



A redox-neutral *ortho* functionalization of aryl boroxines via palladium/norbornene cooperative catalysis is developed. The *ortho* amination and acylation are achieved with carboxylic acid anhydrides and *O*-benzoyl hydroxylamines as an electrophile, respectively, whereas protonation occurs at the *ipso* position. This transformation avoids using either extra oxidants and reductants or stoichiometric bases and acids. In addition, orthogonal chemoselectivity between aryl iodide and boroxine moieties is demonstrated for pathway divergence.

Renhe Li, Feipeng Liu, Guangbin Dong

gbdong@uchicago.edu

HIGHLIGHTS

First redox-neutral direct *ortho* functionalization of aryl boroxines

Proton as the second electrophile coupled at the *ipso* position

Avoiding stoichiometric bases in the Pd/NBE catalysis

Orthogonal chemoselectivity between aryl iodide and boroxine moieties

Li et al., Chem *5*, 1–11
April 11, 2019
https://doi.org/10.1016/j.chempr.2019.02.005

Please cite this article in press as: Li et al., Redox-Neutral *ortho* Functionalization of Aryl Boroxines via Palladium/Norbornene Cooperative Catalysis, Chem (2019), https://doi.org/10.1016/j.chempr.2019.02.005

Chem

CellPress

Article

Redox-Neutral *ortho* Functionalization of Aryl Boroxines via Palladium/Norbornene Cooperative Catalysis

Renhe Li,[1,3] Feipeng Liu,[1,2,3] and Guangbin Dong[1,4,*]

SUMMARY

Palladium/norbornene (Pd/NBE) cooperative catalysis, also known as the Catellani reaction, has become an increasingly useful method for site-selective arene functionalization; however, certain constraints still exist because of its intrinsic mechanistic pathway. Herein, we report a redox-neutral *ortho* functionalization of aryl boroxines via Pd/NBE catalysis. An electrophile, such as carboxylic acid anhydrides or *O*-benzoyl hydroxylamines, is coupled at the boroxine *ortho* position, and a proton as the second electrophile is introduced at the *ipso* position. This reaction does not require extra oxidants or reductants and avoids stoichiometric bases or acids, thereby tolerating a wide range of functional groups. In particular, orthogonal chemoselectivity between aryl iodide and boroxine moieties is demonstrated, which could be used to control reaction sequences. Finally, a deuterium-labeling study supports the *ipso* protonation pathway. This unique mechanistic feature could inspire the development of a new class of Pd/NBE-catalyzed transformations.

INTRODUCTION

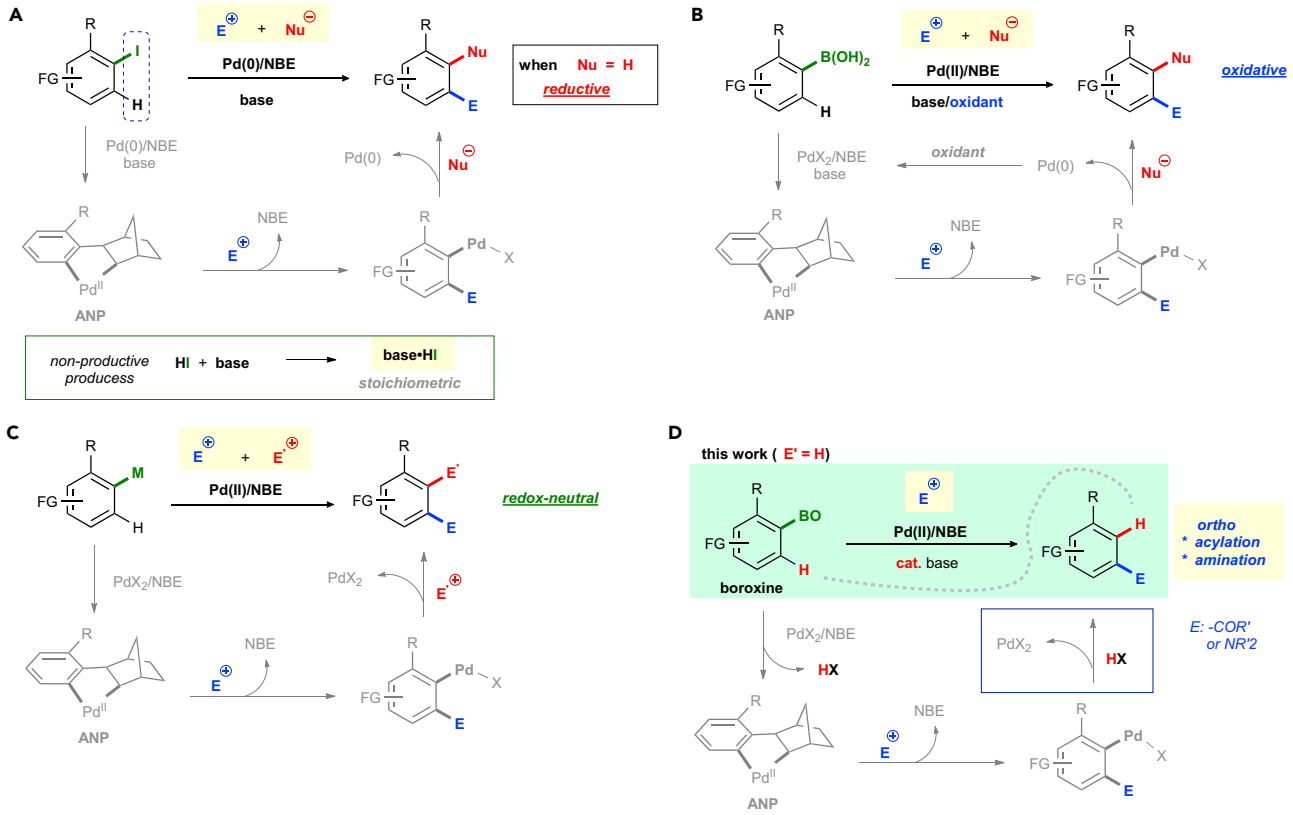
Site-selectivity control still represents an ongoing quest in organic synthesis.[1,2] Especially, site-selective functionalization of arenes has been playing a key role in preparing aromatic moieties ubiquitously found in drugs and agrochemicals. Recently, the palladium/norbornene (Pd/NBE) cooperative catalysis, pioneered by Catellani[3] and Lautens,[4] has emerged as a useful set of tools to access polysubstituted arenes. In a typical Catellani reaction, a nucleophile and an electrophile are coupled at the *ipso* and *ortho* positions, respectively, through selective reactions with the aryl-NBE palladacycle (ANP) intermediate (Scheme 1A).[3–33] In particular, when the nucleophile is a hydride equivalent, a reductive *ortho* functionalization is realized. While efficient, the Catellani reaction contains a non-productive process, which is the removal of the generated acid (HX) with stoichiometric bases. In addition, the reaction needs to be terminated by a nucleophile or reductant in order to reform the Pd(0) catalyst. Moreover, the compatibility between the nucleophile and the electrophile is an inevitable concern, and typically, only masked or weak nucleophiles are suitable. Very recently, Zhang[34] and Zhou[35] concurrently reported a novel arylboronic-acid-based Catellani reaction also through coupling an electrophile-nucleophile pair, but stoichiometric bases and oxidants were still required (Scheme 1B).

