Title	Development of Synthetic Methods for Organoboron Compounds Using Transition-Metal-Catalysis and Mechanochemistry
Author(s)	Pang, Yadong
Citation	北海道大学. 博士(工学) 甲第14022号
Issue Date	2020-03-25
DOI	10.14943/doctoral.k14022
Doc URL	http://hdl.handle.net/2115/78311
Type	theses (doctoral)
File Information	PANG_YADONG.pdf

Ph.D. thesis

Development of Synthetic Methods for Organoboron Compounds Using Transition-Metal-Catalysis and Mechanochemistry

（遷移金属触媒とメカノケミストリーによる

有機ホウ素化合物の合成法の開発）

Hokkaido University

Graduate School of Chemical Science and Engineering

Organoelement Laboratory

Yadong Pang

2020

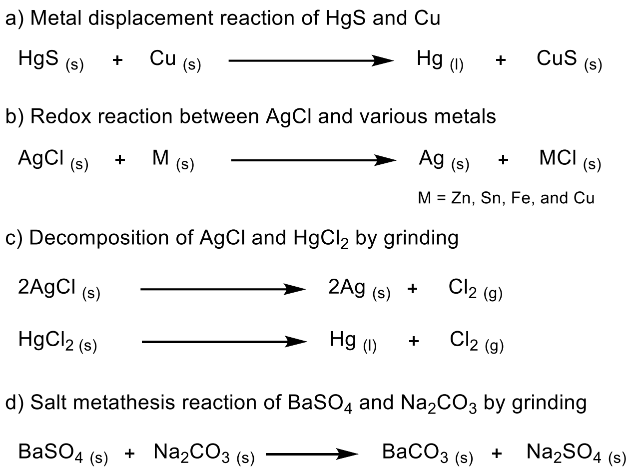
Contents

General Introduction

Mechanochemistry, which uses mechanical energy to facilitate chemical reactions by grinding, stretching, shearing, or other types of mechanical action, has experienced explosive growth in the past two decades.[1] It is re-emerging as a technique for organic synthesis, which was well known in the area of crystal engineering and polymorphism. Recently, mechanochemical synthesis becomes more and more prevalent and has been extensively exploited in materials science, polymer chemistry, inorganic synthesis, and organic synthesis due to its exclusive advantages including the avoidance of potentially harmful organic solvents and external heating, shorter reaction times, simpler operational handling, and improved or new selectivity.[2] Given these benefits, the International Union of Pure and Applied Chemistry (IUPAC) selected mechanochemistry in 2019 as one of the ten chemistry innovations that will most likely change the world, highlighting the recent increased interest in mechanochemistry among researchers in a variety of research areas.[3]

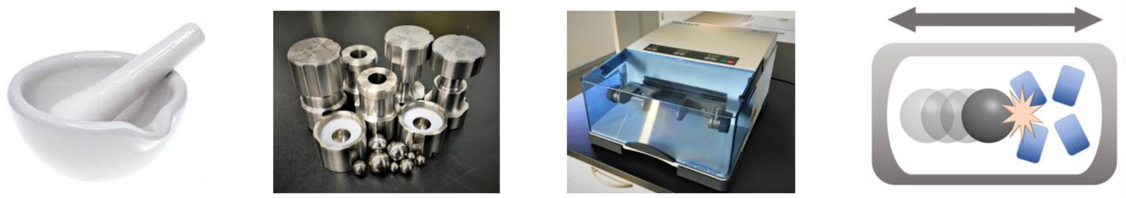
The roots at early historical beginnings of mechanochemistry can be found even in primitive Stone Age, as some building materials such as clay could be produced by grinding. Within this context, the mortar and pestle have appeared consistently throughout the history of humanity. The mortar and pestle, which is also employed in most modern laboratories, is a general instrument across many cultures worldwide. Traditionally, the mortar and pestle have been used to pound and grind solids together as observed in food ingredients, medicines, and materials. In a copper mortar with a copper pestle, mercury can be obtained by grinding cinnabar—a bright scarlet to a brick-red form of mercury(II) sulfide (HgS) (Scheme 1a). This is the earliest document related to mechanochemistry, which was written on a booklet titled "On Stones" by Theophrastus of Eresus in 315 BC.[4] However, nothing explicit is known about the use of mechanochemistry for the next 2000 years due to without any written records, although it is plausible that some mechanochemical reactions could be carried out while manual grinding of two or more solids together.

Several milestones in mechanochemistry were not reported until the 19th century. Faraday, who published a paper in 1820, described a method called "dry way" of reducing silver chloride (AgCl) by grinding with zinc, tin, iron, and copper in a mortar (Scheme 1b).[5] This paper can be considered as the beginning of systematic scientific studies on mechanochemistry, and several organic and inorganic transformations induced by manual grinding followed. After several years, there are also some representative contributions during the 19th century. In 1866, Carey Lea observed that mercuric chloride ($HgCl_2$) and silver chloride (AgCl) rapidly decomposed upon grinding at room temperature, while heating both solids just lead to phase transformations, no decomposed (Scheme 1c).[6] His observations not only showed that mechanical action could induce chemical changes, but also that the changes may be different from the reactions caused by heat. This experiment is his most crucial finding, which makes him earn the mantle called "father of mechanochemistry." In 1880, another contributor Spring reported his studies in his first major paper, which is related to the salt metathesis reaction between barium sulfate ($BaSO_4$) and sodium carbonate (Na_2CO_3) (Scheme 1d).[7] Importantly, at that period, it is considered that this metathesis reaction is difficult to be carried out in solution due to the poor solubility of $BaSO_4$. However, it was readily accomplished by manual grinding in the solid-state. This work highlighted the unique feather of mechanochemistry for chemical transformations, which could not be carried out in solution. In 1919, Ostwald included mechanochemistry in his terminology of chemical science appearing in the classification of a textbook together with thermochemistry, electrochemistry, and photochemistry, which is the first time to claim that mechanochemistry became an accepted separate branch of chemistry.[4]



Scheme 1. Early inorganic mechanochemical reactions that were performed in a mortar and pestle. a) Metal displacement of HgS and Cu, which formed elemental Hg by Theophrastus of Eresus. b) Redox reaction between AgCl and various metals in the solid-state by Faraday. c) Decomposition of AgCl and $HgCl_2$ into its elemental components by grinding by Carey Lea. d) Salts metathesis reaction of $BaSO_4$ and Na_2CO_3 by Spring.

However, progress in mechanochemistry was relatively slow during the first half of the 20th century due to a large number of significant developments that occurred in the underlying sciences and experimental techniques such as X-ray crystallography and quantum mechanics. Moreover, these mechanochemical reactions behave using the mortar, and the pestle (Fig. 1a) is highly operator dependent, as each individual may impart different levels of energy and is susceptible to variable factors involved in both human and environment leading to the poor reproducibility. At the same time, running reactions for longer than a few minutes also becomes challenging, and depends on the operator’s stamina. Therefore, there is no fascination in mechanochemical reactions until the electronic milling devices appeared. Nowadays, mechanochemical reactions are preferentially carried out using automated ball mills, a basic type of grinder, comprising a closed reaction jar (vessel) charged with ball bearings (Fig. 1b). They can conduct a similar function to grinding instead of the mortar and the pestle, but also in a reproducible manner and for longer reaction times. In the author’s laboratory, they use the mixer mill (Fig. 1c) which is always called shaker or vibration mill. In this case, the reaction jars are mounted horizontally and rapidly shaken from side to side at the desired frequency causing the enclosed balls bearing to shear and grind the reagents together (Fig 1d).



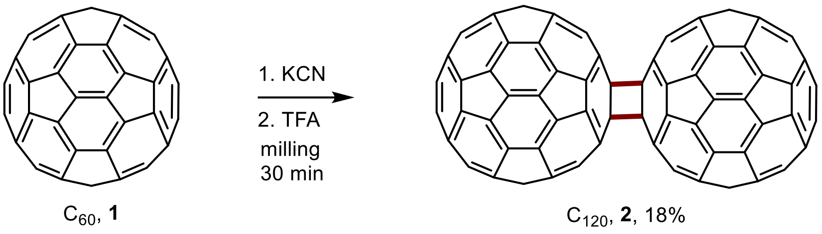
a) mortar and pestle b) jars and balls c) mixer mill d) mixer mill schematic

Fig. 1. Pictures of a) mortar and pestle, b) jars and balls, c) mixer mill, d) mixer mill schematic.

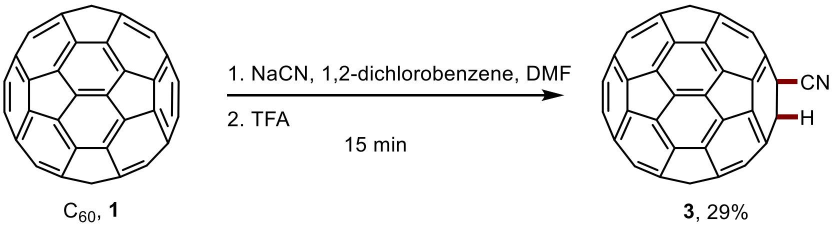
As the development of the mechanochemical equipment, more and more reactions using mechanochemistry are conducted by chemists. Due to its exclusive, fantastic advantages—avoidance of potentially harmful organic solvents and simpler operational handling, mechanochemistry is not only utilized in the domain of inorganic chemistry and metallurgy,[8] but also has become a powerful technique in all areas of chemistry, including organic,[9] organometallic,[10] and supramolecular chemistry,[11] as well as materials science.[12] Since the 21st century, a diverse range of carbon-carbon bond formation reactions, carbon-heteroatom bond formation reactions, condensations, and redox reactions using mechanochemistry have been reported. Compared to the traditional organic reactions in solution, besides the advantages which chemists all should know, including avoidance of organic solvents, inert atmosphere, and reduced reaction times, the organic reactions using mechanochemistry remain three aspects who are especially interested in. They include activity enhancement, selectivity enhancement, and different reaction products or different reactivity.

Recently, a number of methods for the functionalization of fullerene have been reported due to the unique electronic and structural properties of fullerene and its functionalized derivatives.[13] However, fullerene and fullerene-related materials, such as carbon nanotubes and graphite, often have low solubility in organic solvents and water, which can make their functionalization and application challenges. Because of the avoidance of organic solvents, mechanochemical techniques have been used to tackle these problems. In 1997, Komatsu and co-workers developed the first method for the synthesis of a fullerene dimer, C_{120} **2,** using mechanochemistry (Scheme 2a).[14a] Fullerene dimer C_{120} **2** could be obtained in 30 min with 18% yield by milling fullerene C_{60} **1** with KCN followed by a trifluoroacetic acid wash. However, this dimer C_{120} **2** could not be obtained under solution-based conditions. Wudl and co-workers only obtained cyano functionalized fullerene, **3** by stirring fullerene with NaCN in a solvent mixture of 1,2-dichlorobenzene and DMF (Scheme 2b).[14b]

a) Dimerizaiton of fullerene under mechanochemical conditions



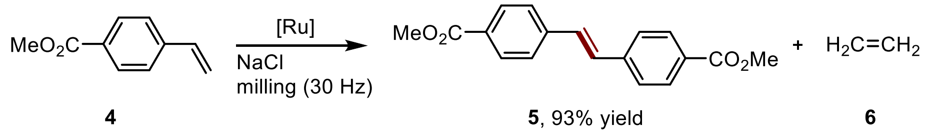
b) Cyano functionalized fullerene under solution-based conditions



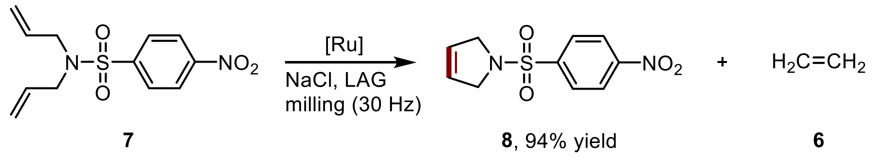
Scheme 2. Methods for the functionalization of fullerene. a) Dimerization of fullerene under mechanochemical conditions. b) Cyano functionalized fullerene under solution-based conditions.

Olefin metathesis is one of the most versatile and powerful tools for the formation and interconversion of C–C double bonds, which can be applied to medicinal chemistry and natural product synthesis.[15] However, in that context, the solid-state has remained almost unexplored as a medium for olefin metathesis. In 2015, Friščić and co-workers described the development of a first mechanochemical approach for ruthenium-catalyzed olefin metathesis, including cross-metathesis and ring-closing metathesis (Scheme 3).[16] In this study, authors used commercially available catalysts to achieve high-yielding, rapid, room-temperature metathesis of solid or liquid olefins on a multigram scale using either no or only a catalytic amount of a liquid. The broad importance of olefin metathesis and industrial demands for developing cleaner, sustainable synthetic techniques render the presented approach to the metathesis of solid olefins an important step in the development of industrially attractive solvent-free organic syntheses.

a) Ruthenium-catalyzed cross-metathesis of solid olefins under mechanochemical conditions



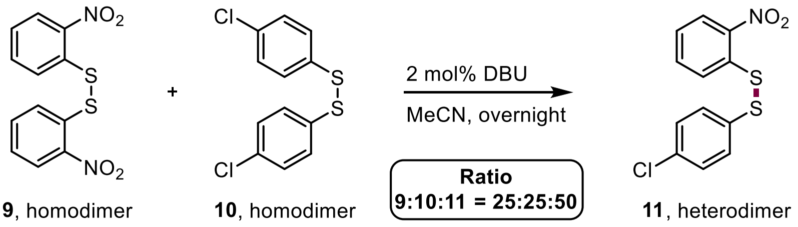
b) Ruthenium-catalyzed ring-closing metathesis of solid olefins under mechanochemical conditions



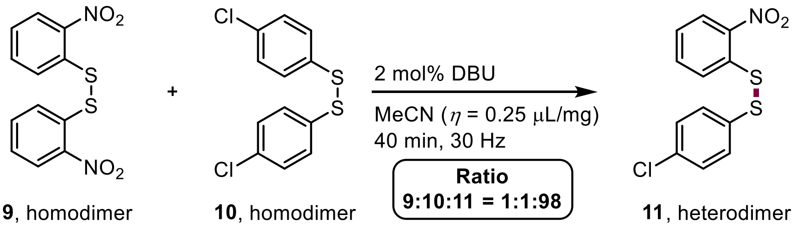
Scheme 3. Ruthenium-catalyzed olefin metathesis under mechanochemical conditions. a) Ruthenium-catalyzed cross-metathesis of solid olefins under mechanochemical conditions. b) Ruthenium-catalyzed ring-closing metathesis of solid olefins under mechanochemical conditions.

As well as activity enhancement, mechanochemistry has been used to alter or control the selectivity of reaction outcomes. In 2010, Friščić and co-workers demonstrated that thermodynamic equilibrium could be obtained under mechanochemical conditions. It was shown that there was a significant difference in the position of equilibrium under mechanochemical and solution-based conditions when they used the base-catalyzed metathesis of aromatic disulfides as a model reaction.[17] In dilute acetonitrile solution, homodimer **9**, homodimer **10**, and heterodimer **11** could be obtained in a ratio of 1:1:2 (Scheme 4a). However, both liquid-assisted-grinding (LAG) and neat grinding led to the almost complete conversion of homodimers **9** and **10**, and afforded 98% heterodimer **11** (Scheme 4b). These different equilibrium compositions could be explained by crystal packing effects, which do not exist in solution but are a factor for consideration under mechanochemical conditions.

a) Aromatic disulfides metathesis under solution-based conditions

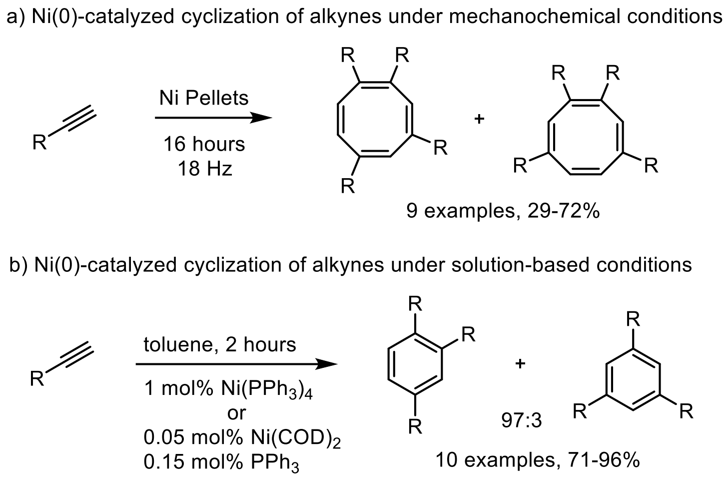


b) Aromatic disulfides metathesis under mechanochemical conditions



Scheme 4. Aromatic disulfide metathesis reaction. a) aromatic disulfide metathesis reaction under solution-based conditions. b) aromatic disulfide metathesis reaction under mechanochemical conditions.

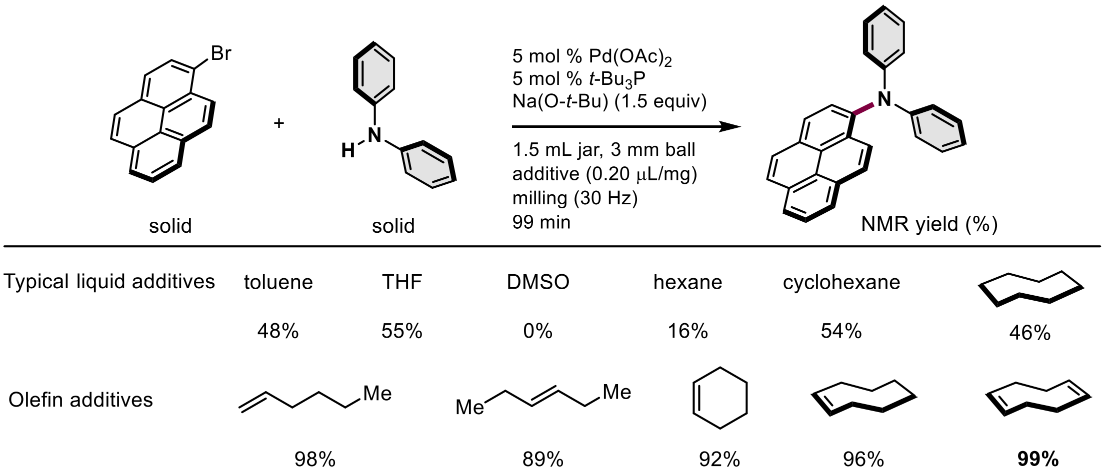
In 2016, Guan, Mack, and co-workers developed a method for the cyclotetramerization of alkynes to afford cyclooctatetraenes using recyclable Ni(0) pellets as the .catalyst under mechanochemical conditions (Scheme 5a).[18a] Compared to the mechanochemical conditions, reactions carried out under solution-based conditions, catalyzed by Ni(0) complexes, yielded the major products as an aromatic trimer (Scheme 5b).[18b] This study demonstrates that mechanochemistry may provide different reaction products compared to conventional solution-based methods.


a) Ni(0)-catalyzed cyclization of alkynes under mechanochemical conditions

b) Ni(0)-catalyzed cyclization of alkynes under solution-based conditions

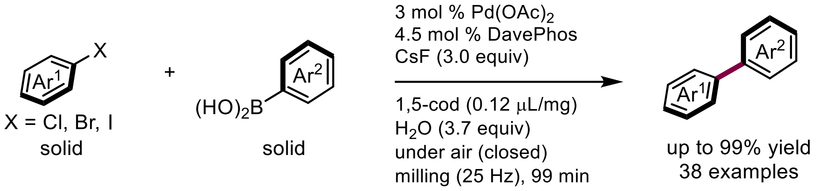
Scheme 5. Nickel(0)-catalyzed cyclization of alkynes. a) Nickel(0)-catalyzed cyclization of alkynes under mechanochemical conditions. b) Nickel(0)-catalyzed cyclization of alkynes under solution-based conditions.

In 2019, Ito, Kubota, and co-workers described a rational strategy that provides a general entry to palladium-catalyzed Buchwald–Hartwig cross-coupling reaction in the solid-state (Scheme 6).[19] Although palladium-catalyzed cross-coupling reactions using mechanochemistry have been reported, the solid-state cross-coupling reactions remained extremely limited. They demonstrated that olefin additives could act as efficient molecular dispersants for the palladium-based catalyst in solid-state media to facilitate the challenging solid-state cross-coupling reaction. Beyond the immediate utility of this protocol, this strategy could inspire the development of industrially attractive solvent-free palladium-catalyzed cross-coupling processes for other valuable synthetic targets.



Scheme 6. Olefin-accelerated solid-state C–N cross-coupling reactions using mechanochemistry.

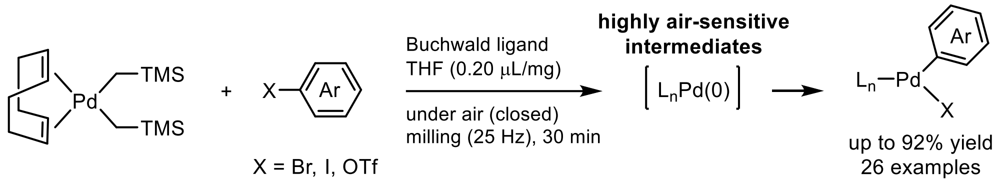
After finding out that olefin additives such as 1,5-cyclooctadiene (1,5-cod) dramatically can accelerate the C–N bond-forming reaction in the solid-state, they turned attention to other cross-coupling reactions such as Suzuki–Miyaura cross-coupling reaction. In 2019, Ito, Kubota, and co-workers also described a strategy about solid-state Suzuki–Miyaura cross-coupling reactions, which can be accelerated by olefin additives using mechanochemistry (Scheme 7).[20] Compared to previous studies, the newly developed protocol is the first broadly applicable mechanochemical protocol for a solid-state palladium-catalyzed organoboron cross-coupling reaction and shows a substantially broadened substrate scope involving unactivated aryl chlorides.



√ fast and scalable **√ operationally simple** **√ broad scope**

Scheme 7. Olefin-accelerated solid-state Suzuki-Miyaura cross-coupling reactions using mechanochemistry.

The Ito group not only demonstrated that solid-state palladium-catalyzed cross-coupling reactions could be carried out by mechanochemistry but also embarked on the moisture- and oxygen-sensitive reagents can be synthesized without inert atmosphere using mechanochemistry. In 2019, Ito, Kubota, and co-workers described that solvent-free mechanochemical synthetic techniques allow using highly oxygen-sensitive palladium(0) species in air for the stoichiometric oxidative addition of aryl halides (Scheme 8).[21] Using mechanochemistry, the preparation of palladium-based oxidative addition complexes no longer requires glove-box or Schlenk-line techniques. The authors presumed that the low diffusion efficiency of gaseous oxygen in the solid-state reaction mixture was identified as the most likely reason for the low impact of atmospheric oxygen on those sensitive organometallic reactions.



√ proceeding efficiently in air **√ without degassed solvents** **√ operationally simple**

Scheme 8. Synthesis of oxidation addition complexes from aryl halide and palladium(0) using mechanochemistry.

Despite the significant progress, transition-metal-catalyzed C–H bond functionalizations using mechanochemistry have remained underdeveloped.[22] The first of these studies towards the catalytic mechanochemical C–H bond functionalizations was reported in 2015 by Bolm and co-workers, who used a rhodium(III) complex to catalyze an oxidative Heck-type reaction in a ball mill.[22a] More recently, mechanochemistry has also been applied to the transition-metal-catalyzed halogenation,[22b] amination,[22c,f,j] olefination,[22d] arylation,[22e] allylation,[22g] alkynylation,[22h] and oxidative cyclization[22i] of C–H bonds. However, to the best of the author's knowledge, a mechanochemical C–H borylation reaction has not been reported to date, even if the development of such a catalytic C–H borylation would be particularly attractive from an industrial perspective.

Chapter 1 describes the first mechanochemical method for an iridium(I)-catalyzed C–H borylation by using a diboron reagent.[23] This reaction was applied to a variety of heteroaromatic compounds, furnishing the corresponding arylboronates in good-to-high yields with excellent regioselectivity. Notably, this mechanochemical C–H borylation does not require the use of inert gas and/or harmful organic solvents. To demonstrate the synthetic utility of this protocol, a one-pot mechanochemical C–H borylation/Suzuki–Miyaura cross-coupling sequence was developed.

In recent years, significant progress has been made concerning organic transformations that are carried out using mechanochemistry. However, most of the above reactions could be considered as the same conception to the solution-based reactions, although the different products or new selectivity could be generated using mechanochemistry. Therefore, the author would like to presume a novel idea to facilitate organic reactions under mechanochemical conditions. Visible-light photo-redox catalysis represents a key recent development in contemporary organic synthesis.[24] In these transformations, the photoexcited catalyst can act as a potent single-electron oxidant, transferring an electron to an acceptor, after which single-electron oxidation of a donor affords the product under concomitant regeneration of the ground state catalyst. Inspired by the unique profile of photo-redox systems based on light irradiation and the utility of ball milling in mechanochemistry, the author hypothesized the redox activation of small organic molecules could be achieved through a mechanistically distinct approach using mechanical energy.[25] In particular, the author envisioned that the agitation of piezoelectric materials[26] via ball milling could generate temporarily highly polarized particles that might act as strong reductants to transfer electrons to small organic molecules, followed by oxidative quenching of a donor, thus inducing the selective formation of bonds in a manner analogous to photo-redox catalysis.

Chapter 2 describes the first example of arylation and borylation reactions using mechanical force and piezoelectric materials.[27] This mechano-redox system, causing by the agitation of piezoelectric materials via ball milling to reduce aryl diazonium salts, can be carried out on gram scale without organic solvents in air, and do not require special operating conditions. This operational simplicity suggests that the present approach may complement existing photo-redox transformations in a practical and environmentally friendly manner. Beyond the immediate benefits of this protocol, this strategy could be applicable to light-sensitive or light-absorbing substrates that cannot be subjected to conventional photo-redox systems.

Chapter 3 describes the first example for the synthesis of (*Z*)-1-bromo-1-alkenylboronate esters *via* copper(I)-catalyzed stereoselective debromoborylation of aliphatic 1,1-debromo-1-alkenes with bis(pinacolato)diboron in the presence of a copper(I) catalyst.[28] The borylation reaction exhibits a wide substrate scope, good functional group compatibility, and affords a variety of (*Z*)-brominated borylation products in moderate to good yields. At the same time, this study is the first example of the selective debromoborylation of 1,1-dibromo-1-alkenes, which is expected to become a powerful synthetic approach to construct a broad range of intermediates and materials.

References

(1) a) D. Tan, F. García, *Chem. Soc. Rev.* **2019**, *48*, 2274; b) T. Friščić, C. Mottillo, H. M. Titi, *Angew. Chem. Int. Ed.* **2020**, *59*, 1018.

(2) a) T. Friščić, *J. Mater. Chem.* **2010**, *20*, 7599; b) S.-E. Zhu, F. Li, G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7535; c) J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007; d) J. L. Howard, Q. Cao, D. L. Browne, *Chem. Sci.* **2018**, *9*, 3080.

(3) F. Gomollón-Bel, *Chem. Int.* **2019**, *41*, 12.

(4) L. Takacs, *Chem. Soc. Rev.* **2013**, *42*, 7649.

(5) M. Faraday, *Q. J. Sci. Lit. Arts* **1820**, *8*, 374.

(6) M. C. Lea, *Br. J. Photogr.* **1866**, *13*, 84.

(7) W. Spring, *Bull. Acad. R. Med. Belg.* **1880**, *49*, 323.

(8) C. Suryanarayana, *Prog. Mater. Sci.* **2001**, *46*, 1.

(9) a) J. G. Hernández, T. Friščić, *Tetrahedron Lett.* **2015**, *56*, 4253; b) J.-L. Do, T. Friščić, *ACS Cent. Sci.* **2017**, *3*, 13.

(10) N. R. Rightmire, T. P. Hanusa, *Dalton Trans.* **2016**, *45*, 2352.

(11) a) T. Friščić, *Chem. Soc. Rev.* **2012**, *41*, 3493; b) D. Braga, L. Maini, F. Grepioni, *Chem. Soc. Rev.* **2013**, *42*, 7638.

(12) a) T. Friščić, W. Jones, *Faraday Discuss.* **2007**, *136*, 167; b) P. Baláž, M. Achimovičová, M. Baláž, P. Billik, Z. Cherkezova-Zheleva, J. M. Criado, F. Delogu, E. Dutková, E. Gaffet, F. J. Gotor, R. Kumar, I. Mitov, T. Rojac, M. Senna, A. Streletskii, K. Wieczorek-Ciurowa, *Chem. Soc. Rev.* **2013**, *42*, 7571; c) C. Mottillo, T. Friščić, *Molecules* **2017**, *22*, 144; d) P. A. Julien, C. Mottillo, T. Friščić, *Green Chem.* **2017**, *19*, 2729.

(13) W. Yan, S. M. Seifermann, P. Pierrat, S. Bräse, *Org. Biomol. Chem.* **2015**, *13*, 25.

(14) a) G.-W. Wang, K. Komatsu, Y. Murata, M. Shiro, *Nature* **1997**, *387*, 583; b) M. Keshavarz-K, B. Knight, G. Srdanov, F. Wudl, *J. Am. Chem. Soc.* **1995**, *117*, 11371.

(15) a) F. Chen, T. Wang, N. Jiao, *Chem. Rev.* **2014**, *114*, 8613; b) A. H. Hoveyda, A. R. Zhugralin, *Nature* **2007**, *450*, 243.

(16) J.-L. Do, C. Mottillo, D. Tan, V. Štrukil, T. Friščić, *J. Am. Chem. Soc.* **2015**, *137*, 2476.

(17) A. M. Belenguer, T. Friščić, G. M. Day, J. K. M. Sanders, *Chem. Sci.* **2011**, *2*, 696.

(18) a) R. A. Haley, A. R. Zellner, J. A. Krause, H. Guan, J. Mack, *AGS Sustainable Chem. Eng.* **2016**, *4*, 2464; b) S. K. Rodrigo, I. V. Powell, M. G. Coleman, J. A. Krause, H. Guan, *Org. Biomol. Chem.* **2013**, *11*, 7653.

(19) K. Kubota, T. Seo, K. Koide, Y. Hasegawa, H. Ito, *Nat. Commun.* **2019**, *10*, 111.

(20) T. Seo, T. Ishiyama, K. Kubota, H. Ito, *Chem. Sci.* **2019**, *10*, 8202.

(21) K. Kubota, R. Takahashi, H. Ito, *Chem. Sci.* **2019**, *10*, 5837.

(22) a) G. N. Hermann, P. Becker, C. Bolm, *Angew. Chem. Int. Ed.* **2015**, *54*, 7414; b) J. G. Hernández, C. Bolm, *Chem. Commun.* **2015**, *51*, 12582; c) G. N. Hermann, P. Becker, C. Bolm, *Angew. Chem. Int. Ed.* **2016**, *55*, 3781; d) K.-Y. Jia, J.-B. Yu, Z.-J. Jiang, W.-K. Su, *J. Org. Chem.* **2016**, *81*, 6049; e) S.-

J. Lou, Y.-J. Mao, D-Q. Xu, J.-Q. He, Q. Chen, Z.-Y. Xu, *ACS Catal.* **2016**, *6*, 3890; f) G. N. Hermann, C. Bolm, *ACS Catal.* **2017**, *7*, 4592; g) X. Jiang, J. Chen, W. Zhu, K. Cheng, Y. Liu, W.-K. Su, C. Yu, *J. Org. Chem.* **2017**, *82*, 10665; h) G. N. Hermann, M. T. Unruh, S.-H. Jung, M. Krings, C. Bolm, *Angew. Chem. Int. Ed.* **2018**, *57*, 10723; i) G. N. Hermann, C. L. Jung, C. Bolm, *Green Chem.* **2017**, *19*, 2520; j) H. Cheng, J. G. Hernández, C. Bolm, *Adv. Synth. Catal.* **2018**, *360*, 1800.

(23) Y. Pang, T. Ishiyama, K. Kubota, H. Ito, *Chem. Eur. J.* **2019**, *25*, 4654.

(24) a) C. Stephenson, T. Yoon, D. W. C. MacMillan, *Visible Light Photocatalysis in Organic Chemistry* (Wiley-VCH, Weinheim, Germany, ed. 1, 2018); b) C. K. Pier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322; c) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075; d) K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035; e) C.-S. Wang, P. H. Dixneuf, J.-F. Soulé, *Chem. Rev.* **2018**, *118*, 7532.

(25) a) J. C. Robertson, M. L. Coote, A. C. Bissmber, *Nat. Rev. Chem.* **2019**, *3*, 290; b) J. Liang, J. M. Fernández, *J. Am. Chem. Soc.* **2011**, *133*, 3528; c) P. Dopieralski, J. Ribas-Arino, P. Anjukandi, M. Krupicka, J. Kiss, D. Marx, *Nature Chem.* **2013**, *5*, 685; d) H. Yan, F. Yang, D. Pan, Y. Lin, J. N. Hohman, D. Solis-Ibarra, F. H. Li, J. E. P. Dahl, R. M. K. Carlson, B. A. Tkachenko, A. A. Fokin, P. R. Schreiner, G. Galli, W. L. Mao, Z.-X. Shen, N. A. Melosh, *Nature* **2018**, *554*, 505.

(26) a) S. Ikeda, T. Takata, M. Komoda, M. Hara, J. N. Kondo, K. Domen, A. Tanaka, H. Hosono, H. Kawazoe, *Phys. Chem. Chem. Phys.* **1999**, *1*, 4485; b) M. Hara, H. Hasei, M. Yashima, S. Ikeda, T. Takata, J. N. Kondo, K. Domen, *Appl. Catal. A-Gen.* **2000**, *190*, 35; c) Z. L. Wang, J. Song, *Science* **2006**, *312*, 242; d) X. Wang, J. Song, J. Liu, Z. L. Wang, *Science* **2007**, *316*, 102; e) Y. Qin, X. Wang, Z. L. Wang, *Nature* **2008**, *451*, 809; f) K.-S. Hong, H. Xu, H. Konishi, X. Li, *J. Phys. Chem. Lett.* **2010**, *1*, 997; g) H. Mohapatra, M. Kleiman, A. P. Esser-Kahn, *Nature Chem.* **2017**, *9*, 135; h) M. B. Starr, J. Shi, X. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 5962; i) M. B. Starr, X. Wang, *Sci. Rep.* **2013**, *3*, 2160; j) H. Lin, Z. Wu, Y. Jia, W. Li, R.-K. Zheng, H. Luo, *Appl. Phys. Lett.* **2014**, *104*, 162907; k) W. Lv, L. Kong, S. Lan, J. Feng, Y. Xiong, S. Tian, *J. Chem. Technol. Biotechnol.* **2017**, *92*, 152.

(27) K. Kubota, Y. Pang, A. Miura, H. Ito, *Science* **2019**, *366*, 1500.

(28) Y. Pang, R. Kojima, H. Ito, *Org. Biomol. Chem.* **2018**, *16*, 6187.

Chapter 1.

Iridium(I)-Catalyzed C–H Borylation Using Mechanochemistry

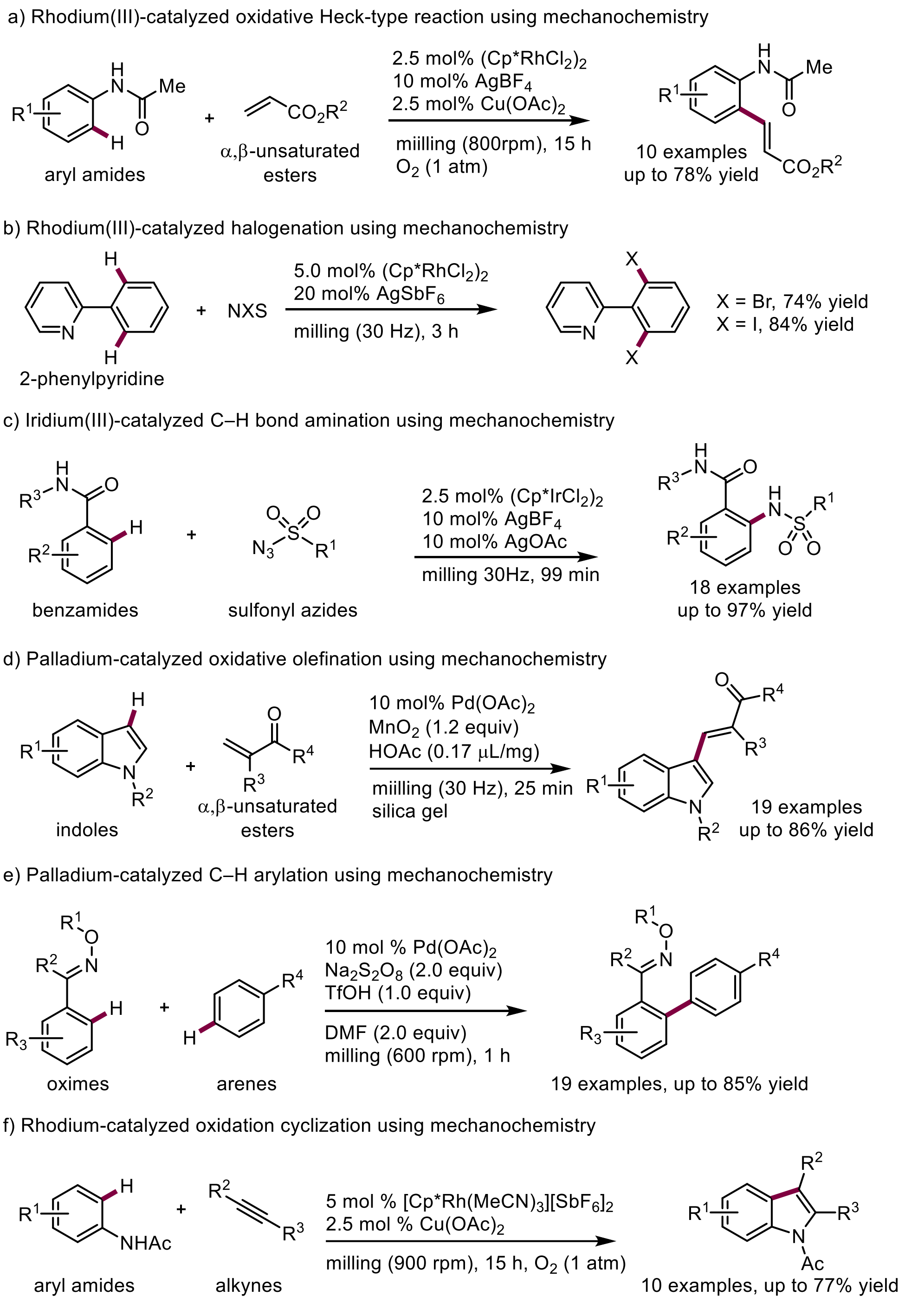
Abstract

Mechanochemistry has been applied to an iridium(I)-catalyzed C–H borylation for the first time. Using either no or only a catalytic amount of a liquid, the mechanochemical C–H borylation of a series of heteroaromatic compounds proceeded under air to afford the corresponding arylboronates in good to excellent yields. The one-pot mechanochemical C–H borylation/Suzuki-Miyaura cross-coupling sequence for the direct synthesis of 2-aryl indole derivatives was also developed. We expect that the present study constitutes an important step in the development of industrially attractive solvent-free C–H bond functionalization processes under air.

Introduction

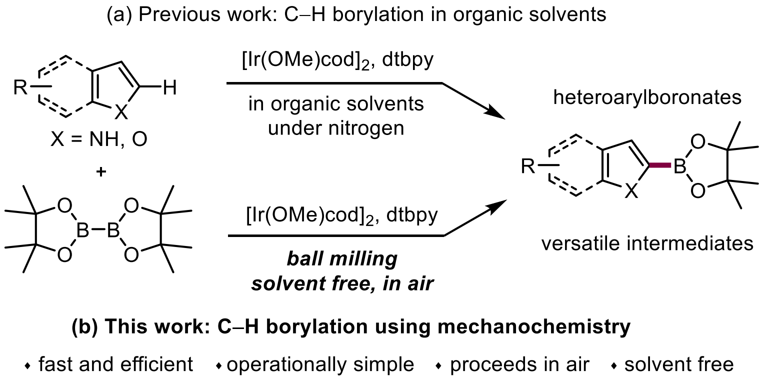
Organoboronic acids and their derivatives, especially arylboronate esters, are powerful and versatile reagents in synthetic chemistry, medicinal and material science because of their high stability, low toxicity, and synthetic utility in various transformations such as the Suzuki-Miyaura cross-coupling reaction.[1] A C–H borylation reaction has become one of the most important synthetic methods since it provides a straightforward way to form a great variety of functionalized organoboron compounds.[2] In particular, iridium(I)-catalyzed aromatic C–H borylation reactions have proven to be one of the most efficient methods and been widely used in the synthesis of complex molecules.[2c,3] Despite the significant progress, however, the exploration of new concepts and reaction media for improving the sustainability of the C–H borylation remains an important research area.[2c,3] In this context, the use of significant amounts of dry and degassed organic solvents and the need for inert gas atmosphere are still limiting factors.

In recent years, significant progress has been made in organic transformations performed under mechanochemical conditions.[4,5] Compared with traditional solvent-based protocols, the advantages of conducting chemical transformations using mechanochemistry include the reduction of harmful organic solvents, the shorter reaction time, the absence of external heating, and the possibility to access different product compositions.[6] Although chemists have successfully applied mechanochemical techniques to mechanistically complex organic reactions, the development of transition-metal-catalyzed C–H bond functionalizations under solvent-free mechanochemical conditions have remained underdeveloped.[7] The first of these studies toward the catalytic mechanochemical C–H bond functionalizations was reported by Bolm et al. in 2015, where a rhodium(III) complex was used to catalyze an oxidative Heck-type reaction in a ball mill.[7a] More recently, mechanochemistry has also been applied to the transition-metal-catalyzed halogenation,[7b] amination,[7c,f,j] olefination,[7d] arylation,[7e] allylation,[7g] alkynylation,[7h] and oxidative cyclization[7i] of C–H bonds (Scheme 1-1). However, to the best of the author's knowledge, a mechanochemical C–H borylation reaction has not ever been reported, even if the development of such a catalytic C–H borylation would be particularly attractive in the industrial field.



Scheme 1-1. Transition-metal-catalyzed C–H bond functionalizations using mechanochemistry. a) Oxidative Heck-type reaction, b) halogenation reaction, c) amination reaction, d) oxidative olefination reaction, e) arylation reaction, f) oxidative cyclization.

Inspired by the previous works in Ito groups about the syntheses of boron-containing compounds, the author would like to develop a C–H borylation protocol using mechanochemistry. Herein, the author reports the first mechanochemical methodology for the iridium(I)-catalyzed C–H borylation with a diboron reagent (Scheme 1-2). This reaction can be applied to various heteroaromatic compounds to form the corresponding arylboronates in good to high yields with excellent regioselectivity. Notably, the mechanochemical C–H borylation does not require the use of inert gases and harmful organic solvents. To demonstrate the synthetic utility, the one-pot mechanochemical C–H borylation/Suzuki-Miyaura cross-coupling sequence has also been developed.

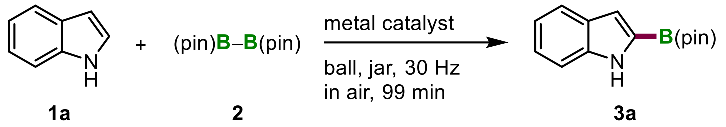


Scheme 1-2. Iridium(I)-catalyzed C–H borylation reactions.

Results and Discussion

Initially, the author used analogous reaction conditions to those reported for a solution process by Hartwig and Miyaura[8] for the mechanochemical C–H borylation of indole **1a** with bis(pinacolato)diboron **2** in the presence of $[\mathrm{Ir(OMe)cod}]_2$ and 4,4'-di-tert-butyl-2,2'-bipyridine (dtbpy) (Table 1-1). Reactions were conducted in a Retsch MM400 mill in a stainless milling jar using one stainless steel ball. Unfortunately, our first attempt to perform this mechanochemical reaction in a milling jar (1.5 mL) was unsuccessful, and the desired product **3a** was not detected (entry 1). The author found that a careful choice of the jar and the ball dramatically improved the efficiency of the mechanochemical C–H borylation (entries 2–5). When using 5.0 mL of a milling jar and 7.5 mm ball of a ball, the C–H borylation product **3a** was obtained in 74% yield upon grinding for 99 min (entry 2). Pleasingly, increasing the loading of **2** from 0.5 mmol to 0.6 mmol, the yield of **3a** improved (84%; entry 6), which is comparable to the yield obtained from the reported solvent-based conditions.[8] In the conventional C–H borylation reactions in solution, one or two of the boryl groups in a diboron reagent **2** can be introduced into the substrates, depending on the conditions applied.[2,8] Interestingly, the author found that both boryl groups in **2** were introduced into **1a** under the current mechanochemical conditions. Next, the author also investigated other transition-metals such as nickel and iron complexes, which are effective catalysts for aromatic C–H borylation reactions in solution (entries 7 and 8).[9] However, no reaction was observed under the applied mechanochemical conditions.

Table 1-1. Optimization of the mechanochemical C–H borylation reaction conditions.[a]

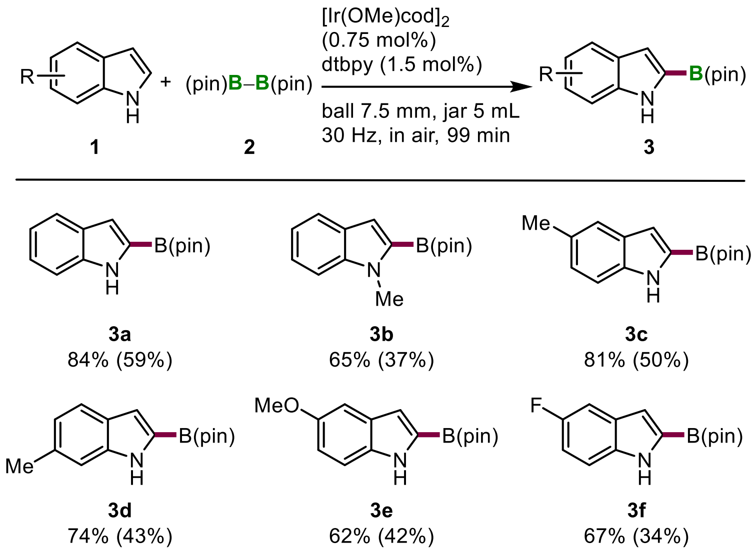


Entry	Catalyst	Ball (diameter, mm)	Milling jar (mL)	NMR yield (%)[b]
1	$[Ir(OMe)cod]_2$/dtbpy	3.0	1.5	0
2	$[Ir(OMe)cod]_2$/dtbpy	7.5	5.0	74
3	$[Ir(OMe)cod]_2$/dtbpy	7.5	25.0	0
4	$[Ir(OMe)cod]_2$/dtbpy	15.0	25.0	0
5	$[Ir(OMe)cod]_2$/dtbpy	3.0	5.0	68
6[c]	$[Ir(OMe)cod]_2$/dtbpy	7.5	5.0	84
7[d]	$Ni(OAc)_2$/ICy·HCl	7.5	5.0	0
8[e]	$Fe(acac)_3$	7.5	5.0	0

[a] Reaction conditions: **1a** (1.0 mmol), **2** (0.5 mmol), $[Ir(OMe)cod]_2$ (0.75 mol%), dtbpy (1.5 mol%), 30 Hz, 99 min. Both jars and balls were made of stainless steel. [b] Yields are based on the amount of **1a** and determined by ^1H NMR spectroscopy. [c] 0.6 mmol of **2** were used. [d] $Ni(OAc)_2$ (5 mol%), 1,3-dicyclohexylimidazolium chloride (ICy·HCl) (5 mol%), and Na(O-t-Bu) (10 mol%) were used instead of the Ir(I)/dtbpy system. [e] $Fe(acac)_3$ (20 mol%) and K_2CO_3 (2.0 equiv) were used instead of the Ir(I)/dtbpy system.

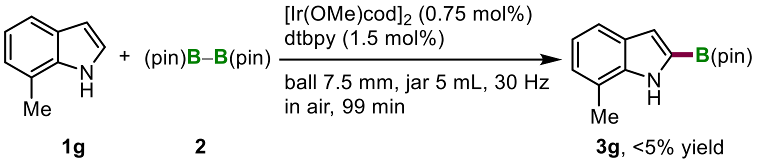
With the optimal reaction conditions in hand (Table 1-1, entry 6), a series of substituted indole substrates was tested to investigate the scope of the mechanochemical iridium(I)-catalyzed C–H borylation in a ball mill (Table 1-2). The C–H borylation reactions proceeded efficiently to give the corresponding C2-borylated indoles in moderate to good yields. The author found that the purification of the boronate esters without loss of the yield seems to be difficult using typical chromatography techniques because they are easily hydrolyzed and protonated in silica gel; thus, the isolated yields were generally lower than the corresponding NMR yields. The methyl-protected indole **1b** reacted with diboron compound **2** to give the borylation product **3b** in good yield (65% NMR yield; 37% isolated yield). The reaction of indoles bearing methyl group at the 5- or 6-positions (**1c** and **1d**) proceeded to afford the corresponding products (**3c** and **3d**) in good to excellent yields (81% and 74% NMR yield, respectively). In addition, a methoxy group (**1e**) and a fluorine (**1f**) did not hamper the mechanochemical C–H borylation process and afforded the corresponding products (**3e** and **3f**) in good yields (62% NMR yield and 67% NMR yield, respectively).

Table 1-2. Substrate Scope of the mechanochemical C–H borylation of indoles.[a]



[a] Reaction conditions: **1** (1.0 mmol), **2** (0.6 mmol), [Ir(OMe)cod]$_2$ (0.75 mol%), dtbpy (1.5 mol%), 30 Hz, 99 min. Yields are based on the amount of **1** and determined by ^{1}H NMR spectroscopy; isolated yields are shown in parentheses.

Unfortunately, the author found that no reaction occurred when 7-methyl-substituted indole **1g** was used as the substrate for the mechanochemical C–H borylation reaction (Scheme 1-3). The author speculated that one possible reason for the observed reactivity difference may be the rheological changes of the reaction mixture upon mechanical grinding.[10] In the case of **1a**, the reaction mixture dramatically changed from a solid-state mixture to a viscous oil (Fig. 1-1a and 1-1b). This dramatical change in rheology would improve the mixing efficiency of the reactants and catalyst, resulted in facilitating the C–H borylation.[10] In contrast, the reaction of **1g**, which has a higher melting point (80°C) compared to that of **1a** (55°C), remained a heterogeneous solid-state mixture even after grinding for 99 min (Fig. 1-1c and 1-1d). These results suggested that the low yields of **3g** might be due to poor mixing of the solid-state reaction mixtures in a ball mill.



Scheme 1-3. Mechanochemical C–H borylation of 7-methyl-substituted indole **1g**.

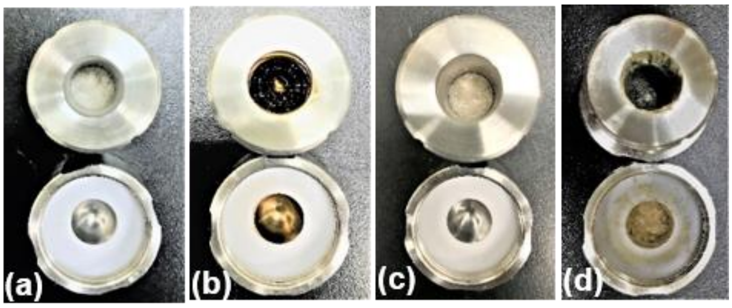
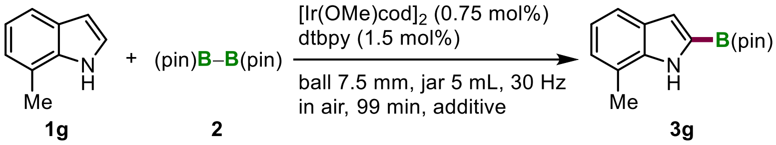


Fig. 1-1. Reaction mixtures after grinding in a ball mill. Reaction mixture containing indole **1a** (a) before and (b) after grinding for 99 min, and that of 7-methyl indole **1g** (c) before and (d) after grinding for 99 min.

Therefore, the author attempted grinding with an abrasive, inert, solid mechanochemical auxiliary to enhance the mixing efficiency (Table 1-3). First, the author used common solid lubricants such as MoS_2, graphite, or polytetrafluoroethylene (PTFE) in the mechanochemical C–H borylation of **1g**. However, no desired product **3g** was detected under these reaction conditions (entries 1–3). The reactions in the presence of inert solid auxiliaries (entries 4–5) or inorganic salts (entries 6–7) were also investigated, resulted in no product formation. Next, the author attempted liquid-assisted-grinding (LAG), which used substoichiometric liquid additives, to improve the reactivity (entries 8–10).[11] The following LAG reactions are all characterized by a 0.25 ratio of μL of liquid added per mg of reactants. Initially, hexane was tested, given that it is frequently employed as reaction solvent for solvent-based iridium(I)-catalyzed C–H borylation reactions. Unfortunately, the reaction in the presence of hexane did not provide the borylation product **3g** (entry 8). In sharp contrast, the use of tetrahydrofuran (THF) dramatically improved the reactivity (88% yield; entry 9). The reaction using CH_2Cl_2 also proceeded smoothly to afford the desired product **3g** in high yield (87% yield; entry 10). The author noted that the reaction mixture containing THF as the LAG additive changed from a solid-state mixture to a viscous oil (See the experimental section).

Table 1-3. Further optimization of the mechanochemical C–H borylation reaction of **1g**.[a]



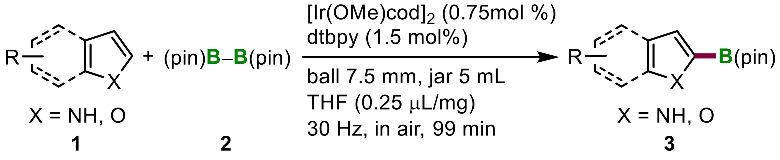
Entry	Additive	NMR yield (%)[b]
1	MoS_2 (80 mg)	0
2	Graphite (50 mg)	0
3	PTFE (50 mg)	0
4	4 Å molecular sieves (50 mg)	0
5	Sea sand (50 mg)	0
6	Tetrabutylammonium iodide (50 mg)	0
7	NaCl (50 mg)	0
8	Hexane (0.25 μL/mg)	0
9	THF (0.25 μL/mg)	88
10	CH_2Cl_2 (0.25 μL/mg)	86

[a] Reaction conditions: **1g** (1.0 mmol), **2** (0.6 mmol), [Ir(OMe)cod]$_2$ (0.75 mol%), dtbpy (1.5 mol%), 30 Hz, 99 min. Yields are based on the amount of **1g** and determined by ^{1}H NMR spectroscopy.

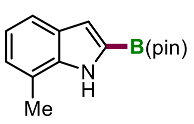
With the modified conditions in hand, a series of substituted indoles having relatively high melting points (>70°C) were tested to investigate the scope of this mechanochemical iridium(I)-catalyzed C–H borylation enabled by LAG (Table 1-4a). Substrates bearing a methyl group at different positions on the aryl ring (**1g** and **1h**) efficiently reacted with **2** to provide the desired borylation products (**3g** and **3h**) in moderate to high yields (88% and 32%, respectively). The relatively low yield of **3h** is probably due to steric hindrance around the reactive C–H bond. Functional groups such as chlorine (**1i**), bromine (**1j**), and ester (**1k**) were tolerated and afforded the corresponding products (**3i–3k**) in moderate to good yields (61–72%). When the *N*-tosyl-protected indole **1l** was used as the substrate, the borylation selectively occurred at the 3-position of the indole to give **3l** because of the steric control of a bulky tosyl group.[12] It should be noted that the substrates in Table 1-4a did not react without the use of THF as a LAG additive. Subsequently, the author turned his attention to the scope of other heteroaryl substrates (Table 1-4b). Pyrroles bearing ester (**1m**) and ketone (**1n**) moieties, which are solid substrates having higher melting points than 70°C, afforded the corresponding borylation products (**3m** and **3n**) in good yield under LAG conditions (64% and

50%, respectively). Without LAG additives, no reaction occurred probably due to poor mixing in the ball mill. Liquid furan derivatives (**1o–1q**) were efficiently borylated to provide the corresponding products (**3o–3q**) in moderate to good yield without the LAG additive (33% and 71% yields). In the case of **1p**, the LAG conditions improved the yield of **3p** to 48%. Interestingly, the mechanochemical C–H borylation of liquid benzofuran (**1r**) did not proceed without a LAG additive. In contrast, the desired product **3r** was obtained in high yield under LAG conditions (93% yield). The results shown in Tables 1-3 and 1-4 suggest that the LAG conditions seem to be robust and can be applied to a wide range of heteroaryl compounds, while the borylation of solid substrates having relatively low melting points (< 70°C) or liquid substrates could proceed efficiently even without a LAG additive.

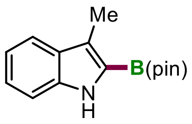
Table 1-4. Substrate scope of mechanochemical C–H borylation with the modified conditions.[a]



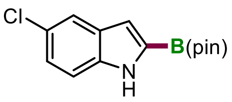
(a) Indoles with relatively high melting points (>70 °C)



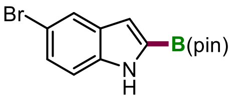
3g
with LAG: 88% (53%)
without LAG: 0%



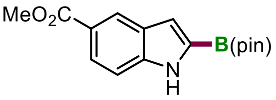
3h
with LAG: 32% (15%)
without LAG: 0%



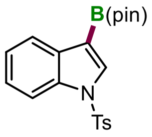
3i
with LAG: 61% (37%)[b]
without LAG: 0%



3j
with LAG: 66% (38%)[b]
without LAG: 0%

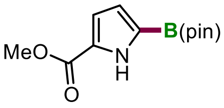


3k
with LAG: 72% (50%)
without LAG: 0%

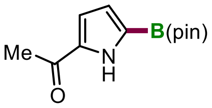


3l
with LAG: 53% (30%)
without LAG: 0%

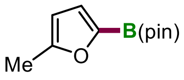
(b) Various heteroaryl substrates



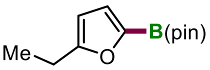
3m
with LAG: 64% (36%)
without LAG: 0%



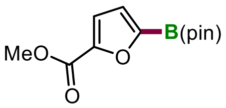
3n
with LAG: 50% (23%)[b]
without LAG: 0%



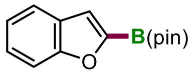
3o
without LAG: 71% (32%)



3p
with LAG: 48% (26%)
without LAG: 33%



3q
without LAG: 62% (60%)



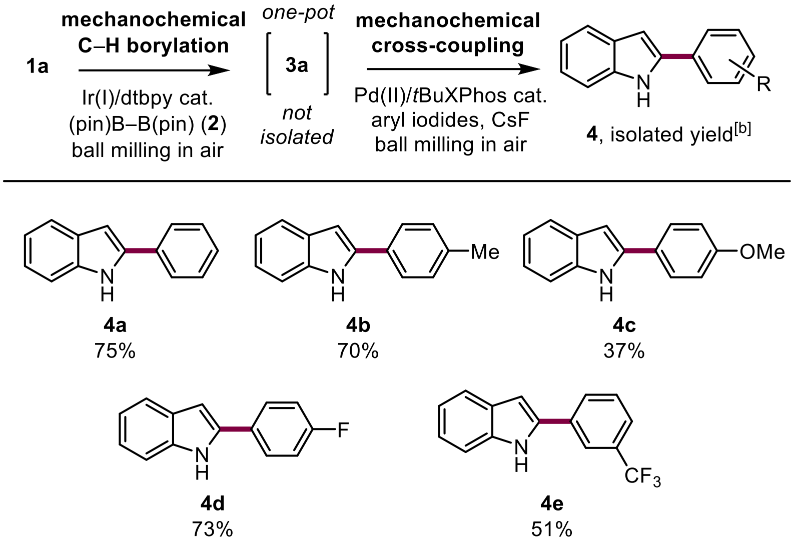
3r
with LAG: 93% (60%)
without LAG: 0%

[a] Reaction conditions: **1** (1.0 mmol), **2** (0.6 mmol), $[Ir(OMe)cod]_2$ (0.75 mol%), dtbpy (1.5 mol%), THF (0.25 μL/mg), 30 Hz, 99 min. Yields are based on the amount of **1** and determined by ^{1}H NMR spectroscopy; isolated yields are shown in parentheses. [b] 0.4 μL/mg THF were used as a LAG additives.

To demonstrate the synthetic utility of the newly developed method, the author also investigated a direct one-pot mechanochemical C–H borylation/Suzuki–Miyaura cross-coupling sequence for the synthesis of 2-aryl indole derivatives from indole **1a** (Table 1-5). The *in situ* obtained 2-borylated indole **3a** was directly subjected to the one-pot cross-coupling with aryl iodides using the palladium/*t*BuXPhos catalyst, which was originally developed by Buchwald and co-workers.[13] Pleasingly, the author found that the desired 2-aryl indoles

(**4a**–**4e**) were formed *via* the one-pot mechanochemical strategy in moderate to good yields (37–75% yields). Notably, the one-pot multi-step transition-metal-catalyzed transformation using mechanochemistry represents a more sustainable synthetic alternative to conventional solution processes.[14]

Table 1-5. Mechanochemical one-pot C–H borylation/Suzuki–Miyaura cross-coupling sequence.[a]



4a 75%

4b 70%

4c 37%

4d 73%

4e 51%

[a] Reaction conditions for the C–H borylation: **1a** (1.0 mmol), **2** (0.6 mmol), $[Ir(OMe)cod]_2$ (0.75 mol%), dtbpy (1.5 mol%), THF (0.25 μL/mg), 30 Hz, 99 min. Reaction conditions for the Suzuki–Miyaura cross-coupling : $Pd(OAc)_2$ (3 mol%), *t*BuXPhos (4.5 mol%), CsF (3.0 mmol), aryl iodide (0.8 mmol), H_2O (3.7 mmol), 30 Hz, 99 min. [b] Isolated yields are based on the amount of aryl iodide.

To gain insight into the C–H borylation reaction using mechanochemistry, preliminary mechanistic studies were carried out. First, the author determined the kinetics of the reaction of a solid substrate, indole **1a**, under the different reaction conditions (Fig. 1-2a). As periodic sampling of the mechanochemical reaction runs requires stopping the mill and opening the jar, each data point was obtained from an individual reaction. Under the conventional solution conditions, the reaction rate was initially high and become slow after 20 min (Fig. 1-2a, orange line). On the other hand, under the developed mechanochemical conditions, the sigmoidal kinetics were observed (Fig. 1-2a, blue line). The reaction did not proceed in the first 60 min and rapidly finished between 60 and 70 min. The author noted that the physical form of the reaction mixture dramatically changed from a solid to a viscous oil appearance during 60 to 70 min (Fig. 1-3). This dramatic change in rheology would improve the mixing efficiency of the reactants and catalyst, resulted in a rapid increase in the reaction rate.[10] Another possible reason for the sigmoidal kinetics would be an induction period (60 min) to form the catalytically active trisboryl iridium complex from the iridium precursor under the mechanochemical conditions.[15,16]

Subsequently, the author investigated the kinetics of the reaction of the liquid substrate, benzofuran **1r** (Fig. 1-2b). He found that there is non-reactive periods of 90 and 50 min before forming the desired borylation product **3r** under both the conventional solution conditions and the present mechanochemical conditions, respectively (Fig. 1-2b, orange and blue lines). Notably, the mechanochemical C–H borylation of **1r** showed much shorter induction period than that of the reaction in solution. Given that no rheological changes in the reaction mixture of **1r** were observed in the mechanochemical conditions (Fig. 1-4), the main reason for the sigmoidal kinetics would be caused by an induction period of the first 50 min to form the catalytically active trisboryl iridium complex from the iridium precursor.[15,16]

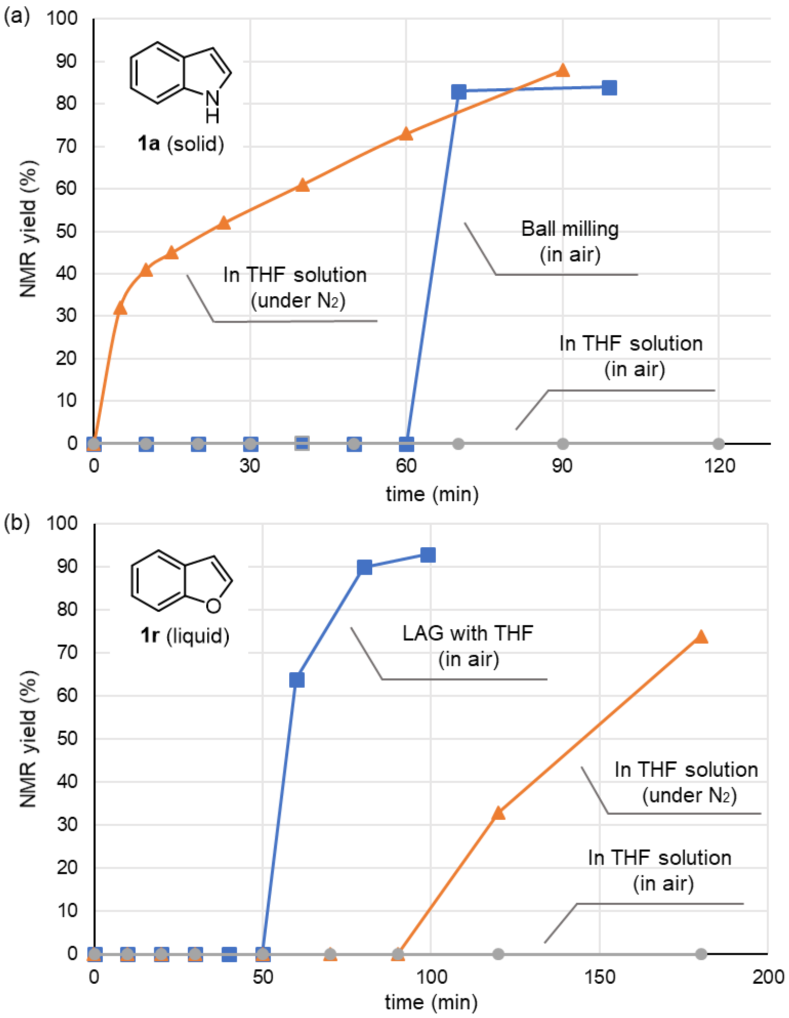


Fig. 1-2. Reaction progress of the iridium(I)-catalyzed C–H borylation under conventional solution conditions or under the developed mechanochemical conditions: (a) indole **1a** (solid) and (b) benzofuran **1r** (liquid).

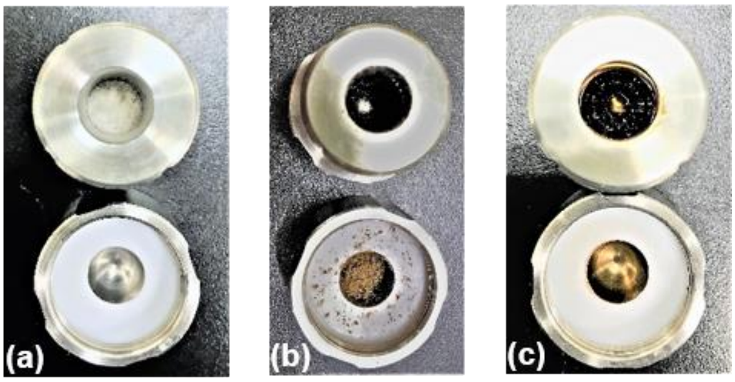


***Fig. 1-3*.** Reaction mixtures containing indole **1a** upon grinding after (a) 0, (b) 60, and (c) 70 min.

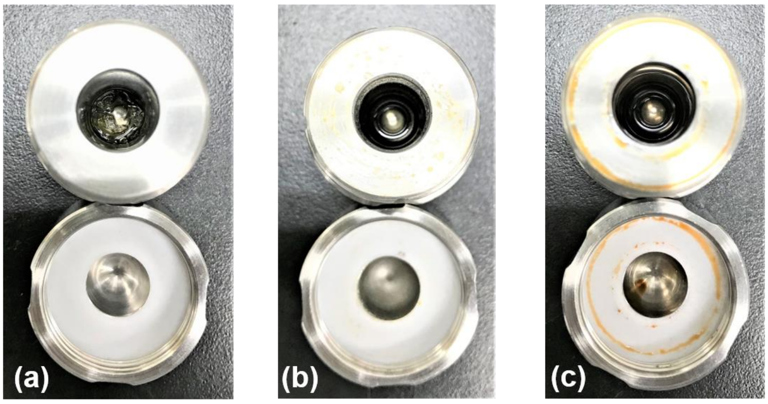


***Fig. 1-4*.** Reaction mixtures containing benzofuran **1r** upon grinding after (a) 0, (b) 60, and (c) 70 min.

It should be noted that no reactions occurred when the C–H borylations were conducted in solution under air (Fig. 1-2a and 1-2b, gray lines), while the mechanochemical C–H borylation reactions can be carried out under air (Fig. 1-2a and 1-2b, blue lines). This is probably because the reaction between sensitive iridium species and gaseous oxygen or water in a ball mill is much slower than that of dissolved oxygen or water in organic solvents.[17] These results highlighted the synthetic utility of the developed C–H borylation protocol in terms of operational simplicity.

Summary

In conclusion, the author has described the first application of mechanochemistry to catalytic C–H borylation reactions. The careful choice of the reaction milling jar, ball, and LAG additives enabled the development of the highly efficient, solvent-free C–H borylation reaction that proceeds under air. Considering the broad importance of the C–H borylation and industrial demands for developing sustainable synthetic methodologies, the present study constitutes an important step in the development of industrially attractive C–H bond functionalization processes. Furthermore, the author expects that this study will open an unexplored reaction environment for the C–H borylation that would exhibit different reactivity and selectivity compared to conventional solution-based reactions. The author is currently studying new catalyst design for the mechanochemical C–H borylation that realizes unique site-selectivity.

Experimental Section

Instrumentation and Chemicals.

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. All reactions were performed using grinding vessels in a Retsch MM 400. Both jars and balls were made of stainless steel. Solvents for reactions were purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^{1}H: 392, 396 or 400 MHz, ^{13}C: 99 or 100 MHz and ^{11}B: 127 MHz). Tetramethylsilane (^{1}H), $CDCl_3$ (^{13}C) and $BF_3 \cdot OEt_2$ (^{11}B) were employed as external standards, respectively. Multiplicity was recorded as follows: s = singlet, brs = broad singlet, d = doublet, t= triplet, q= quartet, m = multiplet. Dibromomethane was used as an internal standard to determine NMR yields. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and an FID detector. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

$[Ir(OMe)cod]_2$ Preparation Procedure.

$[Ir(OMe)cod]_2$ catalyst precursor was prepared according to the reported procedure. A 300 mL 2-necked round bottomed flask was charged with $IrCl_3 \cdot nH_2O$ (3.00 g). The flask was purged with nitrogen and degassed water (24 mL) and ethanol (50 mL) were added. Excess 1,5-cyclooctadiene (12 mL) was added to the resultant dark purple-black solution. The flask was fitted with a reflux condenser and heated with a heating mantle to reflux. The mixture was then reacted for 4 h. Upon completion, a solution with a bright, clear red-orange color was formed. The reaction was cooled and fitted with a distillation apparatus. The solvent removed by distillation and the reaction mixture was left allowing a red crystalline solid to form. The solid was filtered and washed with cold methanol (3 × 10 mL) under nitrogen atmosphere and dried under reduce pressure to afford $[Ir(Cl)cod]_2$ (2.10 g, 66% yield).

A 100 mL round bottomed flask was charged with $[Ir(Cl)cod]_2$ (1.00 g, 1.48 mmol) and KOH (385 mg, 6.86 mmol). The flask was purged with nitrogen and degassed methanol (20 mL) was then added. The reaction was stirred at room temperature for 3 hours under nitrogen, with a continuous flow of nitrogen bubbling through the reaction solvent. Upon completion, no orange-red solid remained and a pale-yellow precipitate had formed. Degassed water (20 mL) was added to the reaction mixture and the vessel was cooled to 0°C for 20 minutes. The yellow solid was filtered under nitrogen atmosphere and washed with water (3 × 10 mL) and cold methanol (3 × 10 mL). The solid was transferred to a round bottom flask and followed by drying under reduced pressure for further 12 hours affording $[Ir(OMe)cod]_2$ (611 mg, 62% yield) as a fine, free-flowing yellow powder.

Substrate Preparation Procedures.

All substrates were commercially available materials except *N*-tosylindole (**1l**). **1l** was prepared according to the reported procedure. Indole (500 mg, 4.26 mmol) as a solution in anhydrous DMF (10 mL) was added to a suspension of NaH (205 mg as a 60% suspension in mineral oil, 5.12 mmol) in anhydrous DMF (10 mL) and stirred at 0°C for 30 min. Tosyl chloride (900 mg, 4.72 mmol) was added dropwise as a solution in anhydrous DMF (5 mL) at 0°C. The resulting solution was allowed to warm to room temperature and stirred for 6 h. Upon completion, the reaction mixture was diluted with water (40 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layer was washed with sat. aq. $NaHCO_3$, brine, and dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel to afford *N*-tosylindole (1.14 g, 98% yield) as a white powder.

General C–H Borylation Procedures.

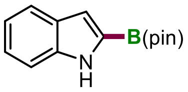
$[Ir(OMe)cod]_2$ (5.0 mg, 0.0075 mmol), 4,4'-di-*tert*-butyl-2,2'-bipyridyl (dtbpy) (4.0 mg, 0.015 mmol), bis(pinacolato)diboron **2** (152.4 mg, 0.60 mmol), and **1a** (117.2 mg, 1.0 mmol) were placed in a jar (5 mL) with a ball (0.75 cm, diameter) under air. Anhydrous THF was also added to the mixture if the reactions are conducted under the LAG conditions. After the jar was closed without the purge with inert gas, the jar was placed in the ball mill (Retsch MM 400, 99 min, 30 Hz). After 99 min, the reaction mixture was passed through a short silica gel column eluting with Et_2O. The crude material was purified by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10) to give the corresponding C–H borylation product **3a** (143.0 mg, 0.59 mmol, 59% yield) as a pale-yellow powder.

General Derivatization Procedures.

$[Ir(OMe)cod]_2$ (5.0 mg, 0.0075 mmol), dtbpy (4.0 mg, 0.015 mmol), bis(pinacolato)diboron **2** (152.4 mg, 0.60 mmol), and **1a** (117.2 mg, 1.0 mmol) were placed in a jar (5 mL) with a ball (0.75 cm, diameter) under air. After the jar was closed without the purge with inert gas, the jar was placed in the ball mill (Retsch MM 400, 99 min, 30 Hz). After 99 min, the jar was opened and charged with $Pd(OAc)_2$ (6.8 mg, 0.03 mmol), *t*BuXPhos (19.1 mg, 0.045 mmol), CsF (455.7 mg, 3.0 mmol), iodobenzene (163.2 mg, 0.8 mmol) and H_2O (67.0 mg, 3.7 mmol). After the jar was closed without the purge with inert gas, the jar was placed in the ball mill (Retsch MM 400, 99 min, 30 Hz). After 99 min, the reaction mixture was passed through a short silica gel column eluting with EtOAc. The crude material was purified by flash chromatography (SiO_2, hexane/ethyl acetate, 99:1 to 98:2) to give the corresponding cross-coupling product **4a** (116.5 mg, 0.60 mmol, 75% yield based on iodobenzene) as a white powder.

Borylation and Derivatization Product Characterizations.

2-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3a).

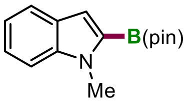


3a

The reaction was conducted with 117.2 mg (1.0 mmol) of **1a**. The product **3a** was obtained in 59% yield (143.0 mg, 0.59 mmol) as a pale yellow powder (m.p. = 102–104°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.36 (s, 12H), 7.04–7.15 (m, 2H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.37 (d, *J* = 8.6 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 8.59 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 84.1 (*C*), 111.2 (*C*H), 113.8 (*C*H), 119.8 (*C*H), 121.6 (*C*H), 123.6 (*C*H), 128.3 (*C*), 138.2 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.2. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{14}H_{18}BNO_2$, 242.1467; found, 242.1469.

1-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3b).

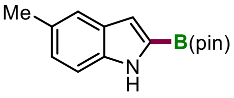


3b

The reaction was conducted with 131.2 mg (1.0 mmol) of **1b**. The product **3b** was obtained in 35% yield (91.0 mg, 0.35 mmol) as a light green powder (m.p. = 96–97°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.36 (s, 12H), 3.96 (s, 3H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.13 (s, 1H), 7.25 (t, *J* = 8.8 Hz, 1H), 7.33 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 32.2 (CH_3), 83.7 (*C*), 109.7 (*C*H), 114.2 (*C*H), 119.3 (*C*H), 121.5 (*C*H), 123.1 (*C*H), 127.8 (*C*), 140.1 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.4. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{15}H_{20}BNO_2$, 256.1623; found, 256.1616.

5-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3c).

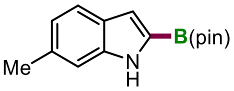


3c

The reaction was conducted with 131.2 mg (1.0 mmol) of **1c**. The product **3c** was obtained in 50% yield (129.0 mg, 0.50 mmol) as a white powder (m.p. = 135–137°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.35 (s, 12H), 2.43 (s, 3H), 6.98–7.08 (m, 2H), 7.26 (d, *J* = 8.6 Hz, 1H), 7.44 (s, 1H), 8.47 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 21.4 (CH_3), 24.8 (CH_3), 84.1 (*C*), 110.9 (*C*H), 113.3 (*C*H), 121.0 (*C*H), 125.5 (*C*H), 128.6 (*C*), 128.9 (*C*), 136.6 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.3. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{20}BNO_2$, 256.1623; found, 256.1611.

6-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3d).

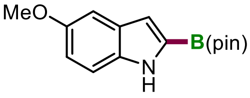


3d

The reaction was conducted with 131.2 mg (1.0 mmol) of **1d**. The product **3d** was obtained in 43% yield (109.6 mg, 0.43 mmol) as a white powder (m.p. = 110–111°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.35 (s, 12H), 2.45 (s, 3H), 6.92 (d, *J* = 8.2 Hz, 1H), 7.04–7.08 (m, 1H), 7.15 (s, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 8.42 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 21.8 (CH_3), 24.8 (CH_3), 84.0 (*C*), 111.0 (*C*H), 113.8 (*C*H), 121.1 (*C*H), 121.8 (*C*H), 126.2 (*C*), 133.6 (*C*), 138.7 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.2. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{20}BNO_2$, 256.1623; found, 256.1612.

5-Methoxy-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3e).

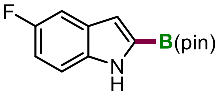


3e

The reaction was conducted with 117.2 mg (1.0 mmol) of **1e**. The product **3e** was obtained in 42% yield (114.7 mg, 0.42 mmol) as a white powder (m.p. = 99–101°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 97:3 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.36 (s, 12H), 3.85 (s, 3H), 6.91 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.01–7.04 (m, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 8.46 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 55.7 (CH_3), 84.1 (*C*), 102.0 (*C*H), 112.0 (*C*H), 113.3 (*C*H), 114.9 (*C*H), 128.6 (*C*), 133.6 (*C*), 154.1 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.3. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{20}BNO_3$, 272.1573; found, 272.1570.

5-Fluoro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3f).

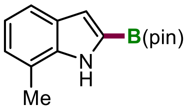


3f

The reaction was conducted with 135.1 mg (1.0 mmol) of **1f**. The product **3f** was obtained in 34% yield (90.4 mg, 0.34 mmol) as a white powder (m.p. = 126–128°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.36 (s, 12H), 6.98 (td, *J* = 9.0, 2.0 Hz, 1H), 7.03–7.08 (m, 1H), 7.24–7.32 (m, 2H), 8.57 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 84.3 (*C*), 105.8 (d, $J_{C\text{-}F}$ = 22.7 Hz, *C*H), 111.8 (d, $J_{C\text{-}F}$ = 9.4 Hz, *C*H), 112.4 (d, $J_{C\text{-}F}$ = 27.3 Hz, *C*H), 113.6 (d, $J_{C\text{-}F}$ = 4.7 Hz, *C*H), 128.4 (d, $J_{C\text{-}F}$ = 9.4 Hz, *C*), 134.8 (*C*), 157.8 (d, $J_{C\text{-}F}$ = 236.0 Hz, *C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.2. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{17}BFNO_2$, 260.1373; found, 260.1379.

7-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3g).

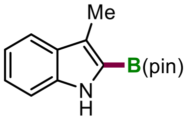


3g

The reaction was conducted with 131.2 mg (1.0 mmol) of **1g**. The product **3g** was obtained in 53% yield (109.6 mg, 0.43 mmol) as a white powder (m.p. = 88–90°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^1H NMR (392 MHz, $CDCl_3$, δ): 1.37 (s, 12H), 2.51 (s, 3H), 6.98–7.05 (m, 2H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.48–7.55 (m, 1H), 8.45 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 16.8 (*C*H_3), 24.8 (*C*H_3), 84.1 (*C*), 114.5 (*C*H), 119.3 (*C*H), 120.0 (*C*H), 120.5 (*C*), 123.9 (*C*H), 127.8 (*C*), 138.0 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.3. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{20}BNO_2$, 256.1623; found, 256.1616.

3-Methyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3h).

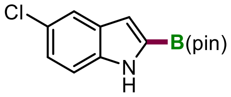


3h

The reaction was conducted with 131.2 mg (1.0 mmol) of **1h**. The product **3h** was obtained in 15% yield (37.4 mg, 0.15 mmol) as a white powder (m.p. = 91–92°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 99:1 to 90:10).

^1H NMR (392 MHz, $CDCl_3$, δ): 1.35 (s, 12H), 2.54 (s, 3H), 7.08 (t, *J* = 7.4 Hz, 1H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 1H), 7.62 (d, *J* = 8.2 Hz, 1H), 8.30 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 10.1 (*C*H_3), 24.9 (*C*H_3), 83.7 (*C*), 111.1 (*C*H), 118.9 (*C*H), 120.0 (*C*H), 123.6 (*C*H), 124.5 (*C*), 128.8 (*C*), 138.0 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.6. HRMS-ESI (*m*/*z*): $[M+H]^+$ calcd for $C_{15}H_{21}BNO_2$, 257.1696; found, 257.1700.

5-Chloro-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3i).

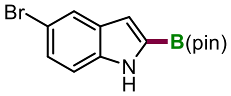


3i

The reaction was conducted with 151.6 mg (1.0 mmol) of **1i**. The product **3i** was obtained in 37% yield (102.1 mg, 0.37 mmol) as a light blue powder (m.p. = 113–115°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.35 (s, 12H), 7.03 (d, *J* = 1.2 Hz, 1H), 7.17 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.27 (t, *J* = 8.8 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 8.61 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 84.3 (*C*), 111.2 (*C*H), 113.2 (*C*H), 120.8 (*C*H), 124.0 (*C*H), 125.4 (*C*), 129.2 (*C*), 136.5 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.2. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{17}BClNO_2$, 276.1077; found, 276.1072.

5-Bromo-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole (3j).

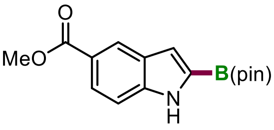


3j

The reaction was conducted with 196.1 mg (1.0 mmol) of **1j**. The product **3j** was obtained in 38% yield (120.1 mg, 0.38 mmol) as a light blue powder (m.p. = 144–145°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^{1}H NMR (396 MHz, $CDCl_3$, δ): 1.36 (s, 12H), 7.03 (s, 1H), 7.22–7.32 (m, 2H), 7.80 (s, 1H), 8.61 (brs, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 24.8 (CH_3), 84.3 (*C*), 112.6 (*C*H), 113.0 (*C*), 113.1 (*C*H), 123.9 (*C*H), 126.4 (*C*H), 130.0 (*C*), 136.7 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.1. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{14}H_{17}BBrNO_2$, 320.0572; found, 320.0563.

Methyl 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-indole-5-carboxylate (3k).

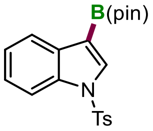


3k

The reaction was conducted with 175.2 mg (1.0 mmol) of **1k**. The product **3k** was obtained in 50% yield (150.3 mg, 0.50 mmol) as a white powder (m.p. = 147–148°C) by flash chromatography (SiO_2, hexane/dichloromethane, 50:50 to 0:100).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.37 (s, 12H), 3.93 (s, 3H), 7.18–7.22 (m, 1H), 7.39 (d, *J* = 9.0 Hz, 1H), 7.93 (dd, *J* = 8.8, 1.4 Hz, 1H), 8.45 (d, *J* = 0.8 Hz, 1H), 8.74 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 51.9 (CH_3), 84.4 (*C*), 110.9 (*C*H), 115.2 (*C*H), 122.0 (*C*), 124.75 (*C*H), 124.80 (*C*H), 127.9 (*C*), 140.5 (*C*), 168.1 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.1. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{16}H_{20}BNO_4$, 300.1522; found, 300.1517.

3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-indole (3l).

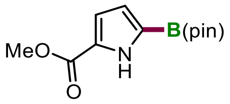


3l

The reaction was conducted with 271.3 mg (1.0 mmol) of **1l**. The product **3l** was obtained in 30% yield (118.7 mg, 0.30 mmol) as a white powder (m.p. = 66–67°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.36 (s, 12H), 2.33 (s, 3H), 7.19–7.32 (m, 4H), 7.80 (d, *J* = 8.6 Hz, 2H), 7.94 (dd, *J* = 7.8, 1.2 Hz, 2H), 8.00 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 21.5 (CH_3), 24.9 (CH_3), 83.5 (*C*), 113.1 (*C*H), 123.0 (*C*H), 123.3 (*C*H), 124.4 (*C*H), 127.0 (*C*H), 129.9 (*C*H), 133.6 (*C*), 135.1 (*C*H), 135.25 (*C*), 135.29 (*C*), 145.0 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 29.6. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{21}H_{24}BNO_4S$, 396.1555; found, 396.1550.

Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrole-2-carboxylate (3m).

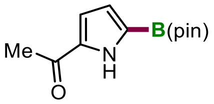


3m

The reaction was conducted with 125.1 mg (1.0 mmol) of **1m**. The product **3m** was obtained in 36% yield (92.4 mg, 0.36 mmol) as a light orange powder (m.p. = 128–130°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 97:3 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.33 (s, 12H), 3.86 (s, 3H), 6.77 (dd, *J* = 3.5, 2.7 Hz, 1H), 6.91 (dd, *J* = 3.9, 2.4 Hz, 1H), 9.50 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (CH_3), 51.5 (CH_3), 84.2 (*C*), 115.5 (*C*H), 120.6 (*C*H), 126.5 (*C*), 161.2 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 27.5. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{18}BNO_4$, 250.1365; found, 250.1362.

1-(5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrrol-2-yl)ethan-1-one (3n).

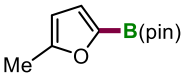


3n

The reaction was conducted with 109.1 mg (1.0 mmol) of **1n**. The product **3n** was obtained in 23% yield (53.8 mg, 0.23 mmol) as an orange powder (m.p. = 81–83°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 95:5 to 90:10).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.33 (s, 12H), 2.45 (s, 3H), 6.76 (dd, *J* = 3.5, 2.7 Hz, 1H), 6.89 (dd, *J* = 3.7, 2.5 Hz, 1H), 9.62 (brs, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (CH_3), 25.9 (CH_3), 84.3 (*C*), 116.4 (*C*H), 120.5 (*C*H), 135.3 (*C*), 188.2 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 27.6. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{18}BNO_3$, 234.1416; found, 234.1415.

4,4,5,5-Tetramethyl-2-(5-methylfuran-2-yl)-1,3,2-dioxaborolane (3o).

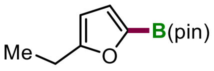


3o

The reaction was conducted with 82.1 mg (1.0 mmol) of **1o**. The product **3o** was obtained in 32% yield (65.0 mg, 0.32 mmol) as a slightly yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 99:1 to 98:2).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.34 (s, 12H), 2.36 (s, 3H), 6.04 (d, *J* = 3.1 Hz, 1H), 6.99 (d, *J* = 3.5 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 13.9 (CH_3), 24.7 (CH_3), 84.0 (*C*), 106.9 (*C*H), 124.8 (*C*H), 157.7 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 26.8. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{17}BO_3$, 207.1307; found, 207.1301.

2-(5-Ethylfuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3p).

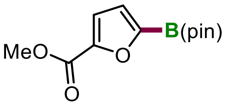


3p

The reaction was conducted with 96.1 mg (1.0 mmol) of **1p**. The product **3p** was obtained in 26% yield (57.5 mg, 0.26 mmol) as a yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 99:1 to 98:2).

^1H NMR (392 MHz, $CDCl_3$, δ): 1.25 (t, *J* = 7.6 Hz, 3H), 1.34 (s, 12H), 2.72 (q, *J* = 7.7 Hz, 2H), 6.05 (d, *J* = 3.1 Hz, 1H), 7.01 (d, *J* = 3.1 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 12.1 (CH_3), 21.6 (CH_2), 24.6 (CH_3), 83.9 (*C*), 105.1 (*C*H), 124.6 (*C*H), 163.5 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 26.8. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{19}BO_3$, 221.1464; found, 221.1465.

Methyl 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)furan-2-carboxylate (3q).

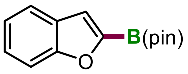


3q

The reaction was conducted with 126.1 mg (1.0 mmol) of **1q**. The product **3q** was obtained in 60% yield (154.8 mg, 0.60 mmol) as a white powder (m.p. = 81–83°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 90:10).

^1H NMR (392 MHz, $CDCl_3$, δ): 1.35 (s, 12H), 3.90 (s, 3H), 7.08 (d, *J* = 3.1 Hz, 1H), 7.20 (d, *J* = 3.1 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (CH_3), 52.0 (CH_3), 84.7 (*C*), 117.9 (*C*H), 124.0 (*C*H), 148.3 (*C*), 159.1 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 26.7. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{12}H_{17}BO_5$, 251.1205; found, 251.1202.

2-(Benzofuran-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3r).

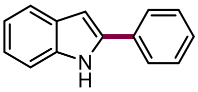


3r

The reaction was conducted with 118.1 mg (1.0 mmol) of **1r**. The product **3r** was obtained in 60% yield (149.4 mg, 0.60 mmol) as a white powder (m.p. = 88–89°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 99:1 to 95:5).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.39 (s, 12H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.40 (s, 1H), 7.57 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (*C*H_3), 84.7 (*C*), 111.9 (*C*H), 119.5 (*C*H), 121.9 (*C*H), 122.7 (*C*H), 125.9 (*C*H), 127.5 (*C*), 157.5 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. ^{11}B NMR (127 MHz, $CDCl_3$, δ): 27.5. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{14}H_{17}BO_3$, 243.1307; found, 243.1302.

2-Phenyl-1*H*-indole (4a).

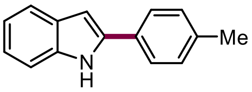


4a

The reaction was conducted with 117.2 mg (1.0 mmol) of **1a**. The product **4a** was obtained in 75% yield (116.5 mg, 0.60 mmol, the yield was based on iodobenzene) as a white powder (m.p. = 190–192°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 99:1 to 98:2).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 6.83 (d, *J* = 1.2 Hz, 1H), 7.12 (t, *J* = 7.4 Hz, 1H), 7.16–7.22 (m, 1H), 7.32 (t, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 8.2 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.64 (t, *J* = 7.6 Hz, 3H), 8.30 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 99.9 (*C*H), 110.9 (*C*H), 120.2 (*C*H), 120.6 (*C*H), 122.3 (*C*H), 125.1 (*C*H), 127.7 (*C*H), 129.0 (*C*H), 129.2 (*C*), 132.3 (*C*), 136.7 (*C*), 137.8 (*C*). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{14}H_{11}N$, 193.0892; found, 193.0893.

2-(*p*-Tolyl)-1*H*-indole (4b).

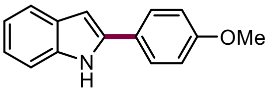


4b

The reaction was conducted with 117.2 mg (1.0 mmol) of **1a**. The product **4b** was obtained in 70% yield (116.0 mg, 0.56 mmol, the yield was based on 4-iodotoluene) as a white powder (m.p. = 196–197°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 99:1 to 98:2).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 2.38 (s, 3H), 6.78 (d, *J* = 1.6 Hz, 1H), 7.08–7.14 (m, 1H), 7.14–7.21 (m, 1H), 7.21–7.27 (m, 2H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.61 (d, *J* = 7.4 Hz, 1H), 8.25 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 21.2 (CH_3), 99.4 (*C*H), 110.8 (*C*H), 120.2 (*C*H), 120.5 (*C*H), 122.1 (*C*H), 125.0 (*C*H), 129.3 (*C*), 129.5 (*C*), 129.7 (*C*H), 136.6 (*C*), 137.6 (*C*), 138.0 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{13}N$, 207.1048; found, 207.1045.

2-(4-Methoxyphenyl)-1*H*-indole (4c).

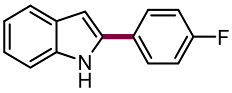


4c

The reaction was conducted with 117.2 mg (1.0 mmol) of **1a**. The product **4c** was obtained in 37% yield (66.2 mg, 0.30 mmol, the yield was based on 4-iodoanisole) as an off-white powder (m.p. = 206–207°C) by washed with ether.

^{1}H NMR (392 MHz, DMSO-*d*$_6$, δ): 3.80 (s, 3H), 6.76 (s, 1H), 6.92–7.12 (m, 4H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 9.0 Hz, 2H), 11.41 (s, 1H). ^{13}C NMR (99 MHz, DMSO-*d*$_6$, δ): 55.7 (CH_3), 97.8 (*C*H), 111.6 (*C*H), 114.8 (*C*H), 119.7 (*C*H), 120.1 (*C*H), 121.5 (*C*H), 125.4 (*C*), 126.8 (*C*H), 129.3 (*C*), 137.4 (*C*), 138.2 (*C*), 159.3 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{13}NO$, 223.0997; found, 223.0995.

2-(4-Fluorophenyl)-1*H*-indole (4d).

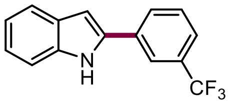


4d

The reaction was conducted with 117.2 mg (1.0 mmol) of **1a**. The product **4d** was obtained in 73% yield (122.9 mg, 0.58 mmol, the yield was based on 1-fluoro-4-iodobenzene) as an orange powder (m.p. = 191–192°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 98:2 to 97:3).

^{1}H NMR (400 MHz, $CDCl_3$, δ): 6.76 (d, J = 1.2 Hz, 1H), 7.10–7.17 (m, 3H), 7.20 (td, J = 7.6, 0.9 Hz, 1H), 7.40 (d, J = 7.6 Hz, 1H), 7.60–7.66 (m, 3H), 8.26 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 99.9 (*C*H), 110.9 (*C*H), 116.0 (d, $J_{C\text{-}F}$ = 21.7 Hz, *C*H), 120.4 (*C*H), 120.6 (*C*H), 122.4 (*C*H), 126.8 (d, $J_{C\text{-}F}$ = 8.5 Hz, *C*H), 128.7 (d, $J_{C\text{-}F}$ = 2.9 Hz, *C*), 129.2 (*C*), 136.8 (*C*), 137.0 (*C*), 162.4 (d, $J_{C\text{-}F}$ = 248.3 Hz, *C*). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{14}H_{10}FN$, 211.0797; found, 221.0798.

2-(3-(Trifluoromethyl)phenyl)-1*H*-indole (4e).



4e

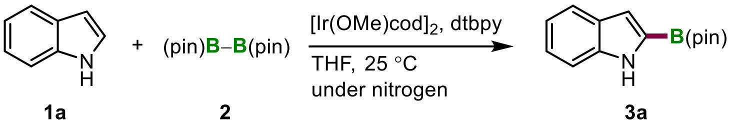
The reaction was conducted with 117.2 mg (1.0 mmol) of **1a**. The product **4e** was obtained in 51% yield (105.4 mg, 0.41 mmol, the yield was based on 1-iodo-3-(trifluoromethyl)benzene) as a white powder (m.p. = 147–148°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 99:1 to 98:2).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 6.91 (d, J = 1.6 Hz, 1H), 7.15 (t, J = 7.4 Hz, 1H), 7.23 (t, J = 7.6 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 7.53–7.60 (m, 2H), 7.65 (d, J = 7.4 Hz, 1H), 7.80–7.86 (m, 1H), 7.89 (s, 1H), 8.35 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 101.2 (*C*H), 111.1 (*C*H), 120.6 (*C*H), 120.9 (*C*H), 121.7 (d, $J_{C\text{-}F}$ = 3.8 Hz, *C*H), 123.0 (*C*H), 124.0 (d, $J_{C\text{-}F}$ = 273.7 Hz, *C*), 124.1 (d, $J_{C\text{-}F}$ = 3.9 Hz, *C*H), 128.2 (*C*H), 129.0 (*C*), 129.5 (*C*H), 131.5 (q, $J_{C\text{-}F}$ = 32.4 Hz, *C*), 133.1 (*C*), 136.2 (*C*), 137.0 (*C*). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{15}H_{10}F_3N$, 261.0765; found, 261.0769.

Kinetic Study

C–H Borylation Procedure of Indole in Solvent under Nitrogen Atmosphere.

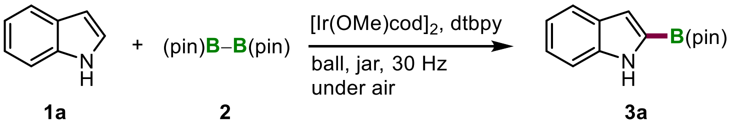
$[Ir(OMe)cod]_2$ (5.0 mg, 0.0075 mmol), dtbpy (4.0 mg, 0.015 mmol), bis(pinacolato)diboron **2** (152.4 mg, 0.60 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. And then dry THF (2.5 mL) was added into the reaction mixture under nitrogen atmosphere. After stirring for 5 min, **1a** (117.2 mg, 1.0 mmol) dissolved in dry THF (2.5 mL) was added dropwise to the reaction mixture under nitrogen atmosphere. At different time points (5 min, 10 min, 15 min, 25 min, 40 min, 60 min and 90 min), the mixture solution (0.5 mL) was taken into a vial through a needle. After dried under reduce pressure, dibromomethane was added as an internal standard to determine NMR yield of the borylation product.



t (min)	5	10	15	25	40	60	90
NMR yield	32%	41%	45%	52%	61%	73%	88%

C–H Borylation Procedure of Indole in a Ball Mill.

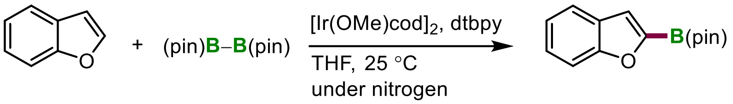
$[Ir(OMe)cod]_2$ (5.0 mg, 0.0075 mmol), dtbpy (4.0 mg, 0.015 mmol), bis(pinacolato)diboron **2** (152.4 mg, 0.60 mmol), and **1a** (117.2 mg, 1.0 mmol) were placed in a jar (5 mL) with a ball (0.75 cm, diameter). After the jar was closed, the jar was placed in the ball mill (Retsch MM 400, 30 Hz). At different time points (10 min, 20 min, 30 min, 40 min, 50 min, 60 min, 70 min and 99 min), the reaction mixture was passed through a short silica gel column eluting with Et_2O. The crude material was added with dibromomethane to determine NMR yield of the product.



t (min)	10	20	30	40	50	60	70	99
NMR yield	0%	0%	0%	0%	0%	0%	83%	84%

C–H Borylation Procedure of Benzofuran in Solvent under Nitrogen Atmosphere.

[Ir(OMe)cod]$_2$ (5.0 mg, 0.0075 mmol), dtbpy (4.0 mg, 0.015 mmol) and bis(pinacolato)diboron **2** (152.4 mg, 0.60 mmol) were placed in an oven-dried reaction vial. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the vial was connected to a vacuum/nitrogen manifold through a needle. And then dry THF (5.0 mL) was added into the reaction mixture under nitrogen atmosphere. After stirring for 5 min, **1r** (118.2 mg, 1.0 mmol) was added dropwise to the reaction mixture under nitrogen atmosphere. At different time points (10 min, 20 min, 30 min, 50 min, 70 min, 90 min, 120 min, and 180 min), the mixture solution (0.5 mL) was taken into a vial through a needle. After dried under reduce pressure, dibromomethane was added as an internal standard to determine NMR yield of the product.

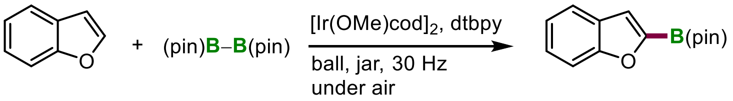


1r **2** **3r**

t (min)	10	20	30	50	70	90	120	180
NMR yield	0%	0%	0%	0%	0%	0%	33%	74%

C–H Borylation Procedure of Benzofuran in a Ball Mill.

[Ir(OMe)cod]$_2$ (5.0 mg, 0.0075 mmol), dtbpy (4.0 mg, 0.015 mmol), bis(pinacolato)diboron **2** (152.4 mg, 0.60 mmol), and **1r** (118.2 mg, 1.0 mmol) were placed in a jar (5 mL) with a ball (0.75 cm, diameter) under air. After the jar was closed, the jar was placed in the ball mill (Retsch MM 400, 30 Hz). At different time points (10 min, 20 min, 30 min, 40 min, 50 min, 60 min, 80 min and 99 min), the reaction mixture was passed through a short silica gel column eluting with Et$_2$O. The crude material was added with dibromomethane to determine NMR yield of the product.



1r **2** **3r**

t (min)	10	20	30	40	50	60	80	99
NMR yield	0%	0%	0%	0%	0%	64%	90%	93%

References

1) *Boronic Acids: Preparation and Applications in Organic synthesis, Medicine and Materials,* 2nd revised ed. (Ed.: D. G. Hall), Wiley-VCH, Weinheim, 2011.

2) a) T. Ishiyama, N. Miyaura, *J. Organomet. Chem.* **2003**, *680*, 3; b) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890; c) L. Xu, G. Wang, S. Zhang, H. Wang, L. Wang, L. Liu, J. Jiao, P. Li, *Tetrahedron* **2017**, *73*, 7123.

3) The selected pioneering studies on iridium-catalyzed aromatic C–H borylation reactions, see: a) J.-Y. Cho, C. N. Iverson, M. R. Smith III, *J. Am. Chem. Soc.* **2000**, *122*, 12868; b) J.-Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith III, *Science* **2002**, *295*, 305; c) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390–391.

4) For selected reviews on the reaction development using mechanochemistry, see: a) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413; b) G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668; c) T. Friščić, I. Halasz, V. Štrukil, M. Eckert-Maksić, R. E. Dinnebier, *ACS Cent. Sci.* **2017**, *3*, 13; d) J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007; e) T.-X. Métro, J. Martinez, F. Lamaty, *ACS Sustainable Chem. Eng.* **2017**, *5*, 9599; f) T. K. Achar, A. Bose, P. Mal, Beilstein *J. Org. Chem.* **2017**, *13*, 1907; g) O. Eguaogie, J. S. Vyle, P. F. Conlon, M. A. Gîlea, Y. Liang, Beilstein *J. Org. Chem.* **2018**, *14*, 955; h) J. L. Howard, Q. Cao, D. L. Browne, *Chem. Sci.* **2018**, *9*, 3080; i) J. Andersen, J. Mack, *Green Chem.* **2018**, *20*, 1435.

5) For selected recent examples of the mechanochemical methodology, see: a) C. Bolm, R. Mocci, C. Schumacher, M. Turberg, F. Puccetti, J. G. Hernández, *Angew. Chem. Int. Ed.* **2018**, *57*, 2423; b) K. J. Ardila-Fierro, D. E. Crawford, A. Körner, S. L. James, C. Bolm, J. G. Hernández, *Green Chem.* **2018**, *20*, 1262; c) Q. Cao, J. L. Howard, E. Wheatley, D. L. Browne, *Angew. Chem. Int. Ed.* **2018**, *57*, 11339; d) H. Kulla, S. Haferkamp, I. Akhmetova, M. Röllig, C. Maierhofer, K. Rademann, F. Emmerling, *Angew. Chem. Int. Ed.* **2018**, *57*, 5930; e) K. Užareić, N. Ferdelji, T. Mrla, P. A. Julien, B. Halasz, T. Friščić, I. Halasz, *Chem. Sci.* **2018**, *9*, 2525.

6) a) J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007; b) J.-L. Do, T. Friščić, *ACS Cent. Sci.* **2017**, *3*, 13; c) J. L. Howard, M. C. Brand, D. L. Browne, *Angew. Chem. Int. Ed.* **2018**, *57*, 16104.

7) a) G. N. Hermann, P. Becker, C. Bolm, *Angew. Chem. Int. Ed.* **2015**, *54*, 7414; b) J. G. Hernández, C. Bolm, *Chem. Commun.* **2015**, *51*, 12582; c) G. N. Hermann, P. Becker, C. Bolm, *Angew. Chem. Int. Ed.* **2016**, *55*, 3781; d) K.-Y. Jia, J.-B. Yu, Z.-J. Jiang, W.-K. Su, *J. Org. Chem.* **2016**, *81*, 6049; e) S.-J. Lou, Y.-J. Mao, D.-Q. Xu, J.-Q. He, Q. Chen, Z.-Y. Xu, *ACS Catal.* **2016**, *6*, 3890; f) G. N. Hermann, C. Bolm, *ACS Catal.* **2017**, *7*, 4592; g) X. Jiang, J. Chen, W. Zhu, K. Cheng, Y. Liu, W.-K. Su, C. Yu, *J. Org. Chem.* **2017**, *82*, 10665; h) G. N. Hermann, M. T. Unruh, S.-H. Jung, M. Krings, C. Bolm, *Angew. Chem. Int. Ed.* **2018**, *57*, 10723; i) G. N. Hermann, C. L. Jung, C. Bolm, *Green Chem.* **2017**, *19*, 2520; j) H. Cheng, J. G. Hernández, C. Bolm, *Adv. Synth. Catal.* **2018**, *360*, 1800.

8) T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056.

9) a) T. Furukawa, M. Tobisu, N. Chatani, *Chem. Commun.* **2015**, *51*, 6508; b) G. Yan, Y. Jiang, C. Kuang,

S. Wang, H. Liu, Y. Zhang, J. Wang, *Chem. Commun.* **2010**, *46*, 3170.

10) B. P. Hutchings, D. E. Crawford, L. Gao, P. Hu, S. L. James, *Angew. Chem. Int. Ed.* **2017**, *56*, 15252.

11) T. Friščić, S. L. Childs, S. A. A. Rizvi, W. Jones, *CrystEngcomm* **2009**, *11*, 415.

12) J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama, N. Miyaura, *Tetrahedron Lett.* **2002**, *43*, 5649.

13) R. Martin, S. L. Buchwald, *Acc. Chem. Res.* **2008**, *41*, 1461.

14) a) C. Vaxelaire, P. Winter, M. Christmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 3605; b) L. Chen, D. Leslie, M. G. Coleman, J. Mack, *Chem. Sci.* **2018**, *9*, 4650.

15) H. Tamura, H. Yamazaki, H. Sato, S. Sakaki, *J. Am. Chem. Soc.* **2003**, *125*, 16114.

16) T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263; b) M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287.

17) D. C. Waddell, T. D. Clark, J. Mack, *Tetrahedron Lett.* **2012**, *53*, 4510.

Chapter 2.

Redox Reactions Using Ball Milling and Piezoelectric Materials

Abstract

Over the past decade, organic transformations using photoredox catalysis have harnessed light energy to accelerate bond-forming reactions. We have postulated that a general and complementary method for the redox activation of small organic molecules in response to applied mechanical energy could be developed through the piezoelectric effect. Here, we report the first mechanistic paradigm for generating aryl radicals using mechanical force, where the agitation of piezoelectric materials via ball milling generates an electrochemical potential that reduces aryl diazonium salts via single-electron-transfer events. This mechanoredox system can be applied to arylation and borylation reactions under solvent-free mechanochemical conditions using ball milling or hammering in air. Our mechano-redox strategy complements existing photoredox transformations for the synthesis of valuable synthetic targets in a practical and environmentally friendly manner.

Introduction

The implementation of visible-light photoredox catalysis represents a key recent development in contemporary organic synthesis.[1-5] In these photoredox transformations, the photoexcited catalyst can act as a potent single-electron oxidant, transferring an electron to an acceptor (**A**), after which single-electron oxidation of a donor (**D**) affords the product under concomitant regeneration of the ground state catalyst (Fig. 2-1A). The broad success of photoredox catalysis hinges on its ability to selectively activate redox-active organic molecules to enable specific bond-forming reactions with high levels of efficiency and selectivity. As this method can promote challenging chemical transformations that have hitherto been inaccessible, the development of photo-redox catalyst systems is one of the most important breakthroughs in the field of organic synthesis in the last ten years.

There has likewise been substantial parallel progress in mechanochemical organic transformations using ball milling.[6-18] Since the term mechanochemistry has been used for the first time by Ostwald in 1887, mechanochemical synthesis has been extensively exploited in materials science,[6-8] polymer chemistry,[9] and inorganic synthesis,[8] but its application to organic synthesis is more recent.[10-18] Advantages of the approach include the avoidance of potentially harmful organic solvents and external heating, shorter reaction times, and simpler operational handling. In addition, solvent-free mechanochemical reactions are particularly useful for substrates that are poorly soluble in common organic solvents.

Inspired by the unique profile of photoredox systems based on light irradiation and the utility of ball milling in mechanochemistry, the author hypothesized that a general and complementary approach for the redox activation of small organic molecules could be developed through a mechanistically distinct approach using mechanical energy.[19-22] In particular, the author envisioned that the agitation of piezoelectric materials[23-33] via ball milling could generate temporarily highly polarized particles that might act as strong reductants to transfer electrons to small organic molecules, followed by oxidative quenching of a donor, thus inducing the selective formation of bonds in a manner analogous to photoredox catalysis (Fig. 2-1B). Such a solvent-free mechanoredox approach could potentially represent a powerful and attractive strategy to redox systems controlled by light energy to reduce the environmental impact of chemical processes; photoredox approaches, similar to other conventional organic reactions, often require complicated reaction set-ups, significant amounts of dry and degassed organic solvents as well as an inert gas atmosphere.[1-5]

To develop a proof-of-concept study, the author selected commercially available, cheap, and easy-to-handle $BaTiO_3$ nanoparticles as the piezoelectric material (Fig. 2-1B). This choice was motivated by pioneering studies, in which ultrasonic agitation of $BaTiO_3$ produces a suitable electrochemical potential to overcome the water splitting potential (1.23 V)[28, 29] and reduces a *N,N,N′,N′,N″,N″*-hexamethyl[tris(aminoethyl)amine] (Me_6TREN)-ligated $CuBr_2$ complex, which has a reduction potential of –0.30 V (vs. SCE).[29, 34] Surprisingly, although the piezoelectric effect is a well-known phenomenon, there are no examples of its use in organic synthesis. However, the aforementioned inorganic studies suggest that mechanical agitation of $BaTiO_3$ in a ball mill could generate an electrochemical potential suitable for the activation of redox-active small organic molecules in organic synthesis.

The photoredox systems that activate aryl diazonium salts for coupling with heteroarenes[35] or borylation[36] have been reported by König and Yan, respectively. The key step in these transformations is the photochemical reduction of aryl diazonium salts to aryl radical species. Andrieux and Pinson have reported a reduction potential of –0.16 V (vs. SCE) for phenyl diazonium tetrafluoroborate,[37] which was within range for feasible redox activation using $BaTiO_3$. In the postulated mechanism (Fig. 2-1C), the agitation of $BaTiO_3$ via ball milling generates a temporary electrochemical potential in response to mechanical impact. According to the aforementioned inorganic studies,[28, 29] the temporary polarization should be sufficiently persistent to reduce an aryl diazonium salt (**1**) via a SET mechanism analogous to the photoredox reaction, to furnish the corresponding aryl radical **I**. The addition of **I** to heteroarene **2** would afford radical addition intermediate **II**, which would be subsequently oxidized by the hole in the agitated $BaTiO_3$ to form carbocation intermediate **III**.[35] Finally, deprotonation of **III** would lead to arylation product **3**. In the borylation,[36] the generated radical **I** reacts with bis(pinacolato)diboron (**4**), to cleave the B–B bond, resulting in the formation of the boryl substitution product **5** as well as radical anion intermediate **IV**. Subsequently, oxidation of **IV** by the agitated $BaTiO_3$ could form F–B(pin) (**V**) as a byproduct.

Herein, the author describes the first examples of arylation and borylation reactions using mechanically induced piezoelectricity with aryl diazonium salts. This mechanoredox reaction can be carried out on gram scale without organic solvents in air, and do not require special operating conditions. Furthermore, this operational simplicity suggests that the present approach may complement existing photoredox transformations in a practical and environmentally friendly manner.

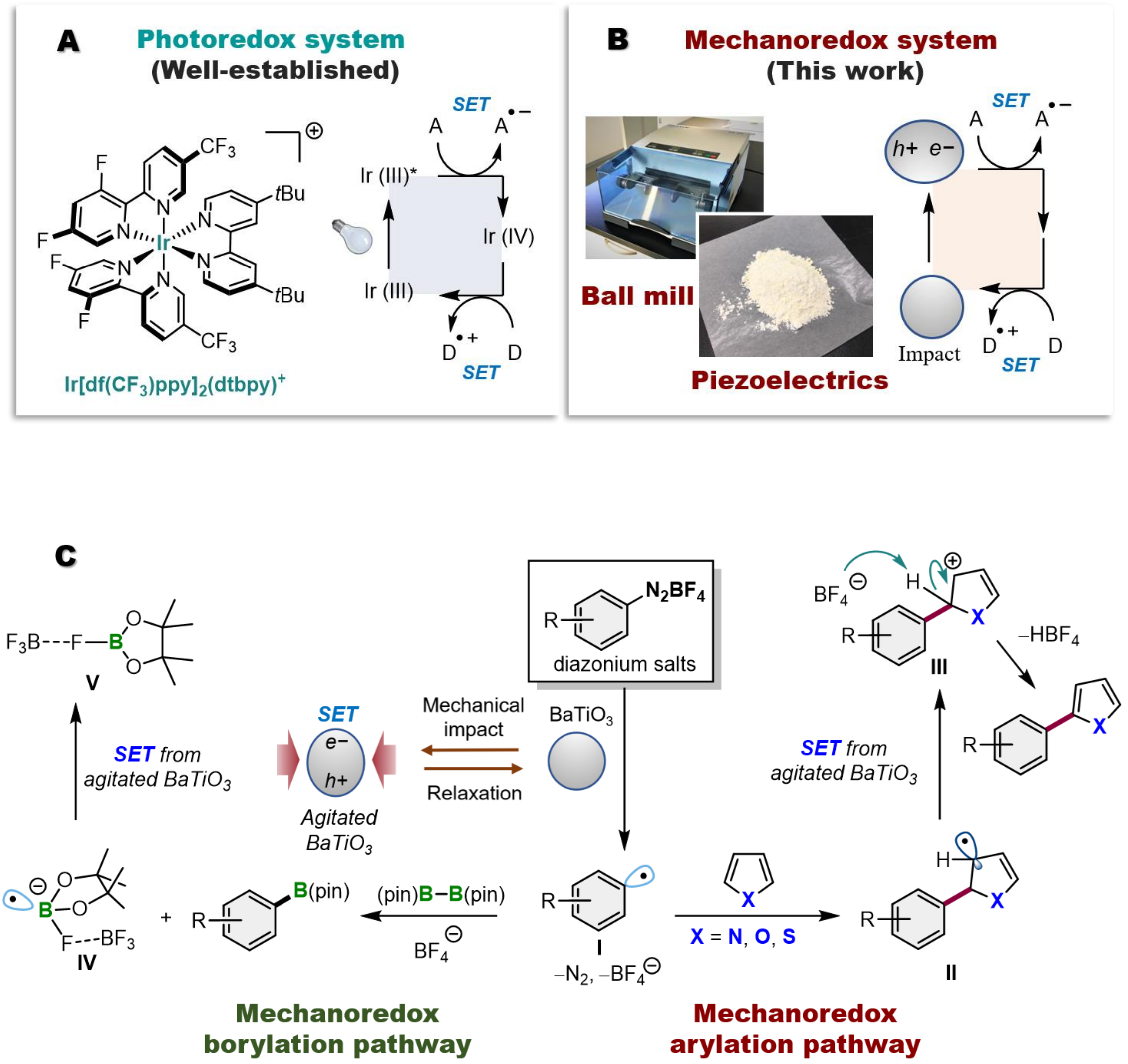
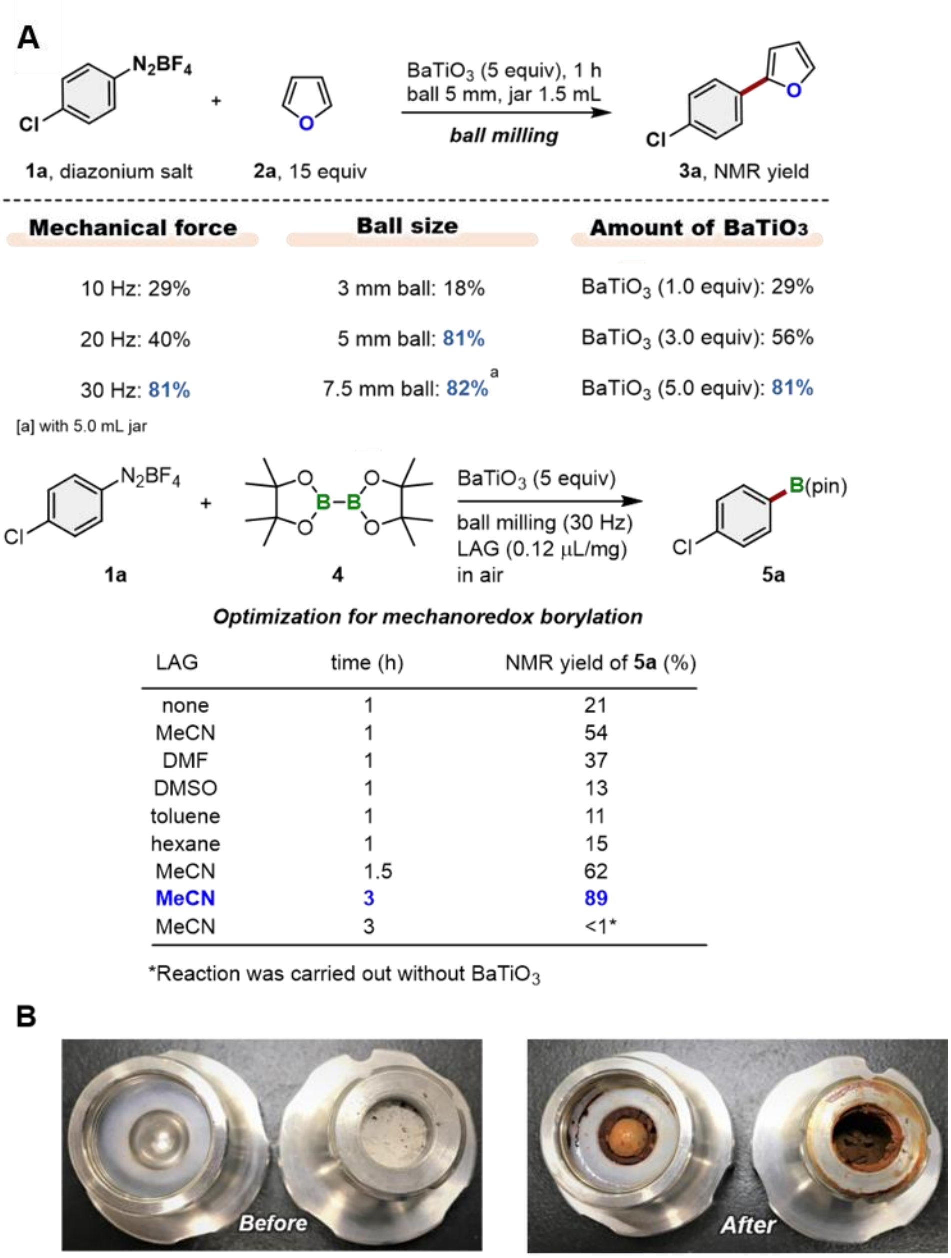


Fig. 2-1. Working hypothesis for a mechanoredox system for the activation of small organic molecules in organic synthesis. (A) A commonly employed photoredox catalyst and a generic photoredox oxidative quenching cycle. (B) Proposed mechanoredox paradigm using a ball mill and a piezoelectric material. (C) Proposed mechanism for the mechanoredox arylation and borylation using $BaTiO_3$ and ball milling. SET: single-electron-transfer.

Results and Discussion

To explore this mechanistic hypothesis, the author first attempted the proposed mechanoredox C–H arylation with **1a** and furan (**2a**) in the presence of commercially available $BaTiO_3$ using a Retch MM400 mixer mill (1.5 mL stainless-steel milling jar with 5 mm diameter stainless-steel ball) (Fig. 2-2A). Pleasingly, the corresponding arylation product (**3a**) was obtained in 40% yield after milling at 20 Hz for 1 h under air. The reaction did not proceed when it was carried out in the absence of $BaTiO_3$, suggesting that the mechanical energy provided by ball milling generated the piezoelectric potential to reduce **1a**. In contrast, even when ultrasound irradiation was applied to the mixture with $BaTiO_3$ in dimethyl sulfoxide (DMSO) under a nitrogen atmosphere, the formation of the product was not observed. A small amount of **3a** was obtained when the reaction was carried out in the presence of $SrTiO_3$, which exhibits piezoelectric properties upon applying in-plain strain.[38] When using non-piezoelectric ceramic materials, such as TiO_2, $BaCO_3$, or Al_2O_3, the reaction did not proceed, which suggests that piezoelectric materials are essential for this arylation reaction. The author found that conducting the reaction at higher ball-milling frequency (30 Hz) significantly improved the yield (81%). This result is consistent with his hypothesis that the required piezoelectric potential is generated by mechanical force provided by the ball milling of $BaTiO_3$. Using other piezoelectric materials, such as $LiNbO_3$ and ZnO, also afforded **3a**, albeit in lower yield (24% and 15%, respectively). Using a bigger jar (5.0 mL) and ball (7.5 mm) provided **3a** in high yield (82%, see experimental section). Product **3a** was isolated by filtration of the obtained crude solid mixture (Fig. 2-2B), followed by column chromatography on silica gel.



Optimization for mechanoredox borylation

LAG	time (h)	NMR yield of **5a** (%)
none	1	21
MeCN	1	54
DMF	1	37
DMSO	1	13
toluene	1	11
hexane	1	15
MeCN	1.5	62
MeCN	**3**	**89**
MeCN	3	<1*

*Reaction was carried out without $BaTiO_3$

Fig. 2-2. Mechanoredox arylation and borylation using mechanical force. (A) Optimization of the mechanoredox arylation reactions. (B) Reaction mixture of the mechanoredox arylation of **2a** after grinding in a ball mill. A stainless-steel milling jar (1.5 mL) and a stainless-steel ball (diameter: 5 mm) were used. See experimental section for details.

The author then investigated the possibility of mechano-redox borylation using the same setup (Fig. 2-2A). He found that the borylation of **1a** with **4** in the presence of $BaTiO_3$ afforded the desired arylboronate (**5a**) in 21% yield. Next, the author attempted to improve the reactivity by using liquid-assisted-grinding (LAG), in which a substoichiometric amount of liquid is added.[39] In all LAG reactions, the ratio of liquid additive (μL) to reactant (mg) was

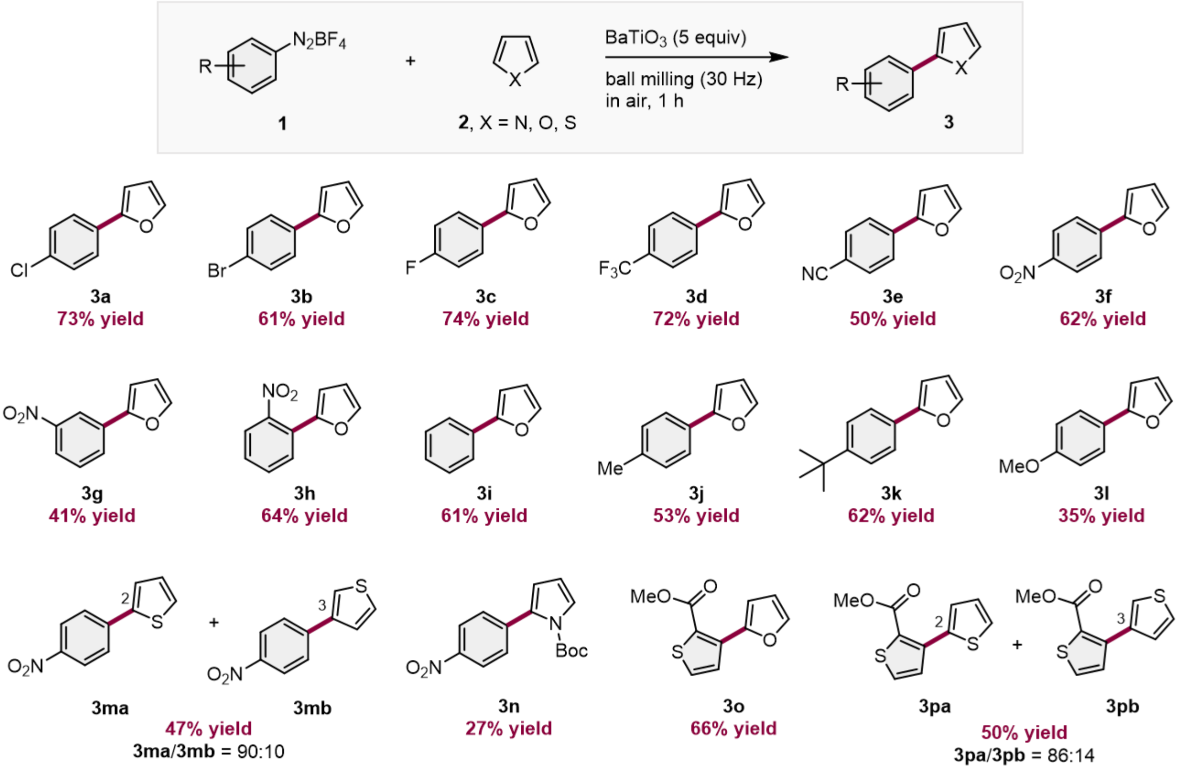
0.12. Use of acetonitrile (MeCN) as the LAG additive improved the yield of **5a**, while other common solvents, such as *N*,*N*-dimethylformamide (DMF), DMSO, toluene, or hexane led to little or no improvement. He also found that prolonging the reaction time led to a higher yield of **5a** (89%) when MeCN was used as the LAG additive. Using a bigger jar (5.0 mL) and ball (7.5 mm) did not significantly affect the transformation (86%, see experimental section). The reaction without $BaTiO_3$ did not proceed, supporting the author's mechanistic hypothesis. Compared with the analogous photoredox reaction, the present mechanoredox borylation exhibited much faster reaction kinetics and a better product yield.[36]

Subsequently, the author explored the scope of the mechanoredox arylation reaction with various aryl diazonium salts using a 5 mL stainless-steel milling jar with a 7.5-mm diameter stainless-steel ball (Fig. 2-3A). Electron-deficient aryl diazonium salts (**1a**–**1h**) were converted into the desired products (**3a**–**3h**) in good yield under the optimized conditions. Simple aromatic substrates (**1i**–**1k**) also reacted to give the corresponding products (**3i**–**3k**) in good yield. However, in the case of an electron-rich methoxy-substituted diazonium salt (**1l**), the product (**3l**) was obtained in relatively low yield. This was probably due to the relatively high reduction potential of **1l**. Other heteroarenes, namely, thiophene and pyrrole, successfully reacted to form the desired products (**3m** and **3n**). Arylation reactions using thienyl diazonium salts afforded the corresponding heterobiaryls (**3o** and **3p**), which are typical structural motifs for organic semiconductors.[40] Minor regioisomers (**3mb** and **3pb**) were observed as competing products in the reactions with thiophene, whereas the photoredox system developed by König and co-workers, using Eosin Y, produced **3ma** and **3pa** as single isomers.[35] The author also confirmed that the developed mechanoredox borylation conditions were applicable to a variety of aryl diazonium salts (Fig. 2-3B).

To demonstrate the practical utility of this protocol, the author investigated a gram-scale synthesis of heterobiaryls under the developed mechanoredox conditions, as well as the recycling of $BaTiO_3$ (Fig. 2-4A and 2-4B). The mechanoredox C–H arylation of furan (**2a**) with **1o** was carried out on an 8-mmol scale in a 25-mL stainless-steel ball-milling jar with one 15-mm diameter stainless steel ball, affording **3o** in 71% yield (Fig. 2-4A). After separation from the crude reaction mixture and washing, $BaTiO_3$ could be reused for the mechanoredox arylation of furan (**2a**) under the same reaction conditions at least three times before the yield of **3k** declined substantially (Fig. 2-4B).

Direct C–H arylation of polycyclic aromatic hydrocarbons (PAHs) has attracted considerable interest[41, 42] on account of their role in organic light-emitting diodes, organic photovoltaics, organic semiconductors, and organic thin-film transistors. With this in mind, the author conducted a preliminary investigation of the feasibility of the C–H arylation of PAHs using this mechanoredox approach (Fig. 2-4C). The reaction of **1f** with pyrene (**6a**) in the presence of $BaTiO_3$ and a small amount of MeCN as the LAG additive afforded the desired C–H arylation product (**7a**) in good yield with high regioselectivity (92:8). Furthermore, coronene (**6b**) was also arylated in moderate yield under the mechanoredox conditions. When the arylation of coronene (**6b**) was attempted via König's photoredox procedure using Eosin Y, no reaction occurred.[35] This was probably due to the low solubility of coronene (**6b**) in the polar solvents required for such photoredox reactions. These results demonstrate the promising potential of the mechanoredox arylation as an operationally simple, mild, and solvent-free route to synthesize functionalized PAHs from poorly soluble substrates that are incompatible with photoredox conditions.

A *Scope of mechano-redox arylation*



B *Scope of mechano-redox borylation*

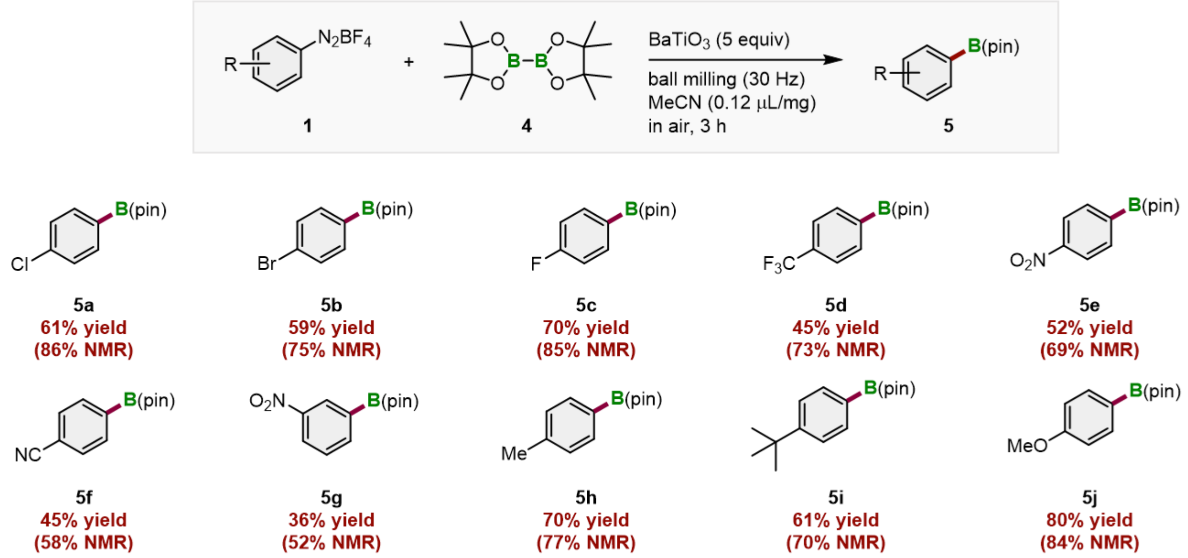
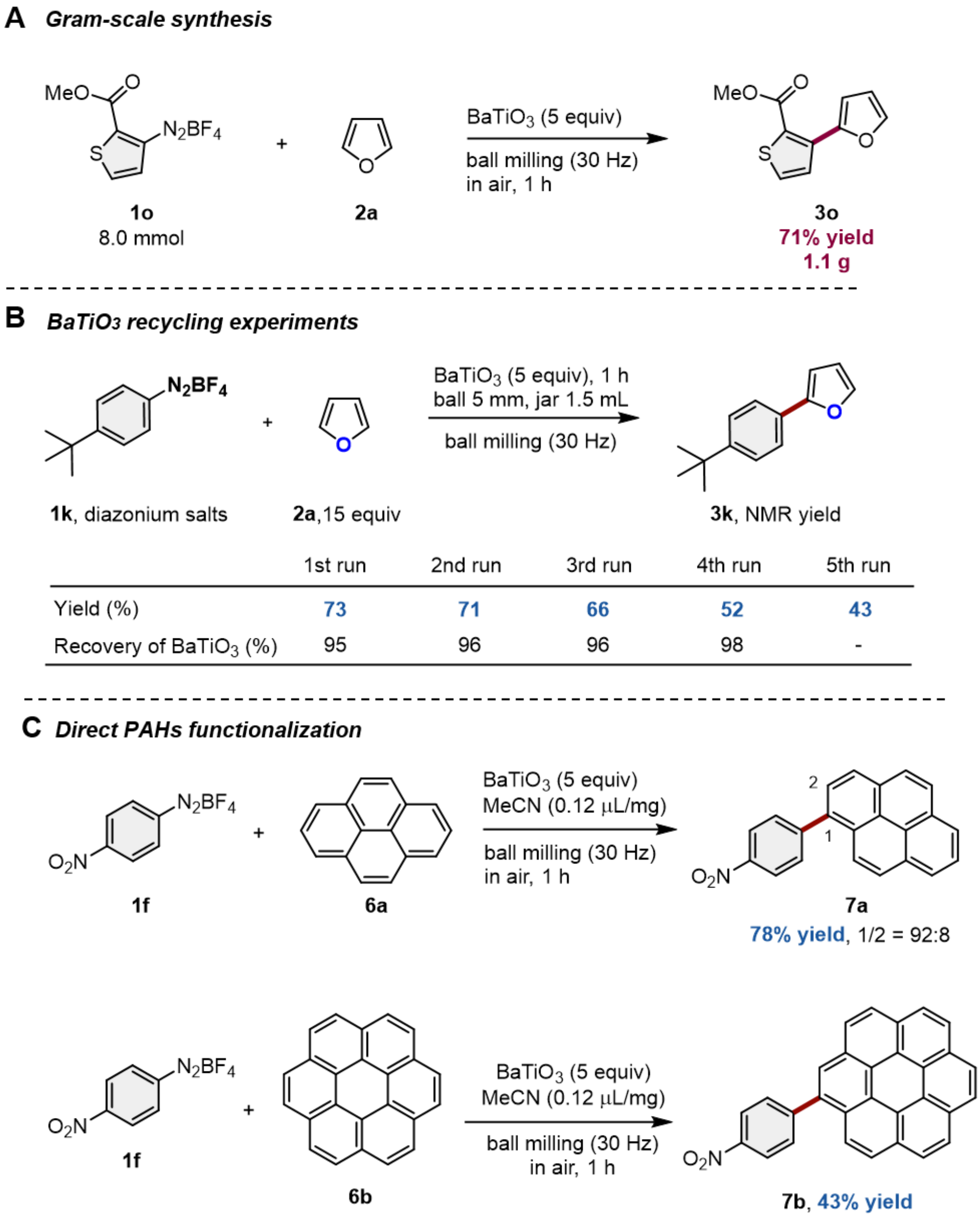


Fig. 2-3. Scope of the mechanoredox arylation and borylation reactions using aryl diazonium salts. Data for each entry (in bold) are reported as isolated yield percentages. ^{1}H NMR integrated yields are shown in parentheses. (A) Substrate scope of the mechanoredox arylation of heteroaromatic compounds. (B) Substrate scope of the mechanoredox borylation of aryl diazonium salts. Reactions were performed at 0.3 mmol scale using a stainless-steel milling jar (5 mL) and stainless-steel ball (diameter: 7.5 mm). Arylation conditions: **1** (0.3 mmol), **2** (4.5 mmol), BaTiO$_3$ (1.5 mmol). Borylation conditions: **1** (0.3 mmol), **4** (0.3 mmol), BaTiO$_3$ (1.5 mmol), MeCN (0.12 µL/mg). See experimental section for details.



	1st run	2nd run	3rd run	4th run	5th run
Yield (%)	73	71	66	52	43
Recovery of $BaTiO_3$ (%)	95	96	96	98	-

Fig. 2-4. Exploration of a gram-scale synthesis, catalyst recycling, and the arylation of polyaromatic hydrocarbon compounds. (A) Mechanoredox arylation of **2a** with **1o** on the gram scale using a 25-mL ball-milling jar (picture on the right). (B) $BaTiO_3$ recycling experiments using **1k** and **2a**. (C) Mechanoredox arylation of the polyaromatic hydrocarbons **6** with **1f**. See experimental section for details.

The author postulated that the mechanoredox C–H arylation and borylation were proceeding via SET events, in which an aryl radical is generated through piezoelectric reduction (Fig. 2-1C); this assumption is supported by the results of preliminary mechanistic investigations (Fig. 2-5). When 2,2,6,6-tetramethylpiperidinoxyl (TEMPO) (**8**) was treated with aryl diazonium salt **1a** in the absence of furan (**2a**), the TEMPO-trapped intermediate **9** was obtained (Fig. 2-5A). Furthermore, the addition of TEMPO (**8**) to a reaction mixture containing **1a**, furan (**2a**), and $BaTiO_3$ halted the arylation process, and the TEMPO-trapped intermediates **9** and **10** were detected (Fig. 2-5A). Compound **10** might have been formed through the reaction of TEMPO (**8**) with the intermediate **II** (Fig. 2-1C), followed by oxidative aromatization by $BaTiO_3$ or atmospheric oxygen. Overall, the identified compounds suggest that the mechano-redox activation with $BaTiO_3$ proceeds via a radical pathway.

The author used a scanning electron microscopy (SEM) analysis to confirm that the mechanical stimulus provided by ball milling is transferred onto the $BaTiO_3$ particles under the applied conditions (Fig. 2-5B).[24] The SEM image of commercially available $BaTiO_3$ powder shows a regular shape of the $BaTiO_3$ particles before the reaction (approximate size: <75 μm) [Fig. 2-5B (i)]. Subsequently, the powder was subjected for 60 min to ball milling at 30 Hz and then analyzed by SEM. The resulting image clearly shows a dramatic distortion of the shape and a decrease in the size of the $BaTiO_3$ particles [Fig. 2-5B (ii)]. These results suggest that the mechanical stimulus provided by ball milling is efficiently transferred onto the $BaTiO_3$ particles, which would result in the generation of localized electrochemical potentials on the surface of the $BaTiO_3$ particles that can be used for the activation of the aryl diazonium salts.

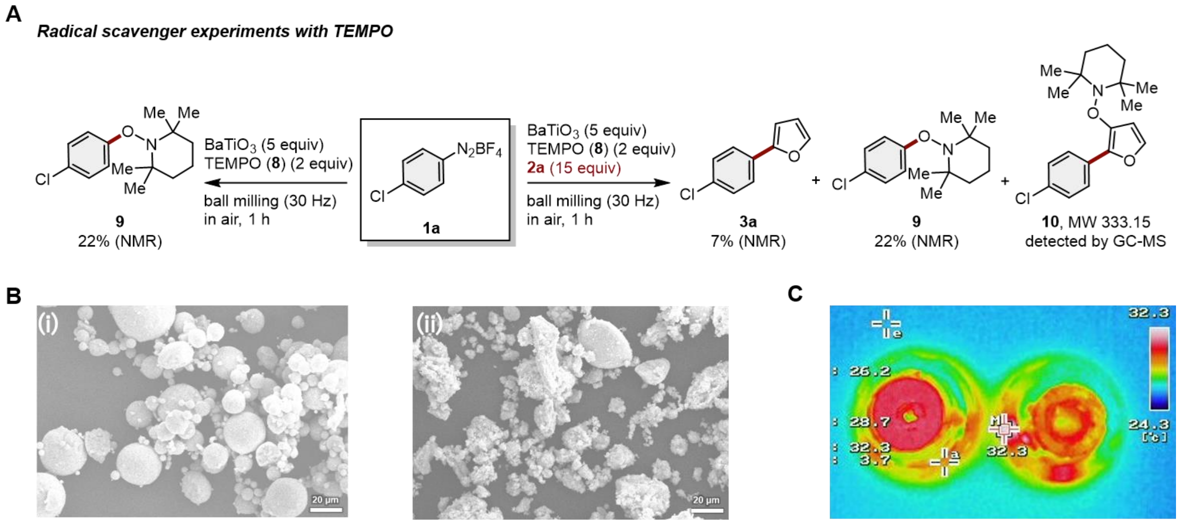


Fig. 2-5. Mechanistic studies. (A) Radical scavenger experiments. (B) SEM images of $BaTiO_3$ particles (i) before and (ii) after ball milling (30 Hz; 60 min); scale bars in the TEM images (bottom right): 20 μm. (C) Thermographic image of the milling jar after the mechanoredox arylation of **2a** with **1a**. See experimental section for details.

To investigate whether the friction during ball milling generates a thermal effect, the temperature inside the milling jar after the mechano-redox arylation of **2a** with **1a** was measured using thermography (Fig. 2-5C). The crude mixtures were prepared under optimized conditions. The obtained image showed that the temperature after arylation in the ball mill was around 30°C, thus discounting the possibility of thermal activation of the aryldiazonium salts to generate aryl radical species by the heat provided from ball milling.

To demonstrate the robustness of the mechano-redox transformations, the author conducted the borylation of **1k** with $BaTiO_3$ in air using a hammer (see experimental section). First, the reaction mixture was prepared by gentle grinding in a mortar. Subsequently, the mixture was wrapped in a piece of a weighing paper and placed in a zipper-locking plastic bag, followed by striking with a hammer over 200 times. Even under these crude conditions, the mechano-redox borylation product **5i** was obtained in 43% yield as assessed by NMR integration.

In addition, the author is currently investigating the mechano-redox C–H trifluoromethylation of aromatic compounds with an electrophilic trifluoromethylation reagent such as the Umemoto reagent.[43] In a preliminary investigation, he has obtained the trifluoromethylation product **13** and **14** in the presence of $BaTiO_3$ under the mechanochemical conditions using ball milling (Fig. 2-6). Only trace amounts of the product were obtained in the absence of $BaTiO_3$, suggesting that the mechanical energy provided by ball milling generates the piezoelectric potential required to activate the trifluoromethylation reagent.

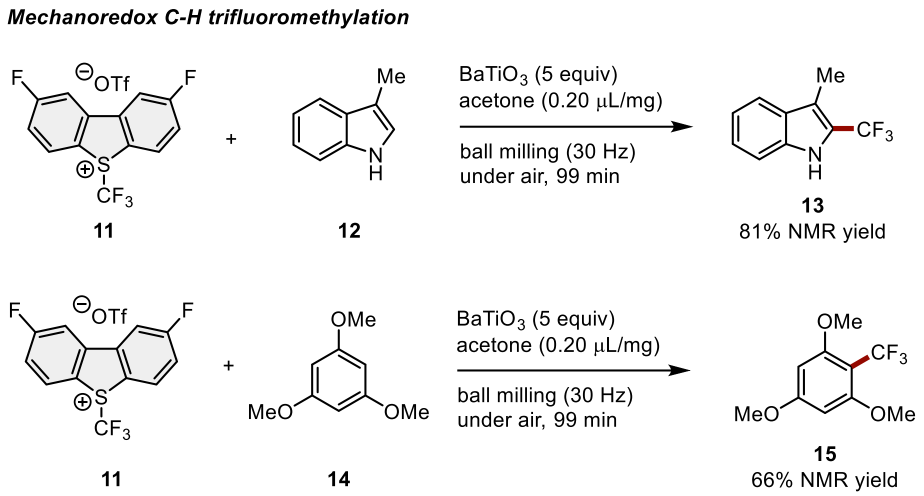


Fig. 2-6. Preliminary investigation of mechanoredox trifluoromethylation reactions. Reactions were performed at 0.3 mmol scale using a stainless-steel milling jar (5 mL) and stainless-steel ball (diameter: 7.5 mm). Reaction conditions: **11** (0.3 mmol), **12** (0.6 mmol), **14** (0.6 mmol), $BaTiO_3$ (1.5 mmol), acetone (0.2 μL/mg). Yields are based on the amount of **11** and determined by ^{19}F NMR spectroscopy.

Summary

In conclusion, the present mechanoredox reactions can be carried out on gram scale without organic solvents in air, and do not require special operating conditions. This operational simplicity suggests that the present approach may complement existing photoredox transformations in a practical and environmentally friendly manner. Beyond the immediate benefits of this protocol, the strategy could be applicable to light-sensitive or light-absorbing substrates that cannot be subjected to conventional photo-redox systems.

Experimental Section.

Instrumentation and Chemicals.

Materials were obtained from commercial suppliers and purified by standard procedures unless otherwise noted. $BaTiO_3$ [nanopowder (cubic crystalline phase), <100 nm particle size (BET), ≥ 99% trace metals basis, product No. 467634] was purchased from Sigma-Aldrich Co. LLC. All reactions were performed using grinding vessels in a Retsch MM 400 (Fig. S1). Both jars and balls were made of stainless steel (Fig. S2). Solvents for reactions were purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^1H: 392 and 396 MHz, ^{13}C: 99 and 100 MHz). Tetramethylsilane (^1H) and $CDCl_3$ (^{13}C) were employed as external standards, respectively. Multiplicity was recorded as follows: s = singlet, brs = broad singlet, d = doublet, t= triplet, q= quartet, m = multiplet. Dibromomethane was used as an internal standard to determine NMR yields. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and an FID detector. Scanning Electron Microscope (SEM) observation was performed with a JSM-6500F SEM (JEOL). Pictures of thermography was obtained by using InfRec Thermo GEAR (NEC Avio Infrared Technologies Co., Ltd.). High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

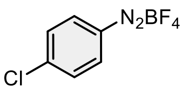
Fig. S1. Retsch MM400 used in this study.

Fig. S2. Stainless ball and jar used in this study.

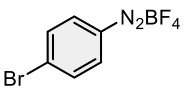
Substrate Preparation Procedures.

All aryldiazonium tetrafluoroborates (**1a**–**1m**) are known compounds and were synthesized from the corresponding anilines according to the reported procedure. The aniline (10.0 mmol) was added to a mixture of 50% fluoroboric acid (3.5 mL) and distilled water (4.0 mL). After cooling to 0 °C, an aqueous solution of sodium nitrite (700 mg, 10.1 mmol, in 1.5 mL H_2O) was added in 0.25 mL portions. After stirring for 30 min, the thick precipitate was collected by filtration and re-dissolved in a minimum amount of acetone. Diethyl ether was added until precipitation of diazonium tetrafluoroborate, which is filtered, washed several times with diethyl ether and dried under vacuum.

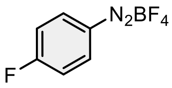
Table S1. Aryldiazonium tetrafluoroborates used in this study.



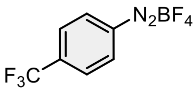
1a



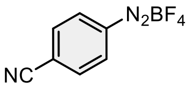
1b



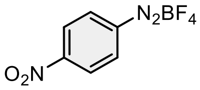
1c



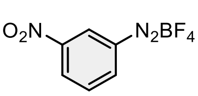
1d



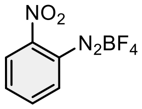
1e



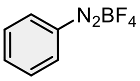
1f



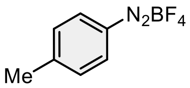
1g



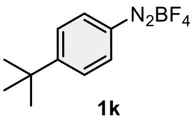
1h



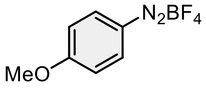
1i



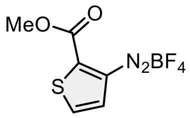
1j



1k



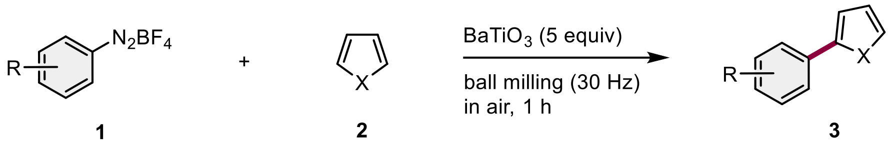
1l



1m

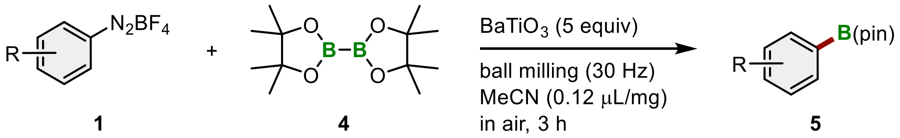
General Arylation and Borylation Procedures.

General Arylation Procedures.



Aryldiazonium tetrafluoroborate (**1**, 0.30 mmol) and $BaTiO_3$ (349.8 mg, 1.5 mmol) were placed in a jar (1.5 mL) with a ball (5.0 mm, diameter) in air. Then distilled furan (**2a**, 306.3 mg, 4.5 mmol) or thiophene (**2b**, 252.4 mg, 3.0 mmol) or 1-Boc-pyrrole (**2c**, 250.8 mg, 1.5 mmol) was added to the mixture. After the jar was closed without the purge with inert gas, the jar was placed in the ball mill (Retsch MM 400, 1 h, 30 Hz). After grinding for 1 h, the reaction mixture was passed through a short silica gel column eluting with diethyl ether. The crude material was purified by flash chromatography (SiO_2, hexane/ethyl acetate) to give the corresponding arylation product **3**.

General Borylation Procedures.



Aryldiazonium tetrafluoroborate (**1**, 0.30 mmol), $BaTiO_3$ (349.8 mg, 1.5 mmol) and bis(pinacolato)diboron (**4**, 76.2 mg, 0.3 mmol) were placed in a jar (1.5 mL) with a ball (5 mm, diameter) under air. Then anhydrous acetonitrile (η = 0.12 µL/mg) was also added to the mixture. After the jar was closed without the purge with inert gas, the jar was placed in the ball mill (Retsch MM 400, 3 h, 30 Hz). After grinding for 3 h, the reaction mixture was passed through a short silica gel column eluting with diethyl ether. The crude material was purified by flash chromatography (SiO_2, hexane/ethyl acetate) to give the corresponding arylation product **5**.

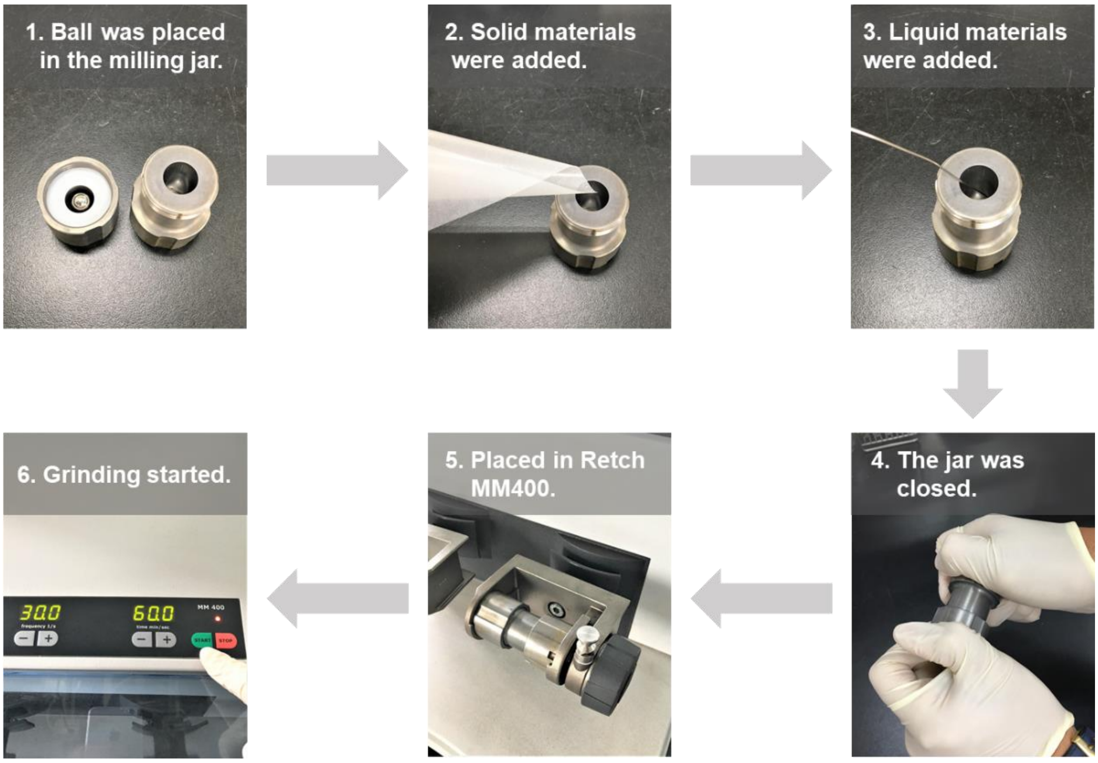
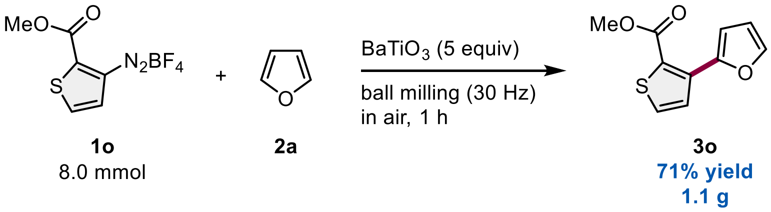


Fig. S3. Procedure of setting up the mechano-redox reactions.

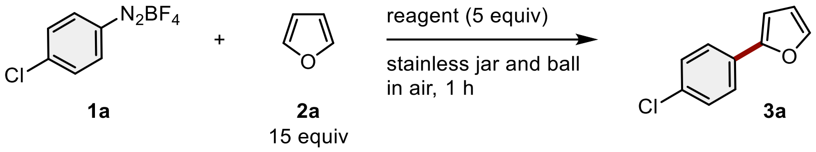
Gram-Scale Arylation Procedures.



Aryldiazonium tetrafluoroborate (**1o**, 2.048 g, 8.0 mmol) and $BaTiO_3$ (9.330 g, 40 mmol) were placed in a jar (25 mL) with a ball (15 mm, diameter) in air. Then distilled furan (**2a**, 8.73 mL, 120 mmol) was added to the mixture. After the jar was closed without a purge with inert gas, the jar was placed in the ball mill (Retsch MM 400, 1 h, 30 Hz). During the reaction, the jar was slightly opened every 5 mins to remove the generated nitrogen gas. After 1 h, the reaction mixture was passed through a short silica gel column eluting with diethyl ether. The crude material was purified by flash chromatography (SiO_2, hexane/ethyl acetate) to give the corresponding arylation product **3o** in 71% yield.

Optimization Studies.

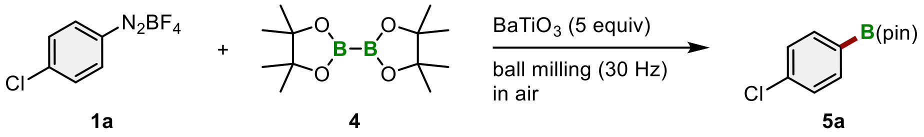
Table S2. Optimization of the Mechano-Redox Arylation.[a]



entry	reagent	milling frequency (Hz)	jar size (mL)	ball size (mm)	yield (%)
1	$BaTiO_3$	20	1.5	5	40
2	none	20	1.5	5	<1
3	$SrTiO_3$	20	1.5	5	3
4	TiO_2	20	1.5	5	<1
5	$BaCO_3$	20	1.5	5	<1
6	Al_2O_3	20	1.5	5	<1
7	$BaTiO_3$	10	1.5	5	29
8	$BaTiO_3$	30	1.5	5	81
9	$BaTiO_3$	30	1.5	3	18
10*b*	$BaTiO_3$	30	1.5	5	56
11*c*	$BaTiO_3$	30	1.5	5	29
12*d*	$BaTiO_3$	30	1.5	5	80
13*e*	$BaTiO_3$	30	1.5	5	72
14	$LiNbO_3$	30	1.5	5	24
15	ZnO	30	1.5	5	4
16	$BaTiO_3$	30	5.0	7.5	82

[a] Reaction performed using Retsch MM400, stainless-steel milling jar and stainless-steel ball. Conditions: **1a** (0.3 mmol), **2a** (4.5 mmol), reagent (1.5 mmol). Yields were determined by ^{1}H NMR analysis with an internal standard. [b] 3.0 equivalent of $BaTiO_3$ was used. [c] 1.0 equivalent of $BaTiO_3$ was used. [d] Reaction time was 1.5 h. [e] Two balls were used.

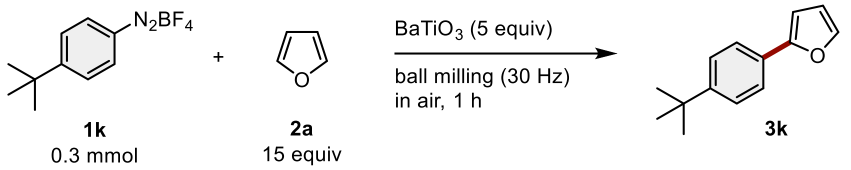
Table S3. Optimization of the Mechano-Redox Borylation.[a]



entry	time (min)	$B_2(pin)_2$ x equiv	LAG additive 0.12 µL/mg	jar size (mL)	ball size (mm)	yield (%)
1	60	2.0	none	1.5	5	22
2	60	2.0	MeCN	1.5	5	47
3	60	1.0	none	1.5	5	21
4	60	1.0	MeCN	1.5	5	54
5	60	1.0	DMF	1.5	5	37
6	60	1.0	DMSO	1.5	5	13
7	60	1.0	toluene	1.5	5	11
8	60	1.0	MeCN	1.5	5	15
9	90	1.0	MeCN	1.5	5	62
10	180	1.0	MeCN	1.5	5	89
11	180	1.0	MeCN	5	7.5	86
12[b]	180	1.0	MeCN	1.5	5	<1

[a] Reaction performed using Retsch MM400, stainless-steel milling jar and stainless-steel ball. Conditions: **1a** (0.3 mmol), **4** (0.3 mmol), $BaTiO_3$ (1.5 mmol). Yields were determined by ^1H NMR analysis with an internal standard. [b] The reaction was carried out without $BaTiO_3$.

$BaTiO_3$ Recycling Experiments.

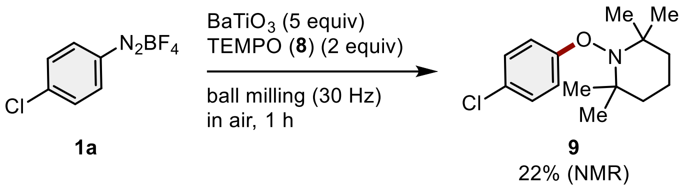


1st run: 73% (NMR), 95% recovery of $BaTiO_3$
2nd run: 71% (NMR), 96% recovery of $BaTiO_3$
3rd run: 66% (NMR), 96% recovery of $BaTiO_3$
4th run: 52% (NMR), 98% recovery of $BaTiO_3$
5th run: 43% (NMR)

After separation from the crude reaction mixture by filtration and washing with ethyl acetate, $BaTiO_3$ was dried under reduce pressure for 3 h and then can be reused for mechano-redox arylation of furan (**2a**) with **1k** under the same reaction conditions as least three times before the yield of the product slowly drops down.

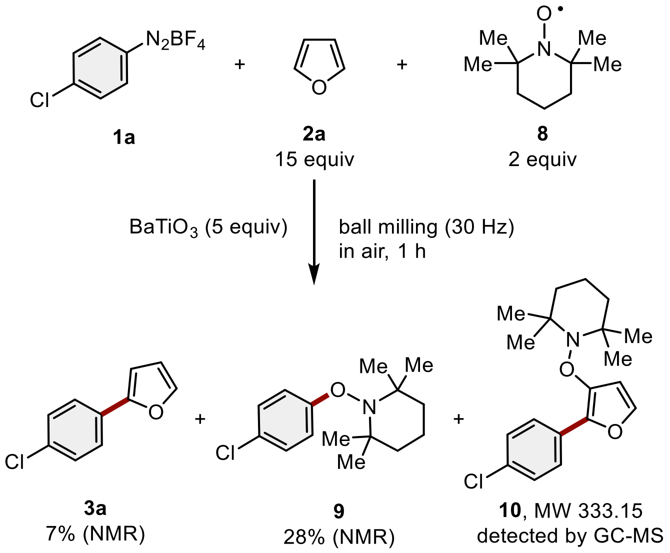
Radical-Trapping Experiments.

Reaction of 1a in the presence of TEMPO (8).



1a (67.9 mg, 0.30 mmol), $BaTiO_3$ (349.8 mg, 1.5 mmol) and TEMPO (**8**, 93.8 mg, 0.6 mmol) were placed in a jar (1.5 mL) with a ball (5 mm, diameter) in air. After the jar was closed without a purge with inert gas, the jar was placed in the ball mill (Retsch MM 400, 1 h, 30 Hz). After grinding for 1 h, the reaction mixture was passed through a short silica gel column eluting with diethyl ether. The crude material was analyzed by ^{1}H NMR with dibromomethane as an internal standard to determine the NMR yield of **9**. The ^{1}H NMR spectra of **9** has already been reported.

Reaction of 1a with 2a in the presence of TEMPO (8).



1a (67.9 mg, 0.30 mmol), $BaTiO_3$ (349.8 mg, 1.5 mmol) and TEMPO (**8**, 93.8 mg, 0.6 mmol) were placed in a jar (1.5 mL) with a ball (5 mm, diameter) in air. Then distilled furan (**2a**, 306.3 mg, 4.5 mmol) was added to the mixture. After the jar was closed without a purge with inert gas, the jar was placed in the ball mill (Retsch MM 400, 1 h, 30 Hz). After grinding for 1 h, the reaction mixture was passed through a short silica gel column eluting with diethyl ether. The crude material was analyzed by ^{1}H NMR with dibromomethane as an internal standard to determine the NMR yield of **9**. The crude mixture was also analyzed by GC-MS measurement, indicating the formation of **10** (t_R = 19 minutes 47 seconds) (Fig. S4).

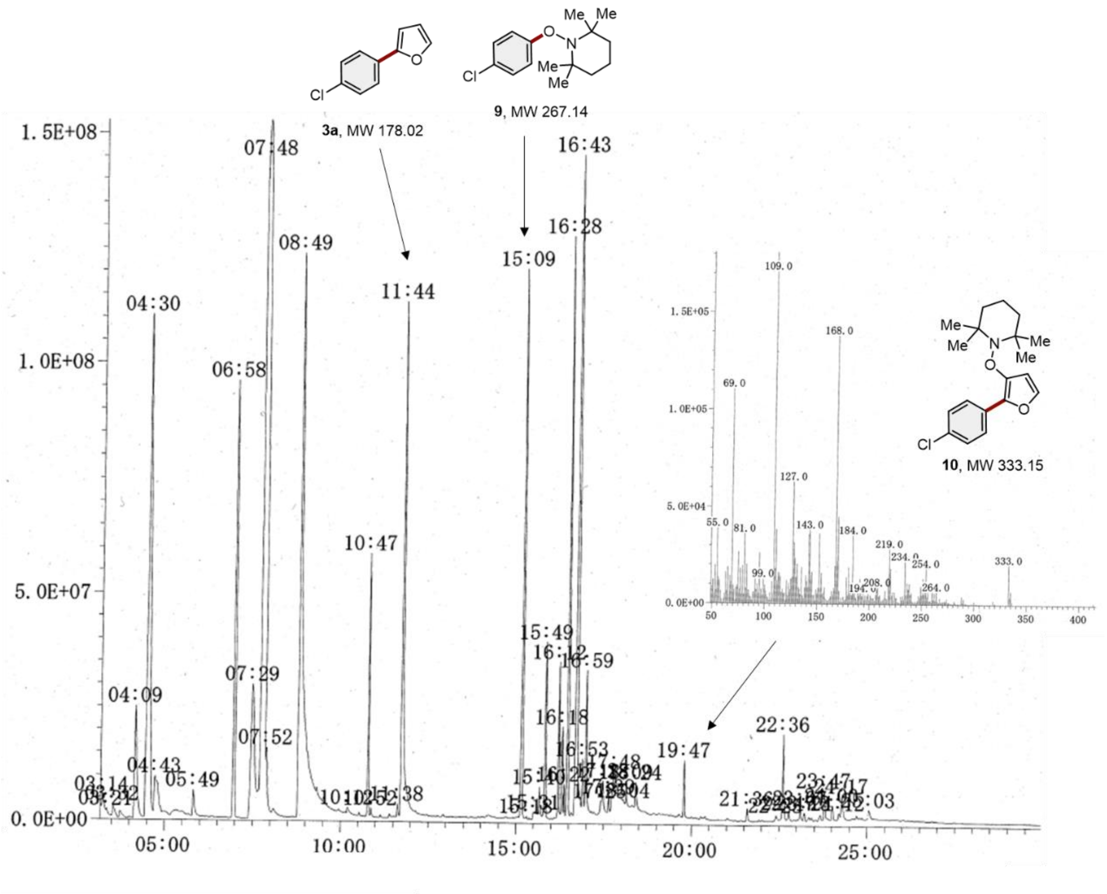


Fig. S4. The GC-MS chart.

Characterization of $BaTiO_3$ Particles by SEM.

The sample of $BaTiO_3$ after ball-mill was prepared by using a Retsch MM 400 (1.5 mL jar, 5 mm ball, 30Hz, 1 h). Additional images were shown in Fig. S5 and Fig. S6.

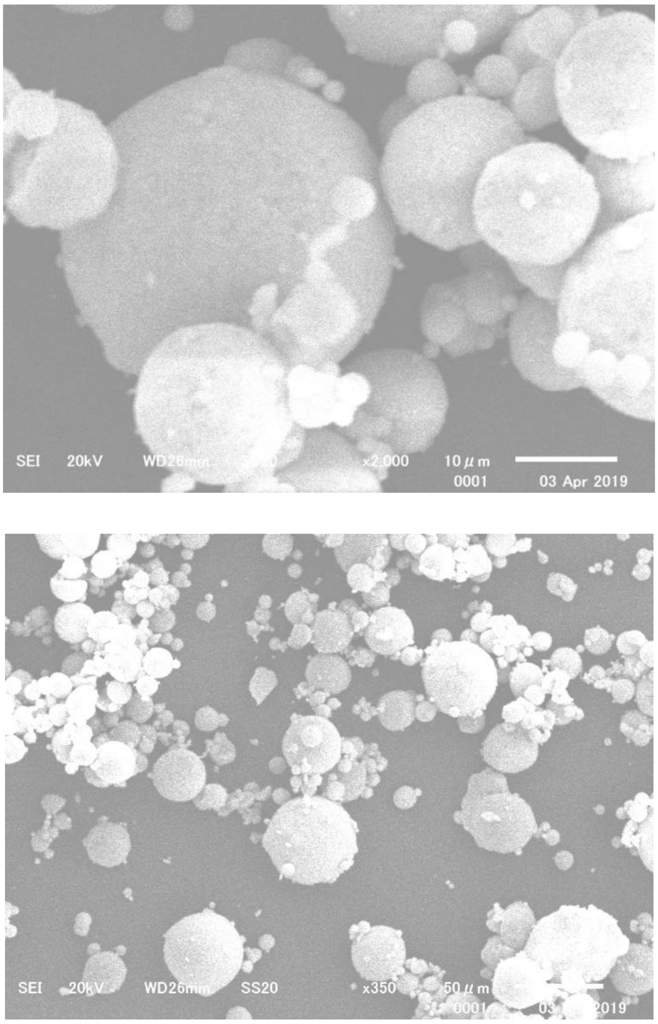


Fig. S5. SEM images of $BaTiO_3$ particles before ball milling.

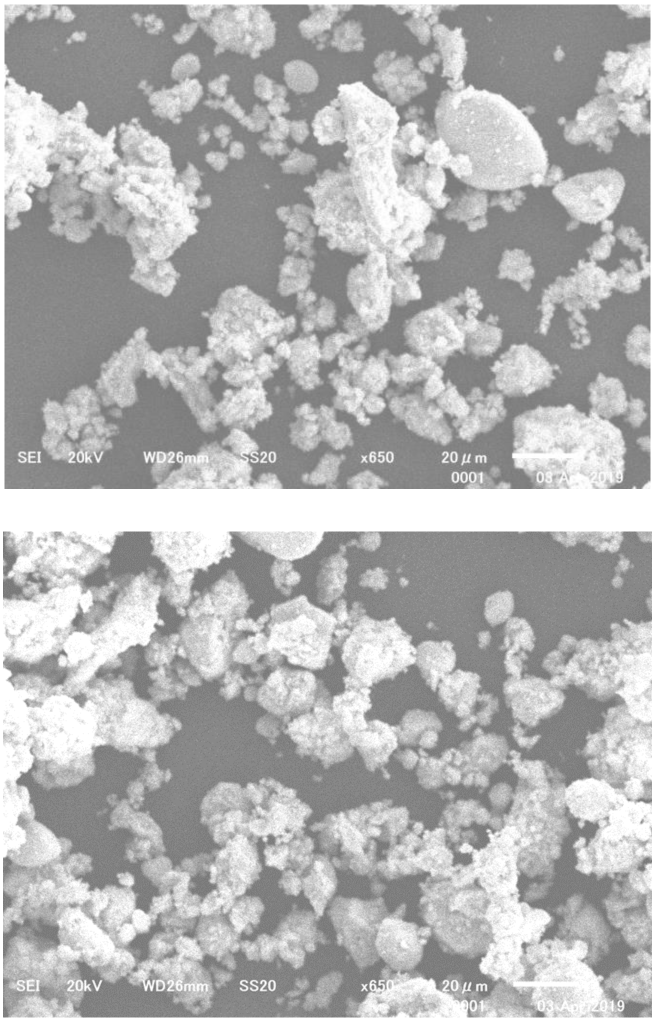


Fig. S6. SEM images of $BaTiO_3$ particles after ball milling (30 Hz, 1 h).

Reaction Temperature Confirmed by Thermography.

The temperature inside the milling jar after the mechano-redox arylation was confirmed by thermography. The crude mixtures were prepared by the following conditions: 0.3 mmol of **1a**; 4.5 mmol of **2a**; 1.5 mmol of $BaTiO_3$ in a stainless-steel ball milling jar (1.5 mL) with a stainless-steel ball (5 mm); 30Hz; 1 h. The obtained image (Fig. S7) showed that the temperature was around 30°C.

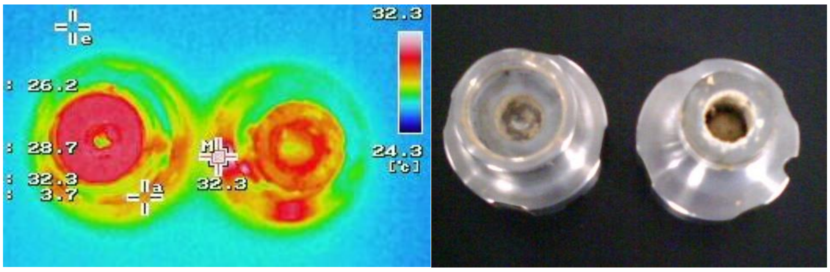


Fig. S7. Temperature inside the milling jar confirmed by thermography.

Mechano-Redox Borylation Using Hammer.

1k (25.4 mg, 0.1 mmol), $BaTiO_3$ (116.6 mg, 0.5 mmol) and bis(pinacolato)diboron (**4**, 24.8 mg, 0.1 mmol) were placed in a mortar. Then anhydrous acetonitrile (20 μL) was added to the mixture. After gentle grinding for 3 mins, the mixture was wrapped in a medicine paper and placed in a zipper locking plastic bag (Fig. S8). Then the mixture was subjected to the mechanical impacts provided by a hammer (Fig. S8). After hitting with a hammer over 200 times, the mixture was filtered and washed with CH_2Cl_2. The solvent was then removed under reduced pressure. The obtained crude mixture was analyzed by ^1H NMR with dibromomethane as an internal standard to determine the yield of the product **5i**.

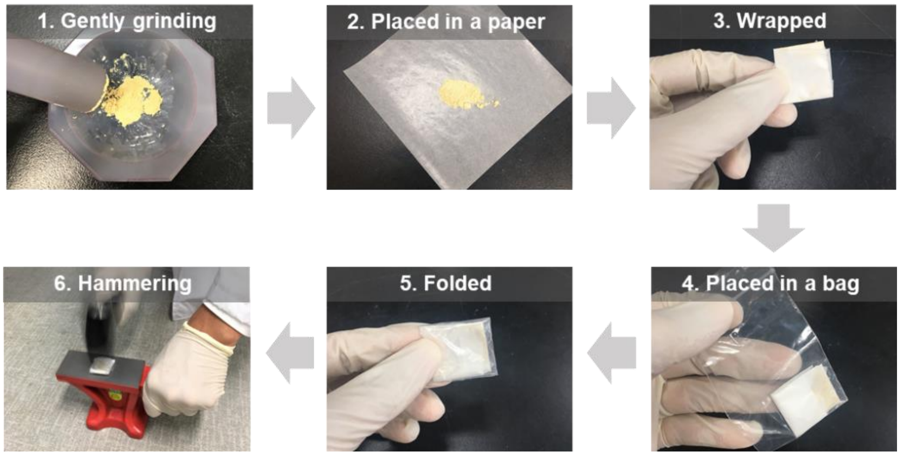
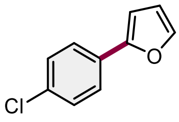


Fig. S8. Mechano-redox borylation using a hammer.

Arylation and Borylation Product Characterizations.

2-(4-Chlorophenyl)furan (3a).

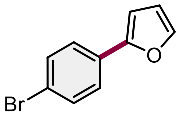


3a

The reaction was conducted with 67.9 mg (0.30 mmol) of **1a**. The product **3a** was obtained in 73% yield (38.9 mg, 0.22 mmol) as a white powder (m.p. = 67–68°C) by flash column chromatography (SiO_2, hexane). ^1H and ^{13}C NMR of the product **3a** were in agreement with the literature.

^1H NMR (392 MHz, $CDCl_3$, δ): 6.47 (dd, *J* = 1.6, 3.1 Hz, 1H), 6.63 (d, *J* = 3.5 Hz, 1H), 7.31–7.38 (m, 2H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 105.4 (*C*H), 111.8 (*C*H), 125.0 (*C*H), 128.8 (*C*H), 129.3 (*C*), 132.9 (*C*), 142.3 (*C*H), 152.9 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_7ClO$, 178.0185; found, 178.0188.

2-(4-Bromophenyl)furan (3b).

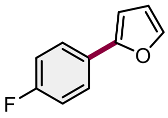


3b

The reaction was conducted with 81.2 mg (0.30 mmol) of **1b**. The product **3b** was obtained in 61% yield (40.6 mg, 0.18 mmol) as a white powder (m.p. =85–86°C) by flash column chromatography (SiO_2, hexane). ^1H and ^{13}C NMR of the product **3b** were in agreement with the literature.

^1H NMR (392 MHz, $CDCl_3$, δ): 6.47 (dd, *J* = 2.0, 3.1 Hz, 1H), 6.65 (d, *J* = 3.5 Hz, 1H), 7.47 (d, *J* = 1.6 Hz, 1H), 7.45–7.56 (m, 4H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 105.5 (*C*H), 111.8 (*C*H), 121.0 (*C*), 125.3 (*C*H), 129.7 (*C*), 131.8 (*C*H), 142.4 (*C*H), 152.9 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_7BrO$, 221.9680; found, 221.9684.

2-(4-Fluorophenyl)furan (3c).

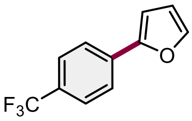


3c

The reaction was conducted with 63.0 mg (0.30 mmol) of **1c**. The product **3c** was obtained in 74% yield (36.0 mg, 0.22 mmol) as a slightly yellow oil by flash column chromatography (SiO_2, hexane). ^1H and ^{13}C NMR of the product **3c** were in agreement with the literature.

^1H NMR (392 MHz, $CDCl_3$, δ): 6.45 (dd, *J* = 1.6, 3.1 Hz, 1H), 6.57 (d, *J* = 3.1 Hz, 1H), 7.03–7.11 (m, 2H), 7.44 (d, *J* = 1.6 Hz, 1H), 7.59–7.66 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 104.6 (*C*H), 111.7 (*C*H), 115.7 (d, $J_{C\text{-}F}$ = 21.5 Hz, *C*H), 125.5 (d, $J_{C\text{-}F}$ = 7.5 Hz, *C*H), 127.2 (d, $J_{C\text{-}F}$ = 3.7 Hz, *C*H), 142.0 (*C*H), 153.1 (*C*), 162.1 (d, $J_{C\text{-}F}$ = 245.8 Hz, *C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_7FO$, 162.0481; found, 162.0482.

2-[4-(Trifluoromethyl)phenyl]furan (3d).

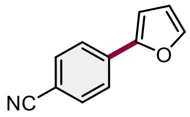


3d

The reaction was conducted with 78.0 mg (0.30 mmol) of **1d**. The product **3d** was obtained in 72% yield (45.8 mg, 0.22 mmol) as a white powder (m.p. = 88–90°C) by flash column chromatography (SiO_2, hexane). ^1H and ^{13}C NMR of the product **3d** were in agreement with the literature.

^1H NMR (392 MHz, $CDCl_3$, δ): 6.50 (dd, *J* = 2.0, 3.1 Hz, 1H), 6.76 (d, *J* = 3.1 Hz, 1H), 7.49–7.52 (m, 1H), 7.62 (d, *J* = 8.2 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 106.9 (*C*H), 111.9 (*C*H), 123.7 (*C*H), 124.2 (d, $J_{C\text{-}F}$ = 271.5 Hz, *C*), 125.7 (q, $J_{C\text{-}F}$ = 3.7 Hz, *C*H), 128.9 (q, $J_{C\text{-}F}$ = 32.3 Hz, *C*), 133.9 (*C*), 143.1 (*C*H), 152.5 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_7F_3O$, 212.0449; found, 212.0442.

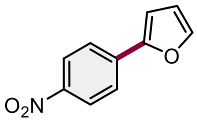
4-(Furan-2-yl)benzonitrile (3e).



3e

The reaction was conducted with 65.1 mg (0.30 mmol) of **1e**. The product **3e** was obtained in 50% yield (25.2 mg, 0.15 mmol) as a slightly yellow powder (m.p. = 65–66°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 95:5). ^{1}H and ^{13}C NMR of the product **3e** were in agreement with the literature. ^{1}H NMR (392 MHz, $CDCl_3$, δ): 6.50–6.55 (m, 1H), 6.81 (d, *J* = 3.1 Hz, 1H), 7.53 (s, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.73 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 108.1 (*C*H), 110.1 (*C*), 112.2 (*C*H), 118.9 (*C*), 123.8 (*C*H), 132.5 (*C*H), 134.5 (*C*), 143.6 (*C*H), 151.9 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_7NO$, 169.0528; found, 169.0531.

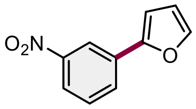
2-(4-Nitrophenyl)furan (3f).



3f

The reaction was conducted with 71.1 mg (0.30 mmol) of **1f**. The product **3f** was obtained in 62% yield (35.1 mg, 0.19 mmol) as a yellow powder (m.p. = 136–137°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 95:5). ^{1}H and ^{13}C NMR of the product **3f** were in agreement with the literature. ^{1}H NMR (392 MHz, $CDCl_3$, δ): 6.55 (dd, *J* = 1.4, 3.3 Hz, 1H), 6.88 (d, *J* = 3.1 Hz, 1H), 7.55–7.60 (m, 1H), 7.78 (d, *J* = 9.0 Hz, 2H), 8.24 (d, *J* = 9.0 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 109.0 (*C*H), 112.4 (*C*H), 123.9 (*C*H), 124.3 (*C*H), 136.4 (*C*), 144.1 (*C*H), 146.3 (*C*), 151.7 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_7NO_3$, 189.0426; found, 189.0427.

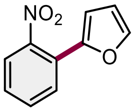
2-(3-Nitrophenyl)furan (3g).



3g

The reaction was conducted with 71.1 mg (0.30 mmol) of **1g**. The product **3g** was obtained in 41% yield (23.3 mg, 0.12 mmol) as a yellow powder (m.p. = 47–48°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 95:5). ^{1}H and ^{13}C NMR of the product **3g** were in agreement with the literature.
^{1}H NMR (392 MHz, $CDCl_3$, δ): 6.53 (dd, *J* = 2.0, 3.1 Hz, 1H), 6.81 (d, *J* = 3.1 Hz, 1H), 7.51–7.58 (m, 2H), 7.96 (d, *J* = 7.4 Hz, 1H), 8.09 (dd, *J* = 1.8, 8.0 Hz, 1H), 8.49 (s, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 107.3 (*C*H), 112.1 (*C*H), 118.5 (*C*H), 121.7 (*C*H), 129.2 (*C*H), 129.7 (*C*H), 132.3 (*C*), 143.3 (*C*H), 148.7 (*C*), 151.5 (*C*). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{10}H_7NO_3$, 189.0426; found, 189.0428.

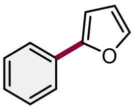
2-(2-Nitrophenyl)furan (3h).



3h

The reaction was conducted with 71.1 mg (0.30 mmol) of **1h**. The product **3h** was obtained in 64% yield (36.0 mg, 0.19 mmol) as a yellow oil by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 95:5). ^{1}H and ^{13}C NMR of the product **3h** were in agreement with the literature.
^{1}H NMR (392 MHz, $CDCl_3$, δ): 6.50 (dd, *J* = 1.8, 3.7 Hz, 1H), 6.67 (d, *J* = 3.5 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.51 (d, *J* = 1.2 Hz, 1H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.67 (d, *J* = 8.2 Hz, 1H), 7.71 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 109.6 (*C*H), 111.8 (*C*H), 123.8 (*C*H), 124.1 (*C*), 128.2 (*C*H), 128.8 (*C*H), 131.8 (*C*H), 143.7 (*C*H), 147.5 (*C*), 148.3 (*C*). HRMS-ESI (*m*/*z*): [M–H]$^+$ calcd for $C_{10}H_6NO_3$, 188.0353; found, 188.0353.

2-Phenylfuran (3i).

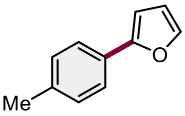


3i

The reaction was conducted with 57.6 mg (0.30 mmol) of **1i**. The product **3i** was obtained in 61% yield (26.0 mg, 0.18 mmol) as a yellow oil by flash column chromatography (SiO_2, hexane). ^1H and ^{13}C NMR of the product **3i** were in agreement with the literature.

^1H NMR (392 MHz, $CDCl_3$, δ): 6.47 (dd, *J* = 1.6, 3.1 Hz, 1H), 6.65 (d, *J* = 3.5 Hz, 1H), 7.22–7.28 (m, 1H), 7.34–7.41 (m, 2H), 7.46 (d, *J* = 2.0 Hz, 1H), 7.64–7.70 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 104.9 (*C*H), 111.6 (*C*H), 123.8 (*C*H), 127.3 (*C*H), 128.6 (*C*H), 130.9 (*C*), 142.0 (*C*H), 154.0 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_8O$, 144.0575; found, 144.0581.

2-(*p*-Tolyl)furan (3j).

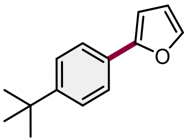


3j

The reaction was conducted with 61.8 mg (0.30 mmol) of **1j**. The product **3j** was obtained in 53% yield (25.2 mg, 0.16 mmol) as a slightly yellow oil by flash column chromatography (SiO_2, hexane). ^1H and ^{13}C NMR of the product **3j** were in agreement with the literature.

^1H NMR (392 MHz, $CDCl_3$, δ): 2.35 (s, 3H), 6.45 (dd, *J* = 2.0, 3.1 Hz, 1H), 6.58 (d, *J* = 3.9 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.43 (d, *J* = 2.0 Hz, 1H), 7.56 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 21.2 (*C*H_3), 104.2 (*C*H), 111.5 (*C*H), 123.7 (*C*H), 128.2 (*C*), 129.3 (*C*H), 137.1 (*C*), 141.6 (*C*H), 154.2 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{10}O$, 158.0732; found, 158.0734.

2-[4-(*tert*-Butyl)phenyl]furan (3k).

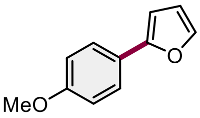


3k

The reaction was conducted with 74.4 mg (0.30 mmol) of **1k**. The product **3k** was obtained in 62% yield (37.3 mg, 0.19 mmol) as a colorless oil by flash column chromatography (SiO$_2$, hexane). ^{1}H and ^{13}C NMR of the product **3k** were in agreement with the literature.

^{1}H NMR (392 MHz, CDCl$_3$, δ): 1.33 (s, 9H), 6.44 (dd, *J* = 1.6, 3.1 Hz, 1H), 6.59 (d, *J* = 3.1 Hz, 1H), 7.37–7.45 (m, 3H), 7.60 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 31.3 (*C*H$_3$), 34.6 (*C*), 104.3 (*C*H), 111.5 (*C*H), 123.6 (*C*H), 125.6 (*C*H), 128.2 (*C*), 141.7 (*C*H), 150.4 (*C*), 154.1 (*C*). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{14}H_{16}O$, 200.1201; found, 200.1200.

2-(4-Methoxyphenyl)furan (3l).

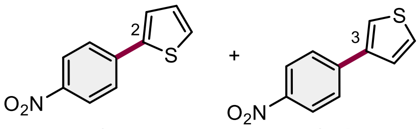


3l

The reaction was conducted with 66.6 mg (0.30 mmol) of **1l**. The product **3l** was obtained in 35% yield (17.9 mg, 0.10 mmol) as a white powder (m.p. = 53–54°C) by flash column chromatography (SiO$_2$, hexane/ethyl acetate, 100:0 to 98:2). ^{1}H and ^{13}C NMR of the product **3l** were in agreement with the literature.

^{1}H NMR (392 MHz, CDCl$_3$, δ): 3.82 (s, 3H), 6.42–6.46 (m, 1H), 6.51 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 2H), 7.40–7.44 (m, 1H), 7.60 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (99 MHz, CDCl$_3$, δ): 55.3 (*C*H$_3$), 103.3 (*C*H), 111.5 (*C*H), 114.1 (*C*H), 124.0 (*C*), 125.2 (*C*H), 141.3 (*C*H), 154.0 (*C*), 159.0 (*C*). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{11}H_{10}O_2$, 174.0681; found, 174.0681.

2-(4-Nitrophenyl)thiophene (3ma).

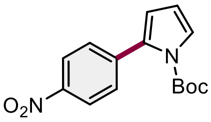


3ma **3mb**

The reaction was conducted with 71.1 mg (0.30 mmol) of **1f**. The product **3ma** and **3mb** were obtained in 47% yield (28.8 mg, 0.14 mmol, **3ma**/**3mb** = 90:10) as a yellow mixture by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 98:2). The isomer ratio values were determined by ^1H NMR analysis of the crude reaction mixture. ^1H and ^{13}C NMR of the major product **3ma** were in agreement with the literature.

For the major isomer **3ma**: ^1H NMR (392 MHz, $CDCl_3$, δ): 7.16 (dd, J = 3.9, 5.1 Hz, 1H), 7.44 (dd, J = 1.2, 5.1 Hz, 1H), 7.48 (dd, J = 1.0, 3.7 Hz, 1H), 7.73–7.77 (m, 2H), 8.21–8.29 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 124.4 (*C*H), 125.7 (*C*H), 126.0 (*C*H), 127.7 (*C*H), 128.7 (*C*H), 140.5 (*C*), 141.6 (*C*), 146.6 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_7NO_2S$, 205.0198; found, 205.0193.

***tert*-Butyl 2-(4-nitrophenyl)-1*H*-pyrrole-1-carboxylate (3n).**

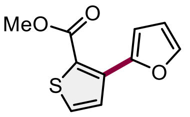


3n

The reaction was conducted with 71.1 mg (0.30 mmol) of **1f**. The product **3n** was obtained in 27% yield (20.8 mg, 0.07 mmol) as a yellow powder (m.p. = 124–125°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 99:1). ^1H and ^{13}C NMR of the product **3n** were in agreement with the literature.

^1H NMR (392 MHz, $CDCl_3$, δ): 1.44 (s, 9H), 6.28 (t, J = 3.3 Hz, 1H), 6.33 (dd, J = 1.6, 3.5 Hz, 1H), 7.41 (dd, J = 2.0, 3.1 Hz, 1H), 7.52 (d, J = 8.6 Hz, 2H), 8.22 (d, J = 8.6 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 27.7 (*C*H_3), 84.5 (*C*), 111.1 (*C*H), 116.5 (*C*H), 122.9 (*C*H), 124.3 (*C*H), 129.5 (*C*H), 132.7 (*C*), 140.7 (*C*), 146.5 (*C*), 148.9 (*C*). HRMS-ESI (*m*/*z*): $[M+Na]^+$ calcd for $C_{15}H_{16}N_2O_4Na$, 311.1002; found, 311.1007.

Methyl 3-(furan-2-yl)thiophene-2-carboxylate (3o).

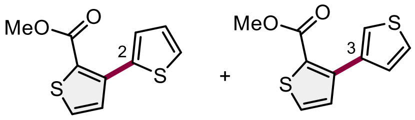


3o

The reaction was conducted with 76.8 mg (0.30 mmol) of **1m**. The product **3o** was obtained in 66% yield (41.2 mg, 0.20 mmol) as a pale yellow oil by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 99:1). ^{1}H and ^{13}C NMR of the product **3o** were in agreement with the literature.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.88 (s, 3H), 6.52 (dd, *J* = 1.6, 3.1 Hz, 1H), 7.44–7.48 (m, 2H), 7.52–7.57 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.0 (CH_3), 112.0 (*C*H), 112.7 (*C*H), 124.0 (*C*), 128.7 (*C*H), 130.3 (*C*H), 136.6 (*C*), 142.1 (*C*H), 148.9 (*C*), 162.2 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_8O_3S$, 208.0194; found, 208.0192.

Methyl (2,3'-bithiophene)-2'-carboxylate (3pa).

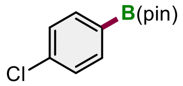


3pa **3pb**

The reaction was conducted with 76.8 mg (0.30 mmol) of **1m**. The product **3pa** and **3pb** were obtained in 50% yield (33.6 mg, 0.15 mmol, **3pa**/**3pb** = 86:14) as a yellow mixture by flash chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 99:1). The isomer ratio values were determined by ^{1}H NMR analysis of the crude reaction mixture. ^{1}H and ^{13}C NMR of the major product **3pa** were in agreement with the literature.

For the major isomer **3pa**: ^{1}H NMR (392 MHz, $CDCl_3$, δ): 3.85 (s, 3H), 7.09 (dd, *J* = 3.5, 5.1 Hz, 1H), 7.24 (d, *J* = 5.5 Hz, 1H), 7.38 (d, *J* = 5.1 Hz, 1H), 7.47 (d, *J* = 5.5 Hz, 1H), 7.58 (d, *J* = 3.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 52.0 (CH_3), 125.9 (*C*), 126.5 (*C*H), 127.1 (*C*H), 128.8 (*C*H), 130.2 (*C*H), 131.4 (*C*H), 136.2 (*C*), 140.1 (*C*), 162.3 (*C*). HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{10}H_8O_2S_2$, 223.9966; found, 223.9966.

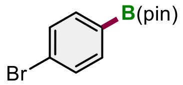
2-(4-Chlorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5a).



5a

The reaction was conducted with 67.9 mg (0.30 mmol) of **1a**. The product **5a** was obtained in 61% yield (43.8 mg, 0.18 mmol) as an orange powder (m.p. = 52–53°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 99:1). ^1H and ^{13}C NMR of the product **5a** were in agreement with the literature.
^1H NMR (392 MHz, $CDCl_3$, δ): 1.34 (s, 12H), 7.34 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 8.6 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 84.0 (C), 128.0 (CH), 136.1 (CH), 137.5 (C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (m/z): $[M\text{-}CH_3]^+$ calcd for $C_{11}H_{13}BClO_2$, 222.0733; found, 222.0734.

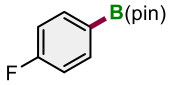
2-(4-Bromophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5b).



5b

The reaction was conducted with 81.2 mg (0.30 mmol) of **1b**. The product **5b** was obtained in 59% yield (50.0 mg, 0.18 mmol) as an orange powder (m.p. = 69–70°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 98:2). ^1H and ^{13}C NMR of the product **5b** were in agreement with the literature.
^1H NMR (392 MHz, $CDCl_3$, δ): 1.34 (s, 12H), 7.50 (dt, J = 1.8, 8.1 Hz, 2H), 7.66 (dt, J = 1.9, 8.5 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 84.0 (C), 126.2 (C), 130.9 (CH), 136.3 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (m/z): $[M–CH_3]^+$ calcd for $C_{11}H_{13}BBrO_2$, 266.0228; found, 266.0235.

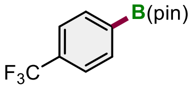
2-(4-Fluorophenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5c).



5c

The reaction was conducted with 63.0 mg (0.30 mmol) of **1c**. The product **5c** was obtained in 70% yield (46.4 mg, 0.21 mmol) as a yellow oil by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 98:2). ^1H and ^{13}C NMR of the product **5c** were in agreement with the literature.
^1H NMR (392 MHz, $CDCl_3$, δ): 1.34 (s, 12H), 7.05 (t, J = 8.6 Hz, 2H), 7.80 (d, J = 7.1 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 83.9 (C), 114.8 (d, $J_{C\text{-}F}$ = 19.7 Hz, CH), 137.0 (d, $J_{C\text{-}F}$ = 8.5 Hz, CH), 165.1 (d, $J_{C\text{-}F}$ = 249.9 Hz, C). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (m/z): $[M–CH_3]^+$ calcd for $C_{11}H_{13}BFO_2$, 206.1029; found, 206.1029.

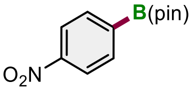
4,4,5,5-Tetramethyl-2-[4-(trifluoromethyl)phenyl]-1,3,2-dioxaborolane (5d).



5d

The reaction was conducted with 78.0 mg (0.30 mmol) of **1d**. The product **5d** was obtained in 45% yield (36.6 mg, 0.13 mmol) as an orange powder (m.p. = 68–69°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 98:2). ^{1}H and ^{13}C NMR of the product **5d** were in agreement with the literature. ^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.36 (s, 12H), 7.61 (d, $J = 8.2$ Hz, 2H), 7.91 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (*C*H_3), 84.3 (*C*), 124.1 (d, $J_{C\text{-}F} = 272.4$ Hz, *C*), 124.3 (q, $J_{C\text{-}F} = 3.7$ Hz, *C*H), 132.8 (q, $J_{C\text{-}F} = 32.2$ Hz, *C*), 135.0 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (*m*/*z*): $[M{-}CH_3]^+$ calcd for $C_{12}H_{13}BF_3O_2$, 256.0997; found, 256.0999.

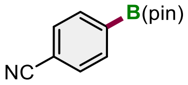
4,4,5,5-Tetramethyl-2-(4-nitrophenyl)-1,3,2-dioxaborolane (5e).



5e

The reaction was conducted with 71.1 mg (0.30 mmol) of **1f**. The product **5e** was obtained in 52% yield (38.8 mg, 0.16 mmol) as a pale orange powder (m.p. = 110–111°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 95:5). ^{1}H and ^{13}C NMR of the product **5e** were in agreement with the literature. ^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.37 (s, 12H), 7.96 (d, $J = 8.6$ Hz, 2H), 8.20 (d, $J = 7.8$ Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.9 (*C*H_3), 84.6 (*C*), 122.4 (*C*H), 135.6 (*C*H), 149.8 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (*m*/*z*): $[M{-}CH_3]^+$ calcd for $C_{11}H_{13}BNO_4$, 233.0974; found, 233.0978.

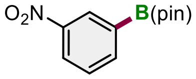
4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile (5f).



5f

The reaction was conducted with 63.0 mg (0.29 mmol) of **1e**. The product **5f** was obtained in 45% yield (29.9 mg, 0.13 mmol) as a white powder (m.p. = 90–100°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 95:5). ^1H and ^{13}C NMR of the product **5f** were in agreement with the literature. ^1H NMR (392 MHz, $CDCl_3$, δ): 1.35 (s, 12H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.88 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (*C*H_3), 84.5 (*C*), 114.5 (*C*), 118.9 (*C*), 131.1 (*C*H), 135.1 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_{12}H_{13}BNO_2$, 213.1076; found, 213.1077.

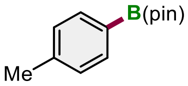
4,4,5,5-Tetramethyl-2-(3-nitrophenyl)-1,3,2-dioxaborolane (5g).



5g

The reaction was conducted with 71.1 mg (0.30 mmol) of **1g**. The product **5g** was obtained in 36% yield (26.5 mg, 0.11 mmol) as a pale yellow powder (m.p. = 72–73°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 95:5). ^1H and ^{13}C NMR of the product **5g** were in agreement with the literature. ^1H NMR (392 MHz, $CDCl_3$, δ): 1.37 (s, 12H), 7.55 (t, *J* = 7.6 Hz, 1H), 8.08–8.12 (m, 1H), 8.30 (ddd, *J* = 1.4, 2.4, 8.2 Hz, 1H), 8.64 (d, *J* = 1.6 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (*C*H_3), 84.6 (*C*), 125.8 (*C*H), 128.7 (*C*H), 129.4 (*C*H), 140.6 (*C*H), 147.8 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_{11}H_{13}BNO_4$, 233.0974; found, 233.0983.

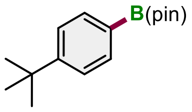
4,4,5,5-Tetramethyl-2-(*p*-tolyl)-1,3,2-dioxaborolane (5h).



5h

The reaction was conducted with 61.8 mg (0.30 mmol) of **1j**. The product **5h** was obtained in 70% yield (46.3 mg, 0.21 mmol) as an orange powder (m.p. = 51–52°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 98:2). ^1H and ^{13}C NMR of the product **5h** were in agreement with the literature. ^1H NMR (392 MHz, $CDCl_3$, δ): 1.33 (s, 12H), 2.36 (s, 3H), 7.18 (d, *J* = 7.8 Hz, 2H), 7.71 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 21.7 (*C*H_3), 24.8 (*C*H_3), 83.6 (*C*), 128.5 (*C*H), 134.8 (*C*H), 141.4 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (*m*/*z*): $[M–CH_3]^+$ calcd for $C_{12}H_{16}BO_2$, 202.1280; found, 202.1276.

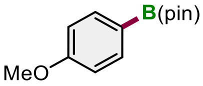
2-[4-(*tert*-Butyl)phenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5i).



5i

The reaction was conducted with 74.4 mg (0.30 mmol) of **1k**. The product **5i** was obtained in 61% yield (47.2 mg, 0.18 mmol) as an orange powder (m.p. = 133–134°C) by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 99:1). ^{1}H and ^{13}C NMR of the product **5i** were in agreement with the literature.
^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.32 (s, 9H), 1.33 (s, 12H), 7.41 (d, *J* = 8.2 Hz, 2H), 7.77 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 31.2 (CH_3), 34.9 (*C*), 83.6 (*C*), 124.7 (*C*H), 134.7 (*C*H), 154.5 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{25}BO_2$, 259.1984; found, 259.1984.

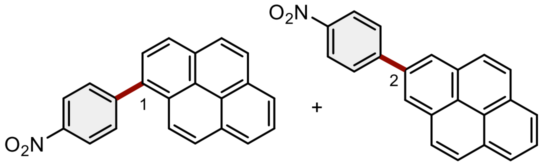
2-(4-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (5j).



5j

The reaction was conducted with 66.6 mg (0.30 mmol) of **1l**. The product **5j** was obtained in 80% yield (56.1 mg, 0.24 mmol) as a yellow oil by flash column chromatography (SiO_2, hexane/ethyl acetate, 100:0 to 99:1). ^{1}H and ^{13}C NMR of the product **5j** were in agreement with the literature.
^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.33 (s, 12H), 3.81 (s, 3H), 6.89 (dt, *J* = 2.1, 8.8 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.8 (CH_3), 55.0 (CH_3), 83.5 (*C*), 113.2 (*C*H), 136.5 (*C*H), 162.1 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[53,54] HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{19}BO_3$, 233.1464; found, 233.1453.

1-(4-nitrophenyl)pyrene (7aa).

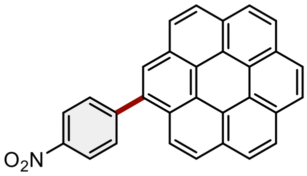


7aa **7ab**

The reaction was conducted with 71.1 mg (0.30 mmol) of **1f** and 303.1 mg (1.5 mmol) of **6a**. The product **7aa** and **7ab** were obtained in 78% yield (75.7 mg, 0.23 mmol, **7aa**/**7ab** = 92:8) by flash column chromatography (SiO_2, hexane/$CHCl_3$, 100:0 to 70:30). The isomer ratio values were determined by ^{1}H NMR analysis of the crude reaction mixture. The absence of the isomer arylated at the 4-position was confirmed by preparation of the authentic sample. ^{1}H and ^{13}C NMR of the major product **7aa** were in agreement with the literature.

For the major isomer **7aa**: ^{1}H NMR (396 MHz, $CDCl_3$, δ): 7.77 (dt, *J* = 2.2, 9.1 Hz, 2H), 7.92 (d, *J* = 7.9 Hz, 1H), 8.00–8.15 (m, 5H), 8.19 (d, *J* = 6.7 Hz, 1H), 8.23 (d, *J* = 7.9 Hz, 2H), 8.37–8.43 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 123.6 (*C*H), 124.1 (*C*H), 124.65 (*C*), 124.71 (*C*H), 124.9 (*C*), 125.3 (*C*H), 125.7 (*C*H), 126.3 (*C*H), 127.1 (*C*H), 127.3 (*C*H), 128.17 (*C*H), 128.24 (*C*), 128.3 (*C*H), 130.7 (*C*), 130.9 (*C*), 131.36 (*C*H), 131.41 (*C*), 134.8 (*C*), 147.1 (*C*), 148.1 (*C*). HRMS-ESI (*m*/*z*): $[M]^+$ calcd for $C_{22}H_{13}NO_2$, 323.0952; found, 323.0954.

1-(4-nitrophenyl)coronene (7b)



7b

The reaction was conducted with 71.1 mg (0.30 mmol) of **1f** and 270.3 mg (0.90 mmol) of **6b**. The product **7b** was purified by flash chromatography (SiO_2, hexane/$CHCl_3$, 100:0 to 0:100), followed by recrystallization from CH_2Cl_2/MeOH to give **7b** in 43% yield (54.4 mg, 0.13 mmol) as an orange powder.

^{1}H NMR (396 MHz, $CDCl_3$, δ): 8.10 (dt, *J* = 2.4, 8.8 Hz, 2H), 8.57 (dt, *J* = 2.0, 8.8 Hz, 2H), 8.80–8.87 (m, 3H), 8.89–8.97 (m, 8H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 122.55 (*C*), 122.61 (*C*), 122.8 (*C*), 123.6 (*C*H), 123.8 (*C*H), 126.24 (*C*H), 126.29 (*C*H), 126.32 (*C*H), 126.45 (*C*H), 126.51 (*C*H), 126.7 (*C*H), 126.88 (*C*H), 126.93 (*C*H), 127.1 (*C*H), 127.5 (*C*), 128.2 (*C*), 128.9 (*C*), 129.1 (*C*), 129.2 (*C*), 131.7 (*C*H), 136.3 (*C*), 148.6 (*C*). HRMS-ESI (*m*/*z*): $[M]^+$ calcd for $C_{30}H_{15}NO_2$, 421.1108; found, 421.1115.

References

1. C. Stephenson, T. Yoon, D. W. C. MacMillan, *Visible Light Photocatalysis in Organic Chemistry* (Wiley-VCH, Weinheim, Germany, ed. 1, 2018).
2. C. K. Pier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322.
3. N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075.
4. C.-S. Wang, P. H. Dixneuf, J.-F. Soulé, *Chem. Rev.* **2018**, *118*, 7532.
5. K. L. Skubi, T. R. Blum, T. P. Yoon, *Chem. Rev.* **2016**, *116*, 10035.
6. T. Friščić, *J. Mater. Chem.* **2010**, *20*, 7599.
7. S.-E. Zhu, F. Li, G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7535.
8. P. Baláž, *Mechanochemistry in Nanoscience and Minerals Engineering* (Springer, 2008).
9. R. Boulatov, *Polymer Mechanochemistry* (Switzerland, Springer, 2015).
10. S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed, D. C. Waddell, *Chem. Soc. Rev.* **2012**, *41*, 413.
11. G.-W. Wang, *Chem. Soc. Rev.* **2013**, *42*, 7668.
12. J.-L. Do, T. Friščić, *ACS Cent. Sci.* **2017**, *3*, 13.
13. J. G. Hernández, C. Bolm, *J. Org. Chem.* **2017**, *82*, 4007.
14. D. Tan, T. Friščić, *Eur. J. Org. Chem.* 2018, 18.
15. J. L. Howard, Q. Cao, D. L. Browne, *Chem. Sci.* **2018**, *9*, 3080.
16. J. Andersen, J. Mack, *Green Chem.* **2018**, *20*, 1435.
17. C. Bolm, J. D. Hernández, *Angew. Chem. Int. Ed.* **2019**, *58*, 3285.
18. F. Gomollón-Bel, *Chem. Int.* **2019**, *41*, 12.
19. J. C. Robertson, M. L. Coote, A. C. Bissmber, *Nat. Rev. Chem.* **2019**, *3*, 290.
20. J. Liang, J. M. Fernández, *J. Am. Chem. Soc.* **2011**, *133*, 3528.
21. P. Dopieralski, J. Ribas-Arino, P. Anjukandi, M. Krupicka, J. Kiss, D. Marx, *Nature Chem.* **2013**, *5*, 685.
22. H. Yan, F. Yang, D. Pan, Y. Lin, J. N. Hohman, D. Solis-Ibarra, F. H. Li, J. E. P. Dahl, R. M. K. Carlson, B. A. Tkachenko, A. A. Fokin, P. R. Schreiner, G. Galli, W. L. Mao, Z.-X. Shen, N. A. Melosh, *Nature* **2018**, *554*, 505.
23. S. Ikeda, T. Takata, M. Komoda, M. Hara, J. N. Kondo, K. Domen, A. Tanaka, H. Hosono, H. Kawazoe, *Phys. Chem. Chem. Phys.* **1999**, *1*, 4485.
24. M. Hara, H. Hasei, M. Yashima, S. Ikeda, T. Takata, J. N. Kondo, K. Domen, *Appl. Catal. A-Gen.* **2000**, *190*, 35.
25. Z. L. Wang, J. Song, *Science* **2006**, *312*, 242.
26. X. Wang, J. Song, J. Liu, L. Wang, *Science* **2007**, *316*, 102.
27. Y. Qin, X. Wang, Z. L. Wang, *Nature* **2008**, *451*, 809.
28. K.-S. Hong, H. Xu, H. Konishi, X. Li, *J. Phys. Chem. Lett.* **2010**, *1*, 997.
29. H. Mohapatra, M. Kleiman, A. P. Esser-Kahn, *Nature Chem.* **2017**, *9*, 135.

30. M. B. Starr, J. Shi, X. Wang, *Angew. Chem. Int. Ed.* **2012**, *51*, 5962.
31. M. B. Starr, X. Wang, *Sci. Rep.* **2013**, *3*, 2160.
32. H. Lin, Z. Wu, Y. Jia, W. Li, R.-K. Zheng, H. Luo, *Appl. Phys. Lett.* **2014**, *104*, 162907.
33. W. Lv, L. Kong, S. Lan, J. Feng, Y. Xiong, S. Tian, *J. Chem. Technol. Biotechnol.* **2017**, *92*, 152.
34. K. Matyjaszewski, *Macromolecules* **2012**, *45*, 4015.
35. D. P. Hari, P. Schroll, B. König, *J. Am. Chem. Soc.* **2012**, *134*, 2958.
36. J. Yu, L. Zhang, G. Yan, *Adv. Synth. Catal.* **2012**, *354*, 2625.
37. C. P. Andrieux, J. Pinson, *J. Am. Chem. Soc.* **2003**, *125*, 14801.
38. J. H. Haeni, P. Irvin, W. Chang, R. Uecker, P. Reiche, Y. L. Li, S. Choundhury, W. Tian, M. E. Hawley, B. Craigo, A. K. Tagantsev, X. Q. Pan, S. K. Streiffer, L. Q. Chen, S. W. Kirchoefer, J. Levy, D. G. Schlom, *Nature* **2004**, *430*, 758.
39. T. Friščić, S. L. Childs, S. A. A. Rizvi, W. Jones, *CrystEngComm* **2009**, *11*, 418.
40. M. E. Cinar, T. Ozturk, *Chem. Rev.* **2015**, *115*, 3036.
41. Y. Segawa, H. Ito, K. Itami, *Nat. Rev. Mater.* **2016**, *1*, 15002.
42. Y. Segawa, T. Maekawa, K. Itami, *Angew. Chem. Int. Ed.* **2015**, *54*, 66.
43. T. Umemoto, B. Zhang, T. Zhu, X. Zhou, P. Zhang, S. Hu, Y. Li, *J. Org. Chem.* **2017***, 82,* 7708.

Chapter 3.

Copper(I)-Catalyzed Debromoborylation of 1,1-Dibromo-1-alkenes

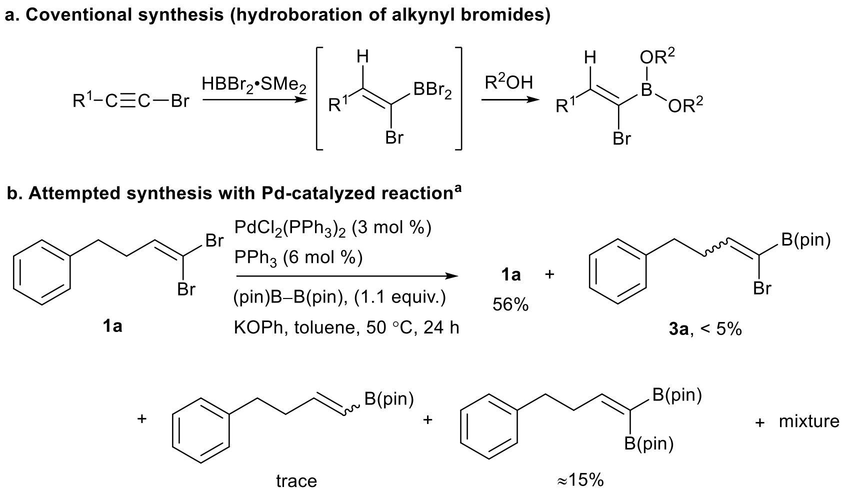
Abstract

A stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes by using copper(I) catalysts to prepare (*Z*)-1-bromo-1-alkenylboronate esters was developed. The debromoborylation of various aliphatic 1,1-dibromo-1-alkenes in the presence of a copper(I) catalyst and bis(pinacolato)diboron proceeded smoothly to produce (*Z*)-1-bromo-1-alkenylboronate esters in good yields with only *Z* geometry, respectively.

Introduction

Organoboronic acids and their derivatives, especially alkenylboronate esters, are powerful and versatile reagents in organic synthesis because of their high stability, low toxicity, and great synthetic utility in many reactions such as the Suzuki–Miyaura cross-coupling reaction.[1] In addition, (*Z*)-1-bromo-1-alkenylboronate esters are also useful organoboron synthetic intermediates in organic synthesis. They are known to undergo cross-coupling reactions with organozinc reagents[2] and the intramolecular nucleophilic substitution reactions with nucleophiles such as hydrides,[3] Grignard reagents,[4] organolithium reagents,[4] allylmagnesium bromide,[5] trimethylsilylmethyllithium,[6] and trimethylgermyllithium.[7] However, there is only one method for the synthesis (*Z*)-1-bromo-1-alkenylboronate esters has been developed: hydroboration of alkynyl bromides (Scheme 3-1a).[2-7] The synthesis of alkynyl halides requires harsh conditions with less functional group compatibility. Therefore, the development of a simple, mild and efficient method for the direct preparation of (*Z*)-1-bromo-1-alkenylboronate esters remains highly desirable. The author's research focuses on the stereoselective debromoborylation of 1,1-dibromo-1-alkenes, which are readily available from the corresponding carbonyl compounds through the Wittig reaction.[8]

To develop a more convenient reaction pathway, the author first considered the palladium-catalyzed borylation with bis(pinacolato)diboron, which was developed by Miyaura and Ishiyama and is a standard procedure for transformation of alkenyl bromide. However, similar to the results that was already reported by Cao's group,[10] the Pd-catalyzed borylation of 1,1-dibromo-1-alkene **1a** failed. Only a small amount of the desired product was obtained in accompany with a monoborylated alkene, a diboryl alkene, and complex mixture (Scheme 3-1b).[9]


a. Coventional synthesis (hydroboration of alkynyl bromides)

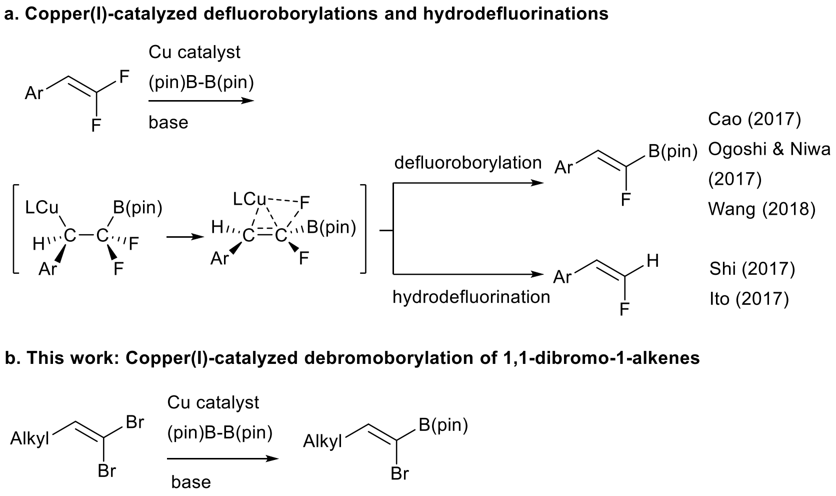
b. Attempted synthesis with Pd-catalyzed reaction[a]

[a]The yields were determined by GC analysis

Scheme 3-1. Synthesis of (Z)-1-bromo-1-alkenylboronate esters.

Very recently, several groups reported copper(I)-catalyzed reactions of 1,1-difluoro-1-alkenes. Three different groups (Cao, Ogoshi and Niwa, and Wang) independently reported monodefluoroborylation reactions of aryl 1,1-difluoro-1-alkenes, with a copper(I) catalyst in the presence of bis(pinacolato)diboron to afford (*Z*)-1-fluoro-1-alkenylboronate esters (Scheme 3-2a).[10-12] This reaction would proceed through the addition of a borylcopper(I) intermediate to 1,1-difluoro-1-alkene and subsequent β-elimination to give the corresponding defluoroborylation products. At the almost same time, Ito and Shi's group also reported selective hydrodefluorinations of aryl 1,1-difluoro-1-alkenes with a copper(I) catalyst for production of monofluoroalkenes, where the same key intermediate would be present (Scheme 3-2a).[13,14]

Inspired by these results and the similar reactivity of F and Br, the author envisioned that the selective debromoborylation of 1,1- dibromo-1-alkenes should be possible. Herein, the author reports a novel and efficient method for the synthesis of (Z)-1-bromo-1-alkenylboronate esters via copper(I)-catalyzed stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes with bis (pinacolato)diboron in the presence of a copper(I) catalyst (Scheme 3-2b).

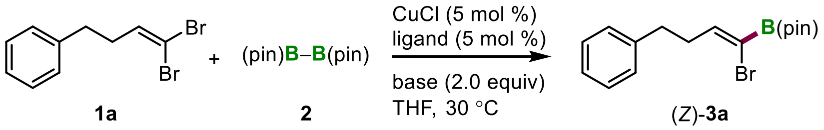


Scheme 3-2. Copper(I)-catalyzed reactions of 1,1-dihalo-1-alkenes

Results and Discussion

This research commenced with the screening of reaction conditions by using the borylation of (4,4-dibromobut-3-en-1-yl)benzene **1a** with bis(pinacolato)diboron as the model reaction (Table 3-1). Initially, a trace amount of the desired product was observed in the absence of a ligand (entry 1). Then, the author found that Xantphos was a preferred ligand among other common ligands such as PPh_3, dppp, dppbz, IPr·HCl, and 1,10-phen (entries 2–7). Further screening of a series of different bases revealed that only NaOMe (2.0 equiv.) could afford the desired product (*Z*)-**3a** in good yield (entries 8–13). In particular, the use of a relatively strong base, sodium *tert*-butoxide, could afford the corresponding bromoalkyne as a major byproduct and no desired product was obtained (entry 10). To the author's delight, this debromoborylation reaction occurred with high (*Z*)-selectivity and no (*E*)-isomer was detected by GC and NMR analyses. The structure of the favourable stereoisomer was confirmed by single-crystal X-ray diffraction analysis of (*Z*)-**3n** (see experimental section).

Table 3-1. Screening of reaction conditions for the debromoborylation of aliphatic 1,1-dibromo-1-alkenes.[a]

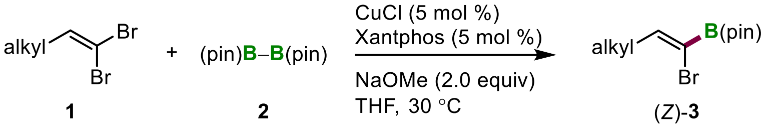


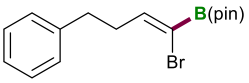
Entry	ligand	base	yield (%)[b]
1	-	NaOMe	4
2	PPh_3[c]	NaOMe	7
3	dppp	NaOMe	61
4	dppbz	NaOMe	58
5	IPr·HCl	NaOMe	13
6	1,10-phen	NaOMe	18
7	Xantphos	NaOMe	85
8	Xantphos	NaOMe[d]	58
9	Xantphos	KOMe	51
10	Xantphos	Na(O-*t*-Bu)	trace[e]
11	Xantphos	KOAc	trace
12	Xantphos	K_2CO_3	trace
13	Xantphos	LiOMe	trace

[a] Reaction conditions: **1a** (0.25 mmol), **2** (0.3 mmol), solvent (1 mL), 3 h. [b] Yields were determined by ^{1}H NMR analysis. [c] 10 mol% was used. [d] 1.5 equiv. was used. [e] 1-Bromo-4-phenyl-but-4-yne was detected in approx. 40% yield by ^{1}H NMR analysis.

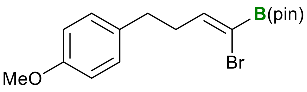
With the optimal reaction conditions in hand (Table 3-1, entry 7), a series of aliphatic 1,1-dibromo-1-alkene substrates that were prepared from aliphatic aldehydes was examined to investigate the scope of the debromoborylation reaction (Table 3-2). The debromoborylation reaction proceeded efficiently to give the corresponding (*Z*)-brominated alkenyl boronate esters **3** in moderate to good yields and no (*E*)-isomer was observed in each case. However, the author found that purification of the boronate esters (*Z*)-**3** without loss was difficult using typical chromatographic techniques because they were easily hydrolyzed in silica gel; thus, the isolated yields were lower than the corresponding NMR yields. Substrates with aryl groups (**1a**–**e**) or a heteroaryl moiety **1f** did not hamper this debromoborylation process and afforded the corresponding products [(*Z*)-**3a**–**f**] in high NMR and moderate isolated yields, [(*Z*)-**3a**, 85% (55%); (*Z*)-**3b**, 77% (52%); (*Z*)-**3c**, 83% (58%); (*Z*)-**3d**, 81% (62%); (*Z*)-**3e**, 71% (55%); (*Z*)-**3f**, 87% (62%)]. The reactions of substrates with simple alkyl chains (**1g**–**j**) gave the desired products in high NMR yields and moderate isolated yields [(*Z*)-**3g**, 92% (59%); (*Z*)-**3h**, 83% (62%); (*Z*)-**3i**, 90% (57%); (*Z*)-**3j**, 85% (58%)]. Substrates with chlorine (**1k**), alkene (**1l**), carbamate (**1m**) and imide (**1n**) functional groups were also tolerated [(*Z*)-**3k**, 77% (57%); (*Z*)-**3l**, 90% (54%); (*Z*)-**3m**, 75% (51%); (*Z*)-**3n**, 66% (50%)]. Unfortunately, when (2,2-dibromovinyl)cyclohexane **1o**, which bears a tertiary carbon at the α-position of the double bond of the 1,1-dibromo-1-alkene, was used as a substrate under the optimal reaction conditions, no reaction occurred and the desired product (*Z*)-**3o** was not obtained, probably because of steric hindrance. Furthermore, when (2,2-dibromovinyl)benzene **1p** was used as a substrate, the starting material was recovered mostly and the desired product (*Z*)-**3p** was also not obtained even under the optimized conditions.

Table 3-2. Scope of the debromoborylation of aliphatic 1,1-dibromo-1-alkenes.[a]

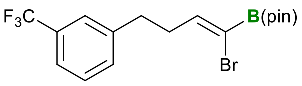




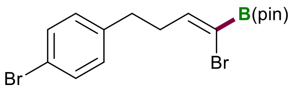
(*Z*)-**3a**
3 h, 85% (55%)



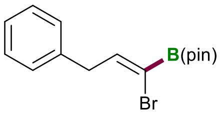
(*Z*)-**3b**
3.5 h, 77% (52%)



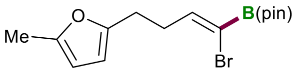
(*Z*)-**3c**
3.5 h, 83% (58%)



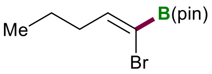
(*Z*)-**3d**
3.5 h, 81% (62%)



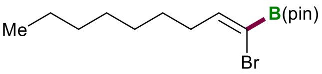
(*Z*)-**3e**
12 h, 71% (55%)



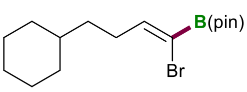
(*Z*)-**3f**
4 h, 87% (62%)



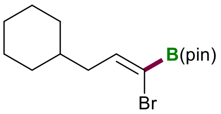
(*Z*)-**3g**
3 h, 92% (59%)



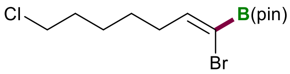
(*Z*)-**3h**
3.5 h, 83% (62%)



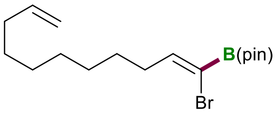
(*Z*)-**3i**
3 h, 90% (57%)



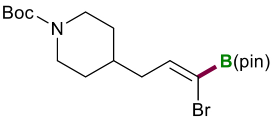
(*Z*)-**3j**
4.5 h, 85% (58%)



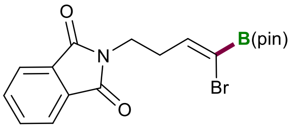
(*Z*)-**3k**
5 h, 77% (57%)



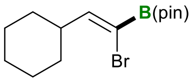
(*Z*)-**3l**
5 h, 90% (54%)



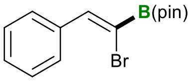
(*Z*)-**3m**
8 h, 75% (51%)



(*Z*)-**3n**[b]
8 h, 66% (50%)



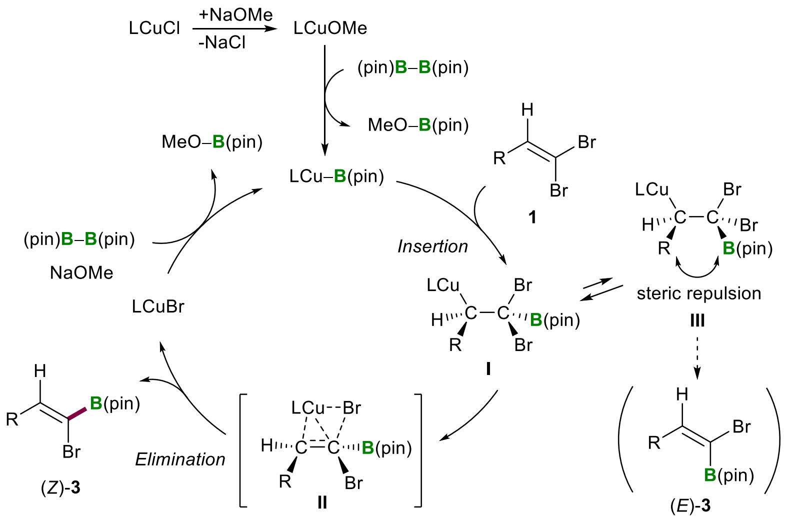
(*Z*)-**3o**
12 h, 0%



(*Z*)-**3p**
12 h, 0%

[a] Reaction conditions: **1** (0.25 mmol), **2** (0.3 mmol), solvent (1 mL). Yields were determined by ^{1}H NMR spectroscopy; isolated yields are shown in parentheses. [b] CuCl (10 mol%), Xantphos (10 mol%), and solvent (1.5 mL) were used.

Based on the above observations and previous reports,[10-15] a mechanism for the copper(I)-catalyzed stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes with bis(pinacolato)diboron is proposed (Scheme 3-3). Initially, transmetallation of the phosphine-ligated copper(I) catalyst LCuOMe, which is generated *in situ* from LCuCl and NaOMe, with bis(pinacolato)diboron provides the nucleophilic phosphine-coordinated borylcopper(I) complex LCu–B(pin). Subsequent insertion of the carbon–carbon double bond of the 1,1-dibromo-1-alkene **1** into the Cu–B bond of the borylcopper(I) complex would lead to the generation of β-borylalkylcopper(I) species **I** with the perfect regioselectivity since forming the C–B bond should be occurred at the more electron-positive olefinic carbon. β-Elimination of the borylalkylcopper(I) intermediate **II** affords the desired product (*Z*)-**3**, along with generation of LCuBr. The other conformational isomer of the intermediate **III**, which can afford (*E*)-**3**, should be less energetically favourable than **II** because of the steric repulsion between the alkyl group and bulky B(pin). This can explain the exclusive formation of the (*Z*)-isomer of **3**. Finally, LCuBr further reacts with bis(pinacolato)diboron and NaOMe to regenerate the active species LCu–B(pin) and complete the catalytic cycle.



Scheme 3-3. Plausible mechanism for the copper(I)-catalyzed stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes with bis(pinacolato)diboron

Summary

In conclusion, the author has developed a new and efficient method to synthesise (*Z*)-1-bromo-1-alkenylboronate esters *via* copper(I)-catalyzed stereoselective debromoborylation of aliphatic 1,1-dibromo-1-alkenes with bis(pinacolato)diboron in the presence of NaOMe and Xantphos at 30 °C. The borylation reaction exhibits a wide substrate scope, good functional group compatibility and affords a variety of (*Z*)-brominated borylation products in moderate to good yields. At the same time, this study is the first example of the selective debromoborylation of 1,1-dibromo-1-alkenes, which is expected to become a powerful synthetic approach to construct a broad range of intermediates and materials.

Experimental Section

Instrumentation and Chemicals.

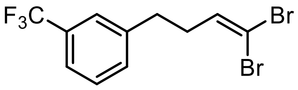
Materials were obtained from commercial suppliers and purified by standards procedures unless otherwise noted. Solvents (Tetrahydrofuran, dehydrated –super–, 41001-05, Kanto Chemical Co., Inc.) for reactions were purchased from commercial suppliers, degassed via three freeze-pump-thaw cycles, and further dried over molecular sieves (MS 4Å). NMR spectra were recorded on JEOL JNM-ECX400P and JNM-ECS400 spectrometers (^{1}H: 392 or 396 MHz, ^{13}C: 99 MHz and ^{11}B: 127 MHz). Tetramethylsilane (^{1}H) $CDCl_3$ (^{13}C) and $BF3{\cdot}OEt_2$ (^{11}B) were employed as external standards, respectively. Multiplicity was recorded as follows: s = singlet, brs = broad singlet, d = doublet, t= triplet, q= quartet, m = multiplet. CuCl (ReagentPlus® grade, 224332-25G, ≥99%) was purchased from Sigma-Aldrich Co., and used as received. Mesitylene was used as an internal standard to determine NMR yields. GLC analyses were conducted with a Shimadzu GC-2014 or GC-2025 equipped with ULBON HR-1 glass capillary column (Shinwa Chemical Industries) and an FID detector. High-resolution mass spectra were recorded at the Global Facility Center, Hokkaido University.

Substrate Preparations

All 1,1-dibromo-1-alkenes were synthesized from corresponding aldehydes through Wittig reaction by using PPh_3 and CBr_4. If aldehydes were not commercially available materials, the aldehydes were synthesized from the corresponding alcohols by Swern oxidation. The synthesized 1,1-dibromo-1-alkenes were subjected to purification by Kugelrohr distillation prior to use. The 1,1-dibromo-1-alkenes (**1c**, **1d**, **1k**, **1l**) were unknown compounds and the other 1,1-dibromo-1-alkenes (**1a**, **1b**, **1e**, **1f**, **1g**, **1h**, **1i**, **1j**, **1m**, **1n**) were known compounds.

Characterizations of 1,1-Dibromo-1-Alkenes Substrates

1-(4,4-Dibromobut-3-en-1-yl)-3-(trifluoromethyl)benzene (1c).

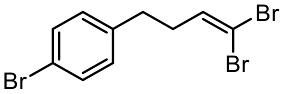


1c

The product **1c** was obtained from corresponding alcohol in 98% yield (two steps, 1.72 g, 4.8 mmol) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 2.43 (dd, *J* = 15.1, 7.6 Hz, 2H), 2.79 (t, *J* = 7.6 Hz, 2H), 6.40 (t, *J* = 7.4 Hz, 1H), 7.34–7.51 (m, 4H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 33.6 (CH_2), 34.3 (CH_2), 90.2 (*C*), 123.2 (d, J_{C-F} = 3.8 Hz, *C*H), 124.2 (d, J_{C-F} = 272.8 Hz, *C*), 125.1 (d, J_{C-F} = 3.8 Hz, *C*H), 129.0 (*C*H), 130.8 (q, J_{C-F} = 32.4 Hz, *C*), 131.8 (*C*H), 136.8 (*C*H), 141.3 (*C*). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{11}H_9Br_2F_3$, 355.90231; found, 355.90137.

1-Bromo-4-(4,4-dibromobut-3-en-1-yl)benzene (1d).

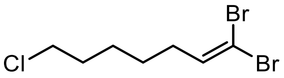


1d

The product **1d** was obtained from corresponding alcohol in 99% yield (two steps, 3.42 g, 9.3 mmol) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 2.39 (q, *J* = 7.7 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 6.38 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 2H), 7.38–7.47 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 33.2 (CH_2), 34.4 (CH_2), 89.9 (*C*), 120.0 (*C*), 130.1 (*C*H), 131.6 (*C*H), 137.1 (*C*H), 139.4 (*C*). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{10}H_9Br_3$, 365.82544; found, 365.82554.

1,1-Dibromo-7-chlorohept-1-ene (1k).

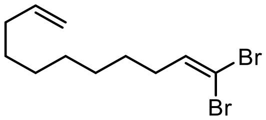


1k

The product **1k** was obtained from corresponding alcohol in 65% yield (two steps, 2.35 g, 8.1 mmol) as a colorless oil.

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.41–1.53 (m, 4H), 1.74–1.84 (m, 2H), 2.07–2.17 (m, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 6.39 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 26.3 (CH_2), 27.1 (CH_2), 32.3 (CH_2), 32.8 (CH_2), 44.8 (CH_2), 89.0 (*C*), 138.3 (*C*H). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_7H_{11}Br_2Cl$, 287.89160; found, 287.89205.

1,1-Dibromoundeca-1,10-diene (1l).



1l

The product **1l** was obtained from corresponding alcohol in 85% yield (two steps, 2.86 g, 9.2 mmol) as a colorless oil.

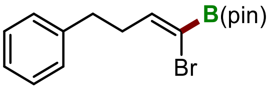
^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.25–1.46 (m, 10H), 2.00–2.13 (m, 4H), 4.93 (ddt, *J* = 9.8, 2.4, 0.8 Hz, 1H), 5.00 (dq, *J* = 17.6, 2.0 Hz, 1H), 5.81 (ddt, *J* = 16.9, 13.3, 6.7 Hz, 1H), 6.38 (t, *J* = 7.3 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 27.8 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 33.0 (CH_2), 33.8 (CH_2), 88.4 (C), 114.2 (CH_2), 138.9 (CH), 139.1 (CH). HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{11}H_{18}Br_2$, 307.97753; found, 307.97750.

General Debromoborylation Procedures.

Copper chloride (1.3 mg, 0.013 mmol), Xantphos (7.3 mg, 0.013 mmol), bis(pinacolato)diboron (76.2 mg, 0.30 mmol) were placed in an oven-dried reaction vial. And then, the vial was transferred to the glove box and NaOMe (27.0 mg, 0.50 mmol) was added to the vial under argon atmosphere. After the vial was sealed with a screw cap containing a Teflon-coated rubber septum, the vial was removed from the glove box and connected to a vacuum/nitrogen manifold through a needle. After dry THF (1 mL) was added to the reaction mixture, **1a** (69.1 mg, 0.24 mmol) was added dropwise to the reaction mixture at 30°C. After the reaction was complete, the mixture was passed through a short silica gel column eluting with Et_2O. The crude material was purified by flash chromatography (SiO_2, hexane/ethyl acetate, 20:1) to give the corresponding debromoborylation product (*Z*)-**3a** (46.1 mg, 0.14 mmol, 55%) as a slightly yellow oil.

Characterizations of Debromoborylation Products.

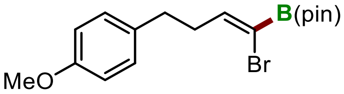
(*Z*)-2-(1-Bromo-4-phenylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3a].



(*Z*)-**3a**

The reaction was conducted with 69.1 mg (0.24 mmol) of **1a**. The product (*Z*)**-3a** was obtained in 55% yield (46.1 mg, 0.14 mmol) as a slightly yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 20:1). ^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.30 (s, 12H), 2.58–2.66 (m, 2H), 2.77 (t, J = 7.8 Hz, 2H), 6.91 (t, J = 6.7 Hz, 1H), 7.17–7.24 (m, 3H), 7.27–7.33 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.6 (CH_3), 33.7 (CH_2), 34.0 (CH_2), 84.6 (*C*), 126.0 (*C*H), 128.2 (*C*H), 128.3 (*C*H), 141.0 (*C*), 148.0 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{22}BBrO_2$, 335.09325; found, 335.09292.

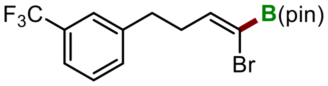
(*Z*)-2-[1-Bromo-4-(4-methoxyphenyl)but-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3b].



(*Z*)-**3b**

The reaction was conducted with 80.0 mg (0.25 mmol) of **1b**. The product (*Z*)**-3b** was obtained in 52% yield (47.2 mg, 0.13 mmol) as a colorless oil by flash chromatography (SiO_2, hexane/ethyl acetate, 20:1). ^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.29 (s, 12H), 2.54–2.63 (m, 2H), 2.71 (dd, J = 9.4, 6.3 Hz, 2H), 3.79 (s, 3H), 6.84 (dd, J = 6.7, 2.0 Hz, 2H), 6.90 (t, J = 6.5 Hz, 1H), 7.13 (dt, J = 9.3, 2.6 Hz, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (CH_3), 32.8 (CH_2), 34.4 (CH_2), 55.2 (CH_3), 84.6 (*C*), 113.8 (*C*H), 129.2 (*C*H), 133.2 (*C*), 148.2 (*C*H), 157.9 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 27.9. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{24}BBrO_3$, 365.10382; found, 365.10351.

(*Z*)-2-{1-Bromo-4-[3-(trifluoromethyl)phenyl]but-1-en-1-yl}-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3c].

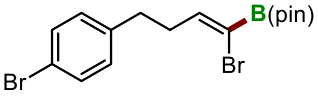


(*Z*)-**3c**

The reaction was conducted with 85.0 mg (0.24 mmol) of **1c**. The product (*Z*)-**3c** was obtained in 58% yield (55.3 mg, 0.14 mmol) as a colorless oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.30 (s, 12H), 2.59–2.67 (m, 2H), 2.83 (dd, *J* = 9.0, 6.7 Hz, 2H), 6.87 (t, *J* = 6.7 Hz, 1H), 7.38–7.49 (m, 4H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.6 (*C*H_3), 33.5 (*C*H_2), 33.7 (*C*H_2), 84.8 (*C*), 123.0 (d, $J_{C–F}$ = 3.8 Hz, *C*H), 124.2 (d, $J_{C–F}$ = 273.8 Hz, *C*), 125.1 (d, $J_{C–F}$ = 3.8 Hz, *C*H), 128.8 (*C*H), 130.6 (d, $J_{C–F}$ = 32.1 Hz, *C*), 131.7 (*C*H), 141.9 (*C*), 147.1 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{17}H_{21}BBrF_3O_2$, 403.08064; found, 403.07908.

(*Z*)-2-[1-Bromo-4-(4-bromophenyl)but-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3d].

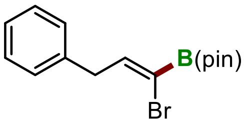


(*Z*)-**3d**

The reaction was conducted with 88.5 mg (0.24 mmol) of **1d**. The product (*Z*)-**3d** was obtained in 62% yield (61.3 mg, 0.15 mmol) as a white solid (m.p. = 64–65°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 20:1).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.30 (s, 12H), 2.55–2.63 (m, 2H), 2.68–2.76 (m, 2H), 6.86 (t, *J* = 6.9 Hz, 1H), 7.09 (d, *J* = 8.2 Hz, 2H), 7.38–7.43 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (*C*H_3), 33.1 (*C*H_2), 33.8 (*C*H_2), 84.8 (*C*), 119.8 (*C*), 130.1 (*C*H), 131.4 (*C*H), 140.0 (*C*), 147.5 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 27.9. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{16}H_{21}BBr_2O_2$, 413.00377; found, 413.00367.

(*Z*)-2-(1-Bromo-3-phenylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3e].

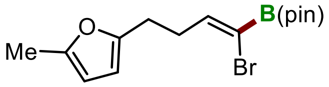


(*Z*)-**3e**

The reaction was conducted with 70.5 mg (0.26 mmol) of **1e**. The product (*Z*)-**3e** was obtained in 55% yield (44.6 mg, 0.14 mmol) as a yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1).

^{1}H NMR (396 MHz, $CDCl_3$, δ): 1.29 (s, 12H), 3.66 (d, *J* = 6.7 Hz, 2H), 6.99 (t, *J* = 6.9 Hz, 1H), 7.20–7.25 (m, 3H), 7.27–7.33 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.6 (*C*H_3), 38.7 (*C*H_2), 84.7 (*C*), 126.4 (*C*H), 128.5 (*C*H), 128.6 (*C*H), 138.2 (*C*), 147.3 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.1. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{15}H_{20}BBrO_2$, 321.07760; found, 321.07687.

(*Z*)-2-[1-Bromo-4-(5-methylfuran-2-yl)but-1-en-1-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3f].

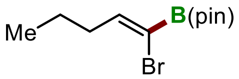


(*Z*)-**3f**

The reaction was conducted with 75.8 mg (0.26 mmol) of **1f**. The product (*Z*)-**3f** was obtained in 62% yield (55.0 mg, 0.16 mmol) as a slightly yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1).

^{1}H NMR (396 MHz, $CDCl_3$, δ): 1.30 (s, 12H), 2.25 (s, 3H), 2.59–2.66 (m, 2H), 2.74 (t, *J* = 7.6 Hz, 2H), 5.85 (dd, *J* = 2.9, 1.0 Hz, 1H), 5.90 (d, *J* = 2.7 Hz, 1H), 6.88 (t, *J* = 6.3 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 13.5 (*C*H_3), 24.7 (*C*H_3), 26.1 (*C*H_2), 30.9 (*C*H_2), 84.7 (*C*), 105.7 (*C*H), 105.8 (*C*H), 147.8 (*C*H), 150.5 (*C*), 152.9 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 27.9. HRMS-EI (*m*/*z*): [M]$^+$ calcd for $C_{15}H_{22}BBrO_3$, 339.08817; found, 339.08676.

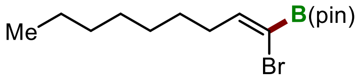
(*Z*)-2-(1-Bromopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3g].



(*Z*)-**3g**

The reaction was conducted with 56.6 mg (0.25 mmol) of **1g**. The product (*Z*)-**3g** was obtained in 59% yield (40.0 mg, 0.15 mmol) as a slightly yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1). ^1H NMR (392 MHz, $CDCl_3$, δ): 0.96 (t, *J* = 7.4 Hz, 3H), 1.30 (s, 12H), 1.49 (sxt, *J* = 7.4 Hz, 2H), 2.28 (dd, *J* = 14.5, 7.4 Hz, 2H), 6.85 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 13.9 (CH_3), 21.0 (CH_2), 24.7 (CH_3), 34.4 (CH_2), 84.6 (*C*), 149.3 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{20}BBrO_2$, 273.07760; found, 273.07773.

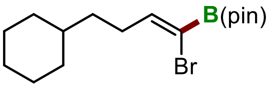
(*Z*)-2-(1-Bromonon-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3h].



(*Z*)-**3h**

The reaction was conducted with 68.5 mg (0.24 mmol) of **1h**. The product (*Z*)-**3h** was obtained in 62% yield (49.1 mg, 0.15 mmol) as a slightly yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1). ^1H NMR (392 MHz, $CDCl_3$, δ): 0.88 (t, *J* = 6.9 Hz, 3H), 1.24–1.35 (m, 20H), 1.40–1.50 (m, 2H), 2.30 (q, *J* = 7.1 Hz, 2H), 6.84 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 14.0 (CH_3), 22.6 (CH_2), 24.7 (CH_3), 27.7 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 31.7 (CH_2), 32.4 (CH_2), 84.5 (*C*), 149.5 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{28}BBrO_2$, 329.14020; found, 329.14013.

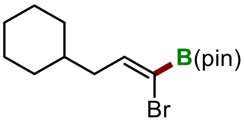
(*Z*)-2-(1-Bromo-4-cyclohexylbut-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3i].



(*Z*)-**3i**

The reaction was conducted with 75.5 mg (0.26 mmol) of **1i**. The product (*Z*)-**3i** was obtained in 57% yield (49.6 mg, 0.14 mmol) as a slightly yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1). ^1H NMR (392 MHz, $CDCl_3$, δ): 0.82–0.95 (m, 2H), 1.17–1.37 (m, 18H), 1.60–1.78 (m, 5H), 2.30 (dd, *J* = 15.9, 6.9 Hz, 2H), 6.83 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (CH_3), 26.2 (CH_2), 26.6 (CH_2), 29.9 (CH_2), 33.1 (CH_2), 35.2 (CH_2), 37.2 (*C*H), 84.6 (*C*), 149.8 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{16}H_{28}BBrO_2$, 341.14020; found, 341.14006.

(*Z*)-2-(1-Bromo-3-cyclohexylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3j].

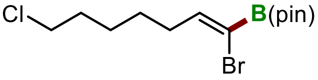


(*Z*)-**3j**

The reaction was conducted with 69.5 mg (0.25 mmol) of **1j**. The product (*Z*)-**3j** was obtained in 58% yield (46.6 mg, 0.14 mmol) as a pink oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1).

^1H NMR (392 MHz, $CDCl_3$, δ): 0.92–1.04 (m, 2H), 1.12–1.25 (m, 3H), 1.30 (s, 12H), 1.40–1.52 (m, 1H), 1.58–1.78 (m, 5H), 2.20 (t, *J* = 7.1 Hz, 2H), 6.86 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 33.1 (CH_2), 37.1 (CH), 40.0 (CH_2), 84.6 (C), 148.3 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{15}H_{26}BBrO_2$, 327.12455; found, 327.12477.

(*Z*)-2-(1-Bromo-7-chlorohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3k].

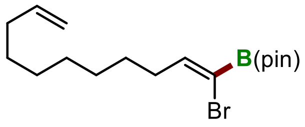


(*Z*)-**3k**

The reaction was conducted with 70.0 mg (0.24 mmol) of **1k**. The product (*Z*)-**3k** was obtained in 57% yield (46.4 mg, 0.14 mmol) as a slightly yellow oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1).

^1H NMR (396 MHz, $CDCl_3$, δ): 1.30 (s, 12H), 1.45–1.52 (m, 4H), 1.75–1.85 (m, 2H), 2.29–2.36 (m, 2H), 3.54 (t, *J* = 6.7 Hz, 2H), 6.83 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (CH_3), 26.5 (CH_2), 26.9 (CH_2), 32.1 (CH_2), 32.3 (CH_2), 44.9 (CH_2), 84.6 (C), 148.7 (CH). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{13}H_{23}BBrClO_2$, 335.06993; found, 335.07008.

(*Z*)-2-(1-Bromoundeca-1,10-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [(*Z*)-3l].

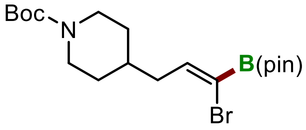


(*Z*)-**3l**

The reaction was conducted with 79.8 mg (0.26 mmol) of **1l**. The product (*Z*)-**3l** was obtained in 54% yield (49.1 mg, 0.14 mmol) as a salmon pink oil by flash chromatography (SiO_2, hexane/ethyl acetate, 25:1).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.28–1.49 (m, 22H), 2.04 (dd, *J* = 13.7, 7.1 Hz, 2H), 2.30 (q, *J* = 7.2 Hz, 2H), 4.91–4.96 (m, 1H), 4.96–5.03 (m, 1H), 5.81 (ddt, *J* = 17.2, 13.7, 6.7 Hz, 1H), 6.84 (t, *J* = 6.7 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.7 (CH_3), 27.7 (CH_2), 28.8 (CH_2), 29.0 (CH_2), 29.2 (CH_2), 32.4 (CH_2), 33.8 (CH_2), 84.6 (*C*), 114.1 (CH_2), 139.1 (*C*H), 149.5 (*C*H). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{17}H_{30}BBrO_2$, 355.15585; found, 355.15485.

Tert-butyl-(*Z*)-4-[3-bromo-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)allyl]piperidine-1-carboxylate [(*Z*)-3m].

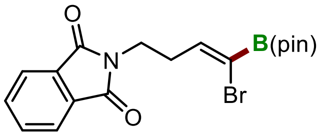


(*Z*)-**3m**

The reaction was conducted with 95.0 mg (0.25 mmol) of **1m**. The product (*Z*)-**3m** was obtained in 51% yield (54.0 mg, 0.13 mmol) as a white solid (m.p. = 82–83°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 10:1).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.12–1.25 (m, 2H), 1.30 (s, 12H), 1.45 (s, 9H), 1.56–1.73 (m, 3H), 2.28 (t, *J* = 6.9 Hz, 2H), 2.58–2.78 (m, 2H), 4.08 (brs, 2H), 6.85 (t, *J* = 6.9 Hz, 1H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.6 (CH_3), 28.4 (CH_3), 31.8 (CH_2), 35.3 (*C*H), 38.9 (CH_2), 43.4 (CH_2), 44.1 (CH_2), 79.2 (*C*), 84.6 (*C*), 146.7 (*C*H), 154.7 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 28.0. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{19}H_{33}BBrNO_4$, 428.17223; found, 427.17182.

(*Z*)-2-[4-Bromo-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-en-1-yl]isoindoline-1,3-dione [(*Z*)-3n].



(*Z*)-**3n**

The reaction was conducted with 92.0 mg (0.26 mmol) of **1n**. The product (*Z*)-**3n** was obtained in 50% yield (51.1 mg, 0.13 mmol) as a white solid (m.p. = 126–127°C) by flash chromatography (SiO_2, hexane/ethyl acetate, 10:1).

^{1}H NMR (392 MHz, $CDCl_3$, δ): 1.29 (s, 12H), 2.71 (dd, *J* = 14.3, 7.3 Hz, 2H), 3.84 (t, *J* = 7.1 Hz, 2H), 6.88 (t, *J* = 6.7 Hz, 1H), 7.69–7.75 (m, 2H), 7.81–7.88 (m, 2H). ^{13}C NMR (99 MHz, $CDCl_3$, δ): 24.6 (CH_3), 31.6 (CH_2), 35.7 (CH_2), 84.7 (*C*), 123.2 (*C*H), 132.0 (*C*), 133.9 (*C*H), 144.2 (*C*H), 168.1 (*C*). The carbon directly attached to the boron atom was not detected, likely due to quadrupolar relaxation.[4,5] ^{11}B NMR (127 MHz, $CDCl_3$, δ): 27.9. HRMS-EI (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{21}BBrNO_4$, 404.07833; found, 404.07791.

Information on Single Crystal X-ray Diffraction Analysis

CCDC 1835168 contains the supplementary crystallographic data for compound (*Z*)-**3n**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References

1. a) *Boronic Acids: Preparation and Applications in Organic Synthesis, Medicine and Materials*, ed. D. G. Hall, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, 2011; b) N. Miyaura, A. Suzuki, *Chem. Rev.* **1995**, *95*, 2457; c) S. Hara, H. Shudoh, S. Ishiyama, A. Suzuki, *Bull. Chem. Soc. Jpn.* **1998**, *71*, 2403; d) P. Y. S. Lam, C. G. Clark, S. Saubern, J. Adams, M. P. Winters, D. M. T. Chan, A. Combs, *Tetrahedron Lett.* **1998**, *39*, 2941; e) G. K. S. Prakash, C. Panja, T. Mathew, V. Surampudi, N. A. Petasis, G. A. Olah, *Org. Lett.* **2004**, *6*, 2205; f) R. H. Volante, *J. Org. Chem.* **2004**, *69*, 566; g) V. Rauniyar, D. G. