

# Pyridine-Catalyzed Radical Borylation of Aryl Halides

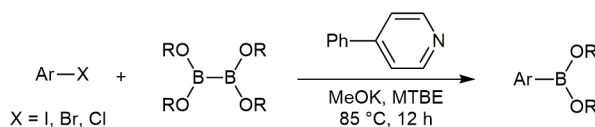
*J. Am. Chem. Soc.* **2017**, *139*, 607–610

Arylboronates are widely used in organic chemistry, and methods that could produce arylboronates from easily available starting materials in a transition-metal-free manner are in high demand. Although there are several precedents in the literature, problems such as the expense of the boron source, low reactivity, and operational inconvenience remain to be solved.

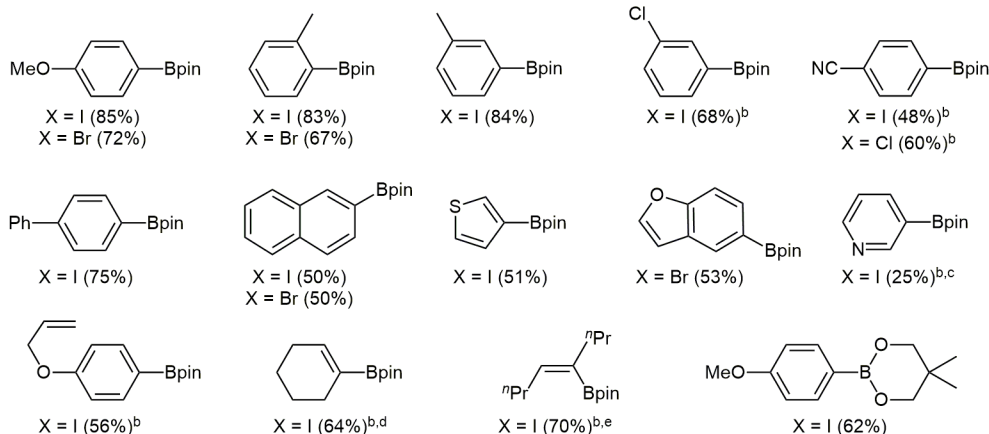
The group of Professor Lei Jiao at Tsinghua University (Beijing, P. R. of China) studied the mechanism of carbon–halogen bond activation of haloarenes by small organic molecules, which is a key step in base-promoted homolytic aromatic substitution (BHAS) reactions (*J. Am. Chem. Soc.* **2016**, *138*, 7151; *Chem. Eur. J.* **2017**, *23*, 65). Professor Jiao said: “As a consequence, we were interested in utilizing the aryl radical generated in this process to synthesize more useful molecules, rather than merely producing biaryl compounds.

Therefore, we hoped to synthesize arylboronates from haloarenes using this carbon–halogen bond activation strategy.”

With this idea in mind, the group first tried to capture the aryl radical directly by using bis(pinacolato)diboron ( $B_2pin_2$ ). “We simply added  $B_2pin_2$  to a BHAS reaction system (ArI/DMEDA/*t*-BuOK in benzene),” said Professor Jiao. “However, only the biaryl product (ArPh) was found and no borylation product could be observed. It seemed that the aryl radical reacted with  $B_2pin_2$  in a low efficiency, as shown in several literature reports.” Professor Jiao’s group stopped attempting this reaction for months, until Li Zhang – a PhD student – found a new publication that reported the formation of pyridine-stabilized boryl radical by the reaction between 4-cyanopyridine and  $B_2pin_2$  (*Angew. Chem. Int. Ed.* **2016**, *55*, 5985). “An idea soon came to his mind that the pyridine-stabilized boryl radical might trap the aryl radical more easily than  $B_2pin_2$



## Reaction scope (some examples):



<sup>a</sup> Reaction conditions: aryl halides (0.5 mmol, 1 equiv), 4-phenylpyridine (20 mol%), MeOK (2 equiv), diboron reagent (2 equiv) in 0.4 mL of MTBE, 85 °C for 12 h. Isolated yields are reported.

<sup>b</sup> MeOK (1.3 equiv) and  $B_2pin_2$  (1.3 equiv) were used.

<sup>c</sup> NMR yield.

<sup>d</sup> 40 mol% of 4-phenylpyridine were used.

<sup>e</sup> *E/Z* = 89:11.

Scheme 1

itself to generate arylboronate, thanks to the persistent radical effect,” said Professor Jiao. “We discussed this new idea and agreed that it was worth trying.”

He continued: “Indeed when we added a catalytic amount of 4-cyanopyridine to the reaction system, the arylboronate product was observed. After optimization of the reaction conditions, the designed borylation reaction for aryl iodides was realized in good yields. However, aryl bromides were found to be less suitable substrates using the conditions above. We therefore sought to boost their reactivity by tuning the electronic nature of the pyridine catalyst, but failed. Fortunately, we finally solved the problem by replacing the *para*-cyano group in the pyridine catalyst by a *para*-phenyl group, which was thought to further stabilize the boryl radical.”

The optimized conditions of the borylation reaction were at that point very simple: just mixing each reaction component and the solvent in a vessel and heating in an oil bath was sufficient. “The reaction is best performed under inert atmosphere, but it is not very sensitive to air – reaction under air produced the desired borylation product with slightly decreased yield,” explained Professor Jiao. “The reaction is scalable if performed in a flask, producing arylboronates on >1 g scale in one batch. The scope of the borylation reaction is broad, including aryl iodides, aryl bromides, activated aryl

chlorides, and alkenyl iodides (Scheme 1).” These features make this method rather attractive for diverse synthetic applications. In particular, for the borylation of aryl iodides, inexpensive pyridine could be used as the catalyst instead of 4-phenylpyridine, making the synthesis more cost-effective. “We believe that this reaction could serve as a good complement to the present synthetic methods for producing arylboronates,” said Professor Jiao.

The mechanism of the reaction is also intriguing. Although experimental results supported the intermediacy of the aryl radical in the borylation process, another question still remained: whether the aryl radical reacts with the pyridine-stabilized boryl radical (the designed radical coupling pathway) or with the ate complex formed by  $B_2pin_2$  and MeOK (the  $S_{RN}1$  pathway). “To solve this problem, we designed a series of competition experiments and found that the preference for borylation compared with a hydrogen atom transfer probe was favored by increasing the amount of the pyridine catalyst,” said Professor Jiao. He concluded: “This piece of evidence strongly supported the C–B bond formation through the interaction between an aryl radical and a pyridine-related boryl species, rather than the ate complex or  $B_2pin_2$ .”

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## About the authors



L. Zhang

**Li Zhang** obtained his B.Sc. degree in chemistry from China Agricultural University (P. R. of China) in 2015. In the same year, he joined Professor Jiao's group at Tsinghua University (P. R. of China) as a Ph.D. candidate. His research interest is the mechanism of radical-based cross-coupling reactions.



Prof. L. Jiao

**Lei Jiao** studied at Peking University (Beijing, P. R. of China) where he received his B.Sc. (2005) and Ph.D. degrees (2010) in chemistry. After postdoctoral research with Professor Thorsten Bach at Technische Universität München (Germany) from 2010 to 2013, he started his independent career as a principle investigator in the Center of Basic Molecular Science at Tsinghua University (P. R. of China) in January 2014. His research group focuses on mechanistic studies of organic reactions, mechanism-based design and development of new catalytic systems, and their application in natural product synthesis. He has received the Thieme Chemistry Journals Award (2014) and Qiu Shi Outstanding Young Scholar Award (2015).