Stimulated by these intrinsic constraints in the Catellani reaction, we felt it could be attractive to develop a redox-neutral arene *ortho* functionalization, in which an aryl nucleophile (e.g., aryl boron compounds) could be coupled with two electrophiles

The Bigger Picture

Poly-substituted aromatics are ubiquitously found in drugs and agrochemicals. To realize streamlined synthesis, it is highly attractive if functional groups can be site-selectively introduced at unactivated positions with common arene starting materials. Here, a method is developed to directly introduce acyl and amino groups at unactivated *ortho* positions of readily available aryl boron compounds. Compared with the known *ortho* functionalization approaches, this method does not require stoichiometric bases, external oxidants, or reductants. Consequently, the reaction is chemoselective: a wide range of functional groups, including highly reactive aryl iodides, can be tolerated. The primary innovation lies in the use of a proton to terminate the *ipso* aryl intermediate and regenerate the active palladium catalyst. This unique mode of reactivity in the palladium/norbornene catalysis should open the door for developing new redox-neutral methods for site-selective arene functionalization.

Please cite this article in press as: Li et al., Redox-Neutral *ortho* Functionalization of Aryl Boroxines via Palladium/Norbornene Cooperative Catalysis, Chem (2019), https://doi.org/10.1016/j.chempr.2019.02.005



Scheme 1. Palladium/Norbornene Cooperative Catalysis

without the need for stoichiometric bases or oxidants (Scheme 1C). Mechanistically, after the *ortho* functionalization with ANP followed by NBE extrusion, the resulting aryl-Pd(II) species could then react with another electrophile (instead of a nucleophile or reductant) to regenerate the Pd(II) catalyst. Seminal work by Lautens has shown that such an aryl-Pd(II) species could attack an adjacent carbonyl group, but this has been limited to an intramolecular transformation.[15] Clearly, many challenges can be envisioned with this redox-neutral strategy, including the difficulty of controlling site-selectivity and the choice of suitable electrophiles. Thus, at this preliminary stage, we have been focused on a simplified system with one electrophile being a proton source (Scheme 1D).[31–33] In this reaction, the acid generated during the ANP formation could be re-coupled at the *ipso* position, which leads to a net proton swap. Herein, we describe our initial development of Pd/NBE-catalyzed redox-neutral acylation and amination using aryl boroxines as substrates, which directly introduces a functional group at the arene *ortho* position without extra stoichiometric oxidants or reductants.

RESULTS AND DISCUSSION

The challenges for developing such a redox-neutral transformation are two-fold. First, given that the aryl-Pd(II) intermediate formed after the NBE extrusion is typically less nucleophilic, protonation of such a species could be difficult.[36] Second, transmetalation of aryl boronates is generally promoted by basic conditions, while the final protonation step requires the presence of an acid. Hence, the compatibility of these two steps could be another concern. We hypothesized that the key for the success of this reaction would be to discover a catalyst system that can promote

[1]Department of Chemistry, University of Chicago, Chicago, IL 60637, USA

[2]Department of Applied Chemistry, China Agricultural University, Beijing 100193, China

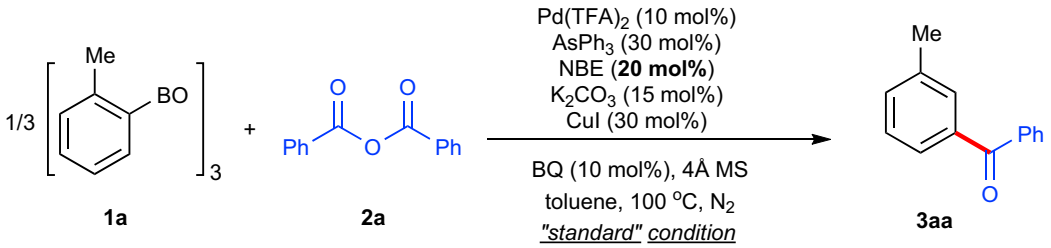
[3]These authors contributed equally

[4]Lead Contact

*Correspondence: gbdong@uchicago.edu

https://doi.org/10.1016/j.chempr.2019.02.005

Please cite this article in press as: Li et al., Redox-Neutral *ortho* Functionalization of Aryl Boroxines via Palladium/Norbornene Cooperative Catalysis, Chem (2019), https://doi.org/10.1016/j.chempr.2019.02.005



1a 2a 3aa

Entry	Change from the "standard" condition	Yield[a]
1	none	65%
2	w/o $Pd(TFA)_2$	0%
3	w/o NBE	0%
4	w/o $AsPh_3$	0%
5	$Pd(OAc)_2$ instead of $Pd(TFA)_2$	43%
6	PPh_3 instead of $AsPh_3$	12%
7	$(2\text{-furyl})_3P$ instead of $AsPh_3$	6%
8	w/o BQ	32%
9	w/o CuI	53%
10	w/o K_2CO_3	51%
11	w/o 4Å MS	43%[b]
12	H_2O (1.0 equiv) instead of 4Å MS	0%
13	commerical "$ArB(OH)_2$" instead of $(ArBO)_3$	52%[c]
14	ArBpin instead of $(ArBO)_3$	0%

Figure 1. Control Experiments for *ortho* Acylation with 2-Tolylboroxine

The reaction was run with 0.2 mmol **1a** (monomer of boroxine) and 0.4 mmol **2a** in 4 mL toluene for 14 h.

[a]Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as the internal standard.

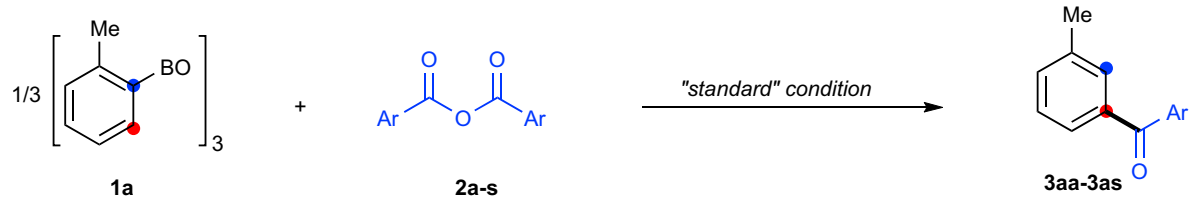
[b]Toluene after freeze-pump-thaw treatment was used.

[c]Purchased from Combi-Blocks, containing 28% free 2-tolylboronic acid determined by ^1H NMR analysis.

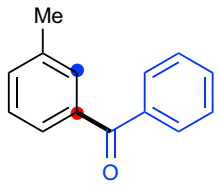
both transmetalation and protonation. The use of arsine-type ligands caught our attention because first, $AsPh_3$ is known to promote fast transmetalation in Stille reactions,[37] and second, $AsPh_3$ was also found to be the most efficient ligand in our previous *meta* C−H arylation reaction,[32] which requires facile de-protonation and re-protonation at the arene *ortho* position.

To test this hypothesis, we studied *ortho* acylation as the model reaction; 2-tolylboroxine (**1a**) and benzoic anhydride (**2a**) were employed as the initial model substrates. After careful evaluation of various reaction parameters (Tables S1–S4), the $Pd(TFA)_2/AsPh_3$ combination indeed provided the desired *ortho* acylation product **3aa** in 65% yield (Figure 1, entry 1). No direct *ipso* substitution between the aryl boroxine and benzoic anhydride was observed in this case. A number of control experiments were subsequently carried out. First, the Pd salt, NBE, and $AsPh_3$ were all essential to this reaction (Figure 1, entries 2–4). Other Pd(II)

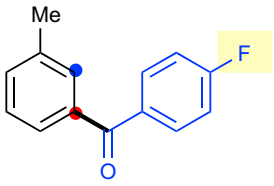
Please cite this article in press as: Li et al., Redox-Neutral *ortho* Functionalization of Aryl Boroxines via Palladium/Norbornene Cooperative Catalysis, Chem (2019), https://doi.org/10.1016/j.chempr.2019.02.005



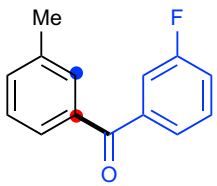
1a + **2a-s** → **3aa-3as**



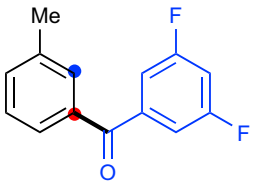
3aa, 65%



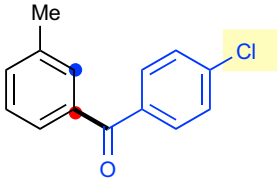
3ab, 74%



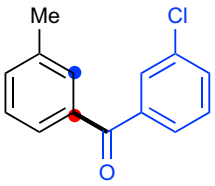
3ac, 67%



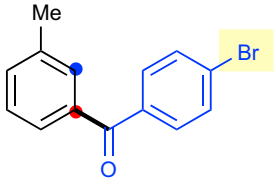
3ad, 62%



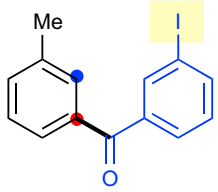
3ae, 66%



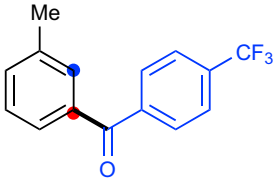
3af, 66%



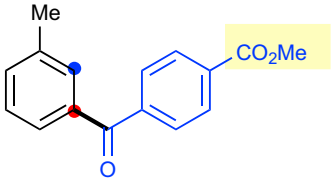
3ag, 61%



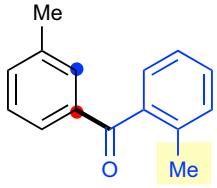
3ah, 31%



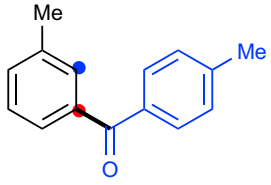
3ai, 63%



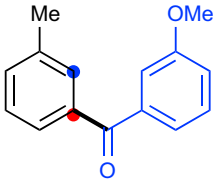
3aj, 53%



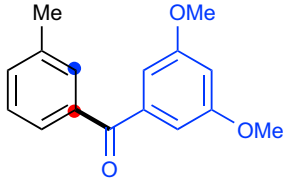
3ak, 48%



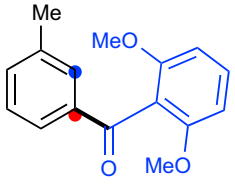
3al, 52%



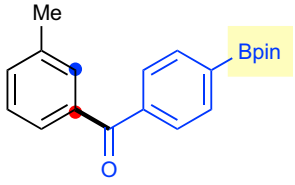
3am, 58%



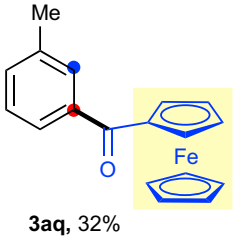
3an, 51%



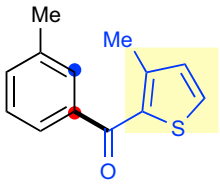
3ao, 37%



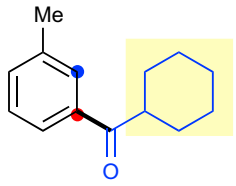
3ap, 41%



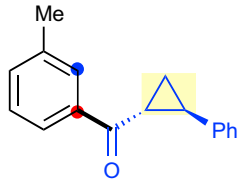
3aq, 32%



3ar, 33%



3as, 50%



3at, 60%

Figure 2. Substrate Scope with Respect to Anhydrides

The reaction was run with 0.3 mmol **1a** and 0.6 mmol **2a** in 4 mL toluene for 14 h.

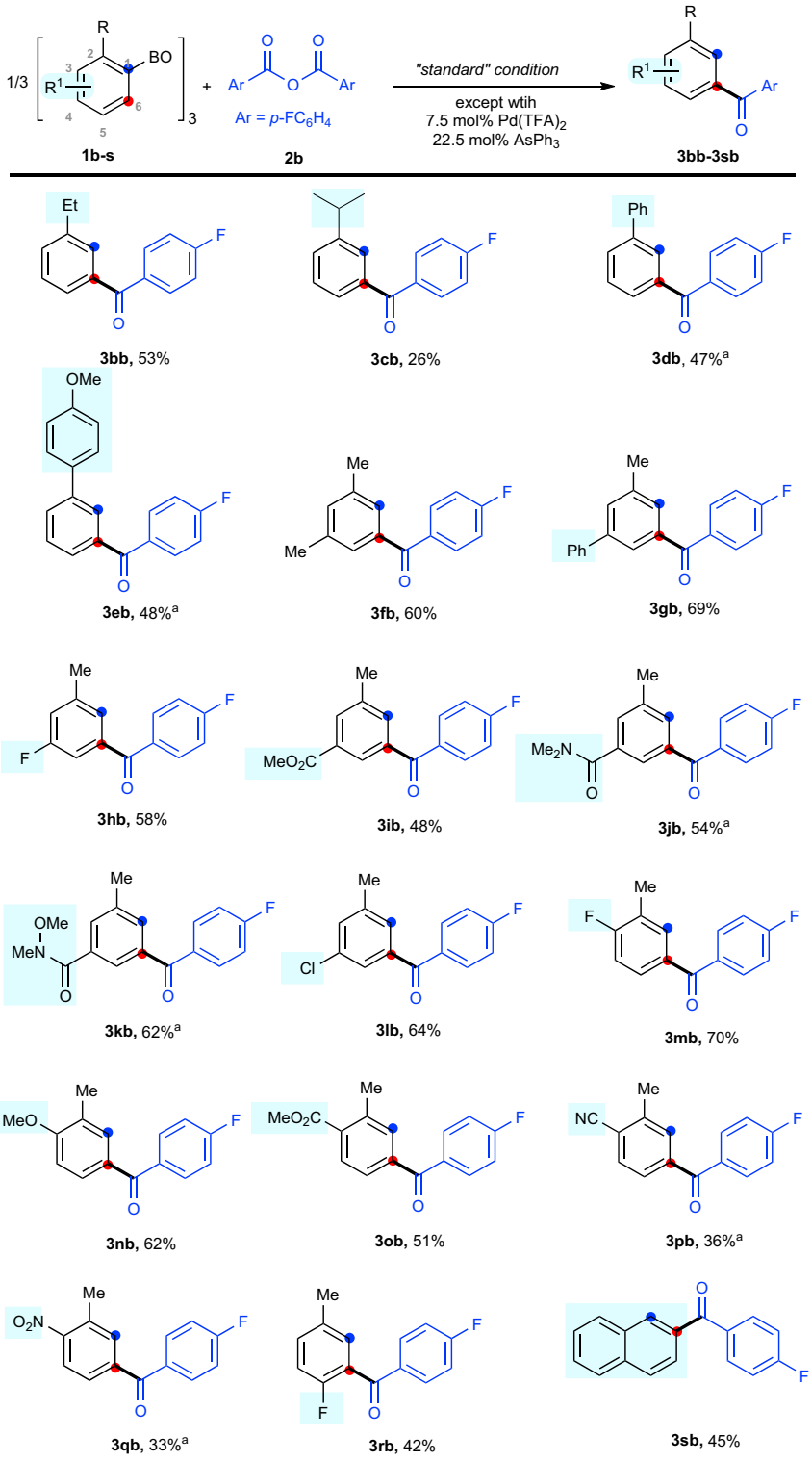
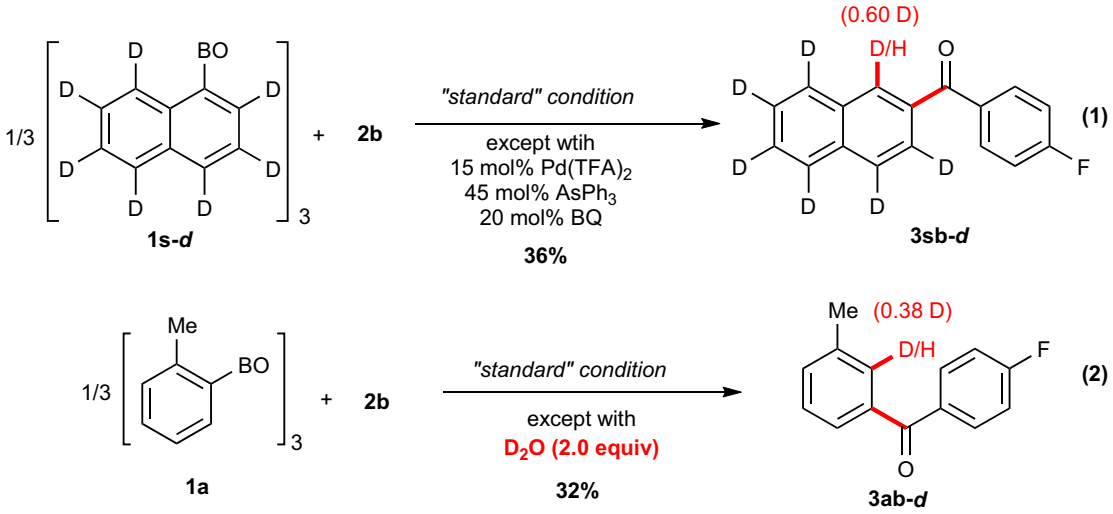


Figure 3. Substrate Scope with Respect to Aryl Boroxines

The reaction was run with 0.3 mmol **1b-s** and 0.6 mmol **2b** in 4 mL toluene for 14 h.

[a]10 mol % of $Pd(TFA)_2$ and 30 mol % of $AsPh_3$ was used.

Please cite this article in press as: Li et al., Redox-Neutral *ortho* Functionalization of Aryl Boroxines via Palladium/Norbornene Cooperative Catalysis, Chem (2019), https://doi.org/10.1016/j.chempr.2019.02.005

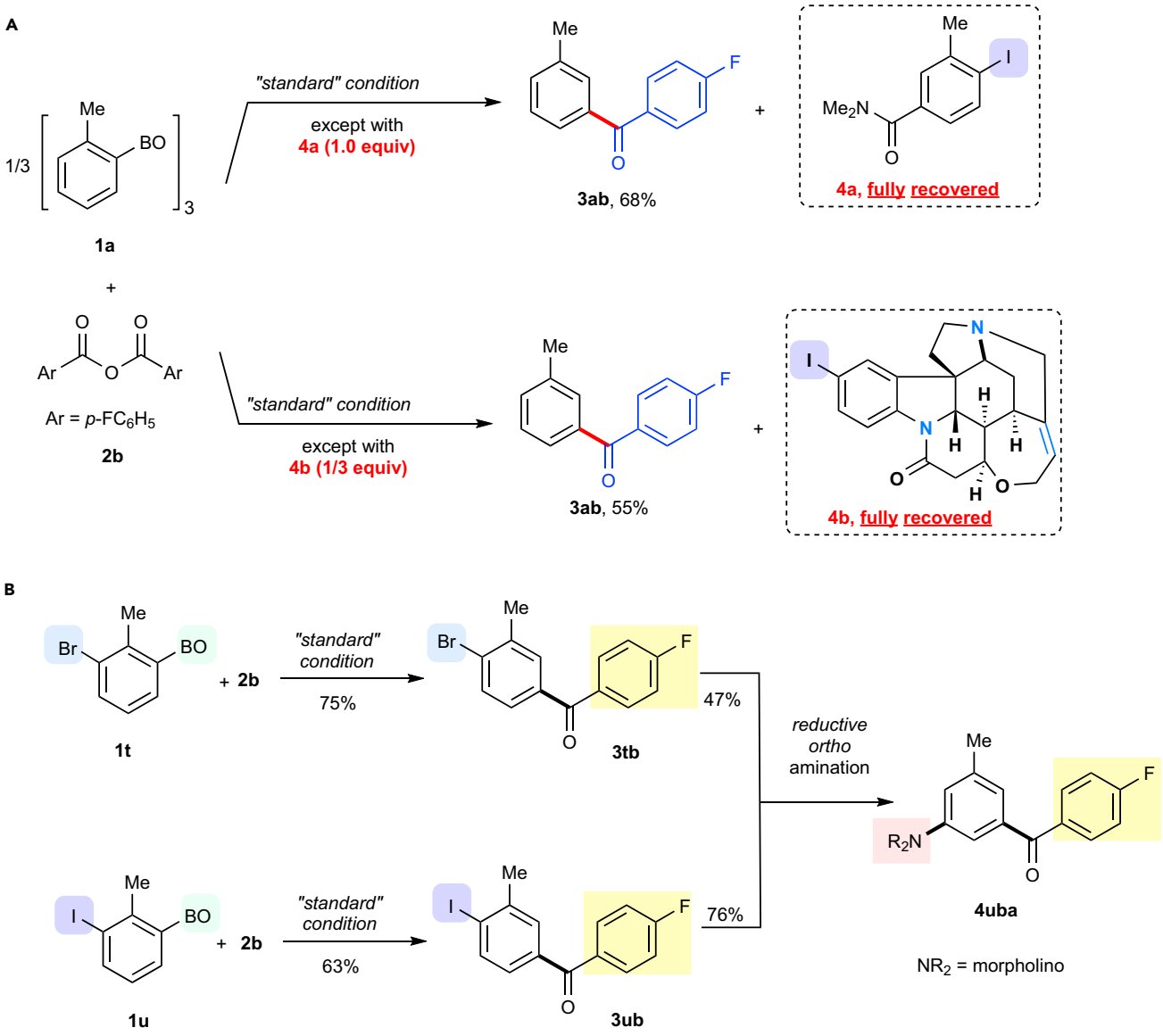


Scheme 2. Deuterium-Labeling Studies

precatalysts or phosphine-based ligands were less efficient (Figure 1, entries 5–7). It is noteworthy that whereas the majority of the prior Pd/NBE-catalyzed reactions used a high loading or excess NBE,[5–10] only 20 mol % NBE was sufficient in this reaction. A catalytic amount of benzoquinone could improve the reaction yield (Figure 1, entry 8), which most likely serves as a Pd(0) scavenger or a π-ligand[38–40] to prevent catalyst decomposition. A catalytic amount of CuI and K_2CO_3 also enhanced the yield, though their roles were not critical (Figure 1, entries 9 and 10).[41] One hypothesis is that a catalytic amount of carbonate base may facilitate the transmetalation of boroxines or promote the concerted metalation deprotonation step to form the ANP. The reaction was sensitive to water, and adding molecular sieves significantly increased the yield (Figure 1, entries 11 and 12). Use of aryl boroxines instead of boronic acids was beneficial, though the commercial "boronic acid" that contains ~28% $ArB(OH)_2$ and ~72% boroxine (Figures S1–S3) still afforded the desired product in 52% yield (Figure 1, entry 13). In contrast, the corresponding pinacol-derived substrate was not reactive, most likely because of its difficulty in the transmetalation step (Figure 1, entry 14).[42]

The scope of the reaction with respect to the acyl part was examined first (Figures 2 and S4–S47). Anhydrides with electron-donating and electron-withdrawing groups all afforded the desired *ortho* acylation products in moderate to good yields. Generally, the more electron-deficient aromatic anhydrides (e.g., **3ab** and **3ae**) gave slightly higher yields than the ones richer in electrons, probably because of their enhanced reactivity toward the ANP intermediate. One important feature is that a number of functional groups, including aryl fluoride (**3ab–3ad**), chloride (**3ae** and **3af**), bromide (**3ag**), iodide (**3ah**; *vide infra* Schemes 3 and 4), trifluoromethyl (**3ai**), ester (**3aj**), and anisole moieties (**3am–3ao**), were tolerated. The *ortho*-substituted aromatic anhydrides (**3ak** and **3ao**) were competent substrates. It is noteworthy that pinacol boronates were compatible (**3ap**), which could serve as a handle for further functionalization. In addition, ferrocene- (**3aq**) and thiophene-derived ketone products (**3ar**) could be isolated in moderate yields. Encouragingly, aliphatic carboxylic acid anhydrides also proved to be suitable coupling partners (**3as** and **3at**).

Next, the scope of the aryl boroxines was explored. Notably, a lower Pd loading (7.5 mol %) was applied in these reactions (Figures 3 and S48–S101). Substitutions

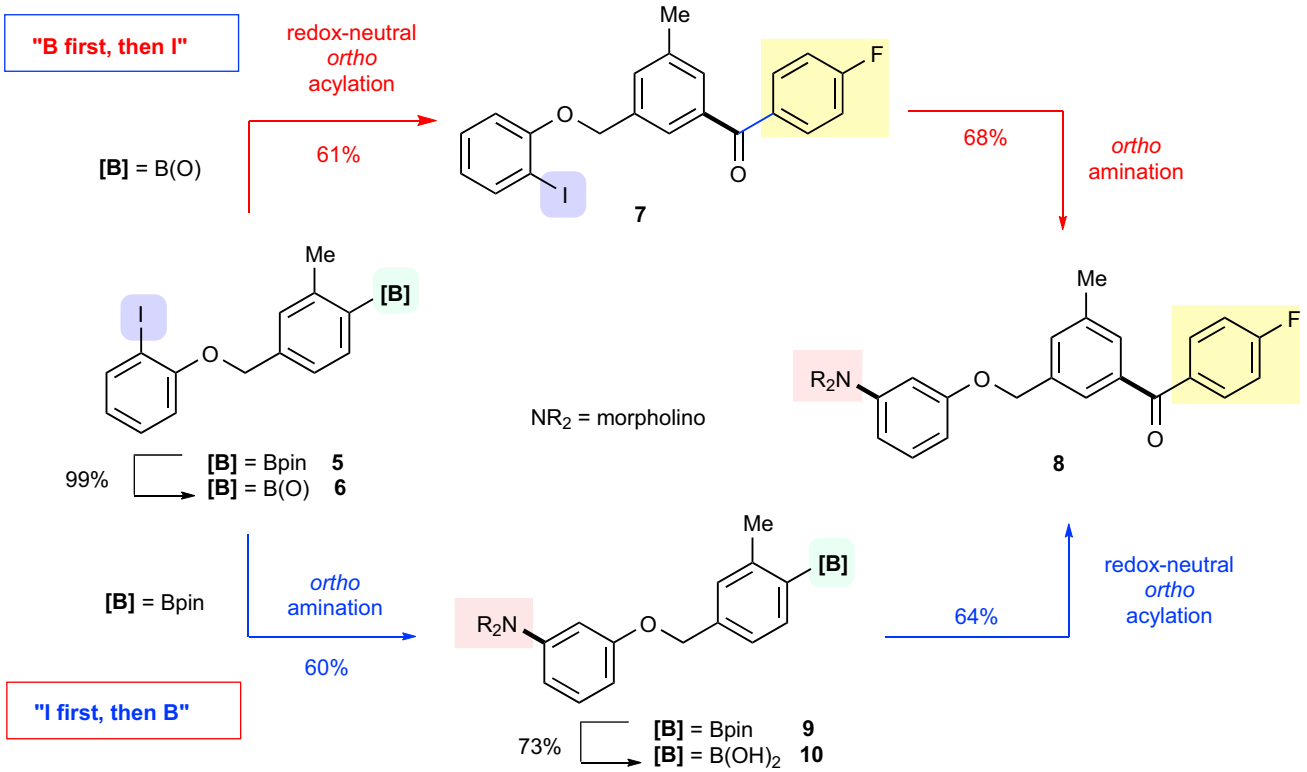


Scheme 3. Tolerance of Aryl Iodide and Bromide Moieties

at the C2–C5 positions of aryl boroxines could all be tolerated. For the *para*-substituted aryl boroxines, aryl fluoride (**3hb**), chloride (**3lb**), ester (**3ib**), amide (**3jb**), Weinreb amide (**3kb**), phenyl (**3gb**), and alkyl groups (**3fb**) were compatible. In addition, aryl boroxines that contain an electron-donating or electron-withdrawing substituent smoothly provided the *ortho* acylation products in moderate to good yields. Although the trend of the electronic effect with the aryl boroxine substrates was not obvious, those bearing a strong electron-withdrawing group at the C3 position (**3pb** and **3qb**) typically gave lower yields. Moreover, a naphthalene-derived substrate (**3sb**) also provided the desired ketone product.

To gain some mechanistic insight into this reaction, deuterium-labeling studies were performed (Scheme 2; Figures S102 and S103). When the fully deuterated substrate **1s-*d*** reacted with anhydride **2b**, the desired product (**3sb-*d***) was isolated with

Please cite this article in press as: Li et al., Redox-Neutral *ortho* Functionalization of Aryl Boroxines via Palladium/Norbornene Cooperative Catalysis, Chem (2019), https://doi.org/10.1016/j.chempr.2019.02.005



Scheme 4. Controlling the Reaction Sequence Enabled by Orthogonal Chemoselectivity

60% deuterium incorporated at the *ipso* position (Scheme 2, Equation 1). The erosion of deuterium incorporation was possibly due to the H-D exchange with adventitious water in the reaction system. To examine the possibility of the H-D exchange, we conducted a reverse control experiment. Using regular 2-toylboroxine **1a** as the substrate, we ran the standard reaction in the presence of 2.0 equiv of D_2O (Scheme 2, Equation 2). Although the reaction still contained a significant amount of molecular sieves, 38% deuterium was nevertheless observed as the *ipso* position of the product. These results are consistent with an *ipso* protonation pathway proposed in Scheme 1D.

One potential merit of aryl-boroxine-mediated reactions is the compatibility of aryl iodide moieties,[35] which are otherwise highly reactive under the typical Pd/NBE catalysis conditions (Scheme 3A).[5–10] First, in the presence of aryl iodide **4a**, *ortho* acylation of 2-tolylboroxine **1a** still proceeded selectively with a full recovery of unreacted aryl iodide **4a**. Encouragingly, a more complex aryl iodide (**4b**) derived from strychnine remained intact under the reaction conditions, whereas the *ortho* acylation with boroxine **1a** provided the desired product (**3ab**) in 55% yield.[43] In addition, substrates bearing halogens and boroxines on the same aromatic ring were tested (Scheme 3B; Figures S128–S140). Gratifyingly, both the aryl bromide (**1t**) and iodide (**1u**) groups survived under the standard *ortho* acylation conditions; such compatibility allows for convenient sequential functionalization of the arene substrates.

Encouraged by the unique chemoselectivity in the aryl-boroxine-mediated reactions, orthogonal reactivity between aryl iodide (I) and boroxine (B) moieties was next explored; if successful, this would provide a convenient way to control the

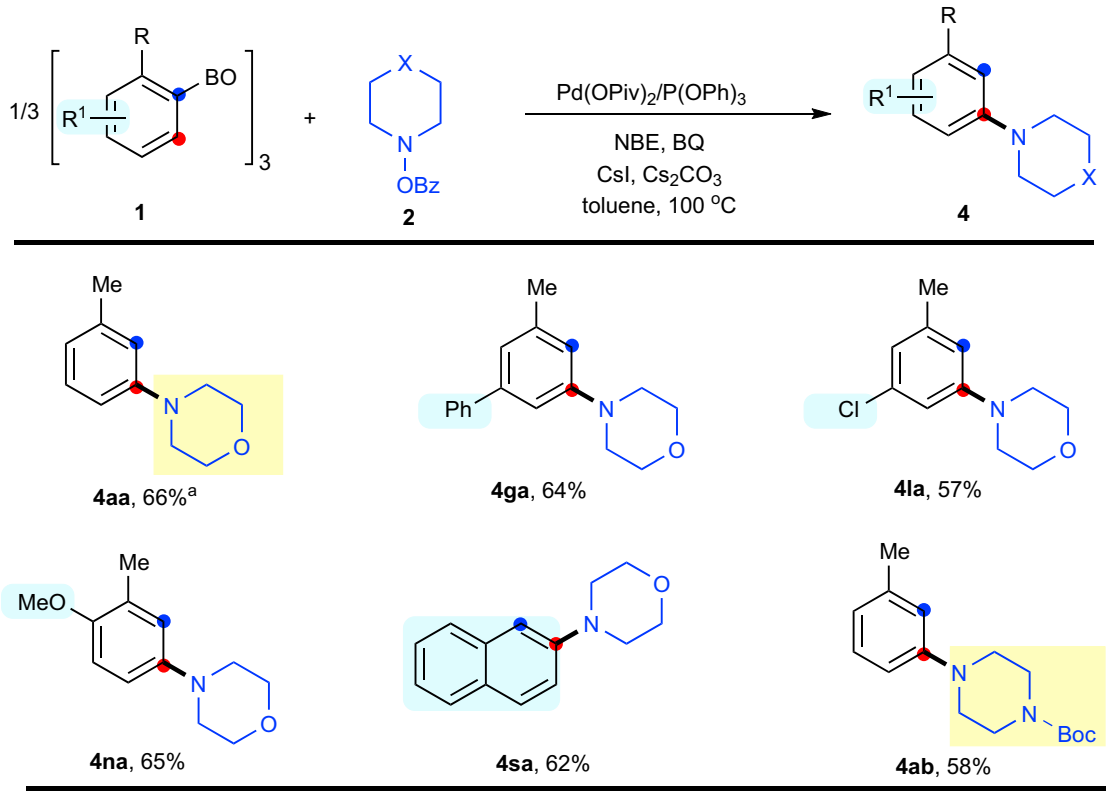


Figure 4. Substrate Scope of the *ortho* Amination Reaction

Reaction conditions: **1** (0.5 mmol), **2** (0.2 mmol), $Pd(OPiv)_2$ (20 mol %), $P(OPh)_3$ (40 mol %), NBE (50 mol %), BQ (15 mol %), Cs_2CO_3 (50 mol %), CsI (50 mol %), toluene (4 mL), 100°C, 12 h.

[a]When 10 mol % Pd was used instead, 55% isolated yield was observed.

reaction sequence without significant alteration of the substrates (Scheme 4; Figures S116–S127). Diaryl compound **5** containing both "I" and "B" groups was employed as the model substrate. First, as expected, the "B first, then I" sequence worked smoothly, which first gave an *ortho* acylation on the boroxine site and then an *ortho* amination on the iodide site. On the other hand, the "I first, then B" sequence was also successful: the Pd(0)-catalyzed reductive *ortho* amination of the aryl iodide tolerated the pinacol boronate moiety; the resulting intermediate after hydrolysis then participated in the Pd(II)-catalyzed *ortho* acylation uneventfully. Thus, without the need to prepare different substrates, the order of the reaction sequence between the boroxine and iodide sites could be controlled by different catalytic systems.

Besides the *ortho* acylation, preliminary success has also been obtained for achieving the *ortho* amination under the redox-neutral conditions (Figures 4 and S104–S115). *O*-benzoyl hydroxylamines were found to be suitable electrophiles. Under modified reaction conditions, the desired *ortho* amination products could be obtained in moderate to good yields without the need of reductants.[17] Phosphite ligands, e.g., $P(OPh)_3$, proved to work better than arsine ligands, whereas other types of ligands were less efficient (Tables S5–S7). To the best of our knowledge, phosphite ligands have not been used in the Pd/NBE catalysis previously. A piperazine-derived electrophile also afforded the desired amination product (**4ab**) in 58% yield. Efforts on further enhancing the efficiency and scope of this *ortho* amination reaction through detailed mechanistic studies are ongoing.

In summary, a redox-neutral Catellani-type transformation is developed using aryl boroxines as substrates. The reaction is enabled by an arsine or phosphite ligand and a Pd(II) catalyst, showing broad functional-group compatibility. Compared with the classical reductive Catellani-type reactions, this approach does not require stoichiometric bases or reductants; in addition, it can tolerate various aryl halide moieties. Although the efficiency of these methods remains to be further improved, the unique mechanistic pathway discovered here could have important implications on developing a new class of Pd/NBE-catalyzed reactions.

EXPERIMENTAL PROCEDURES

Full experimental procedures are provided in the Supplemental Information.

SUPPLEMENTAL INFORMATION

Supplemental Information can be found with this article online at https://doi.org/10.1016/j.chempr.2019.02.005.

ACKNOWLEDGMENTS

Financial support from the University of Chicago and National Institute of General Medical Sciences (1R01GM124414-01A1) is acknowledged. F.L. is supported by a China Scholarship Council fellowship. We thank Dr. Zhe Dong for preliminary investigation and Mr. Jianchun Wang for checking the experiments.

AUTHOR CONTRIBUTIONS

R.L. discovered the reaction and performed the optimization. R.L. and F.L. performed the substrate scope and application. G.D. directed the project and wrote the manuscript with input from all authors. All authors analyzed the results and commented on the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: October 24, 2018
Revised: January 23, 2019
Accepted: February 7, 2019
Published: March 7, 2019

REFERENCES AND NOTES

1. Huang, Z., and Dong, G. (2017). Site-selectivity control in organic reactions: a quest to differentiate reactivity among the same kind of functional groups. Acc. Chem. Res. *50*, 465–471.

2. Toste, F.D., Sigman, M.S., and Miller, S.J. (2017). Pursuit of noncovalent interactions for strategic site-selective catalysis. Acc. Chem. Res. *50*, 609–615.

3. Catellani, M., Frignani, F., and Rangoni, A. (1997). A complex catalytic cycle leading to a regioselective synthesis of o,o′-disubstituted vinylarenes. Angew. Chem. Int. Ed. *36*, 119–122.

4. Lautens, M., and Piguel, S. (2000). A new route to fused aromatic compounds by using a palladium-catalyzed alkylation–alkenylation sequence. Angew. Chem. Int. Ed. *39*, 1045–1046.

5. Catellani, M. (2005). Novel methods of aromatic functionalization using palladium and norbornene as a unique catalytic system. Top. Organomet. Chem. *14*, 21–53.

6. Catellani, M., Motti, E., and Della Ca', N. (2008). Catalytic sequential reactions involving palladacycle-directed aryl coupling steps. Acc. Chem. Res. *41*, 1512–1522.

7. Martins, A., Mariampillai, B., and Lautens, M. (2010). Synthesis in the key of Catellani: norbornene-mediated ortho C–H functionalization. Top. Curr. Chem. *292*, 1–33.

8. Ferraccioli, R. (2013). Palladium-catalyzed synthesis of carbo- and heterocycles through norbornene-mediated ortho C–H functionalization. Synthesis *45*, 581–591.

9. Ye, J., and Lautens, M. (2015). Palladium-catalysed norbornene-mediated C–H functionalization of arenes. Nat. Chem. *7*, 863–870.

10. Della Ca', N., Fontana, M., Motti, E., and Catellani, M. (2016). Pd/Norborene: a winning combination for selective aromatic functionalization via C–H bond activation. Acc. Chem. Res. *49*, 1389–1400.

11. Catellani, M., Motti, E., and Baratta, S. (2001). A novel palladium-catalyzed synthesis of phenanthrenes from ortho-substituted aryl iodides and diphenyl- or alkylphenylacetylenes. Org. Lett. *3*, 3611–3614.

12. Faccini, F., Motti, E., and Catellani, M. (2004). A new reaction sequence involving palladium-catalyzed unsymmetrical aryl coupling. J. Am. Chem. Soc. *126*, 78–79.

13. Mariampillai, B., Alliot, J., Li, M., and Lautens, M. (2007). A convergent synthesis of

polysubstituted aromatic nitriles via palladium-catalyzed C−H functionalization. J. Am. Chem. Soc. *129*, 15372–15379.

14. Martins, A., and Lautens, M. (2008). Aromatic ortho-benzylation reveals an unexpected reductant. Org. Lett. *10*, 5095–5097.

15. Zhao, Y.B., Mariampillai, B., Candito, D.A., Laleu, B., Li, M., and Lautens, M. (2009). Exploiting the divergent reactivity of aryl–palladium intermediates for the rapid assembly of fluorene and phenanthrene derivatives. Angew. Chem. Int. Ed. *48*, 1849–1852.

16. Weinstabl, H., Suhartono, M., Qureshi, Z., and Lautens, M. (2013). Total synthesis of (+)-linoxepin by utilizing the Catellani reaction. Angew. Chem. Int. Ed. *52*, 5305–5308.

17. Dong, Z., and Dong, G. (2013). Ortho vs ipso: site-selective Pd and norbornene-catalyzed arene C–H amination using aryl halides. J. Am. Chem. Soc. *135*, 18350–18353.

18. Zhou, P.-X., Ye, Y.-Y., Liu, C., Zhao, L.-B., Hou, J.-Y., Chen, D.-Q., Tang, Q., Wang, A.-Q., Zhang, J.-Y., Huang, Q.-X., et al. (2015). Palladium-catalyzed acylation/alkenylation of aryl iodide: a domino approach based on the Catellani–Lautens reaction. ACS Catal. *5*, 4927–4931.

19. Dong, Z., Wang, J., Ren, Z., and Dong, G. (2015). Ortho C-H acylation of aryl iodides by palladium/norbornene catalysis. Angew. Chem. Int. Ed. *54*, 12664–12668.

20. Shi, H., Babinski, D.J., and Ritter, T. (2015). Modular C–H functionalization cascade of aryl iodides. J. Am. Chem. Soc. *137*, 3775–3778.

21. Wang, J., Zhang, L., Dong, Z., and Dong, G. (2016). Reagent-enabled *Ortho*-alkoxycarbonylation of aryl iodides via palladium/norbornene catalysis. Chem *1*, 581–591.

22. Sun, F., Li, M., He, C., Wang, B., Li, B., Sui, X., and Gu, Z. (2016). Cleavage of the C(O)–S bond of thioesters by palladium/norbornene/copper cooperative catalysis: an efficient synthesis of 2-(arylthio)aryl ketones. J. Am. Chem. Soc. *138*, 7456–7459.

23. For a recent related intramolecular lactam formation, see: Li, X., Pan, J., Song, S., and Jiao, N. (2016). Pd-catalyzed dehydrogenative annulation approach for the efficient synthesis of phenanthridinones Chem. Sci. *7*, 5384–5389.

24. Li, R., and Dong, G. (2018). Direct annulation between aryl iodides and epoxides through palladium/norbornene cooperative catalysis. Angew. Chem. Int. Ed. *57*, 1697–1701.

25. Cheng, H.G., Wu, C., Chen, H., Chen, R., Qian, G., Geng, Z., Wei, Q., Xia, Y., Zhang, J., Zhang, Y., et al. (2018). Epoxides as alkylating reagents for the Catellani reaction. Angew. Chem. Int. Ed. *57*, 3444–3448.

26. Dong, Z., Lu, G., Wang, J., Liu, P., and Dong, G. (2018). Modular ipso/ortho difunctionalization of aryl bromides via palladium/norbornene cooperative catalysis. J. Am. Chem. Soc. *140*, 8551–8562.

27. Liu, C., Liang, Y., Zheng, N., Zhang, B.-S., Feng, Y., Bi, S., and Liang, Y.-M. (2018). Synthesis of indolines via a palladium/norbornene-catalyzed reaction of aziridines with aryl iodides. Chem. Commun. *54*, 3407–3410.

28. Qian, G., Bai, M., Gao, S., Chen, H., Zhou, S., Cheng, H.G., Yan, W., and Zhou, Q. (2018). Modular one-step three-component synthesis of tetrahydroisoquinolines using a Catellani strategy. Angew. Chem. Int. Ed. *57*, 10980–10984.

29. Wang, J., Li, R., Dong, Z., Liu, P., and Dong, G. (2018). Complementary site-selectivity in arene functionalization enabled by overcoming the ortho constraint in palladium/norbornene catalysis. Nat. Chem. *10*, 866–872.

30. Jiao, L., and Bach, T. (2011). Palladium-catalyzed direct 2-alkylation of indoles by norbornene-mediated regioselective cascade C–H activation. J. Am. Chem. Soc. *133*, 12990–12993.

31. Wang, X.C., Gong, W., Fang, L.Z., Zhu, R.Y., Li, S., Engle, K.M., and Yu, J.Q. (2015). Ligand-enabled meta-C-H activation using a transient mediator. Nature *519*, 334–338.

32. Dong, Z., Wang, J., and Dong, G. (2015). Simple amine-directed meta-selective C–H arylation via Pd/norbornene catalysis. J. Am. Chem. Soc. *137*, 5887–5890.

33. Shi, H., Herron, A.N., Shao, Y., Shao, Q., and Yu, J.Q. (2018). Enantioselective remote meta-C–H arylation and alkylation via a chiral transient mediator. Nature *558*, 581–585.

34. Shi, G., Shao, C., Ma, X., Gu, Y., and Zhang, Y. (2018). Pd(II)-catalyzed Catellani-type domino reaction utilizing arylboronic acids as substrates. ACS Catal. *8*, 3775–3779.

35. Chen, S., Liu, Z.S., Yang, T., Hua, Y., Zhou, Z., Cheng, H.G., and Zhou, Q. (2018). The discovery of a palladium(II)-initiated Borono-Catellani reaction. Angew. Chem. Int. Ed. *57*, 7161–7165.

36. O'Duill, M.L., and Engle, K.M. (2018). Protodepalladation as a strategic elementary step in catalysis. Synthesis *50*, 4699–4714.

37. Farina, V., and Krishnan, B. (1991). Large rate accelerations in the Stille reaction with tri-2-furylphosphine and triphenylarsine as palladium ligands: mechanistic and synthetic implications. J. Am. Chem. Soc. *113*, 9585–9595.

38. Chen, M.S., Prabagaran, N., Labenz, N.A., and White, M.C. (2005). Serial ligand catalysis: a highly selective allylic C−H oxidation. J. Am. Chem. Soc. *127*, 6970–6971.

39. Lin, S., Song, C.X., Cai, G.X., Wang, W.H., and Shi, Z.J. (2008). Intra/intermolecular direct allylic alkylation via Pd(II)-catalyzed allylic C−H activation. J. Am. Chem. Soc. *130*, 12901–12903.

40. Braun, M.G., and Doyle, A.G. (2013). Palladium-catalyzed allylic C–H fluorination. J. Am. Chem. Soc. *135*, 12990–12993.

41. Cu(I) salts are known to promote transmetalation in Stille reactions as a ligand scavenger; see: Farina, V., Kapadia, S., Krishnan, B., Wang, C., and Liebeskind, L.S. (1994). On the nature of the "copper effect" in the Stille cross-coupling J. Org. Chem. *59*, 5905–5911.

42. Lennox, A.J.J., and Lloyd-Jones, G.C. (2014). Selection of boron reagents for Suzuki-Miyaura coupling. Chem. Soc. Rev. *43*, 412–443.

43. The slight decrease in yield was most likely due to the presence of the basic amine moiety in the alkaloid.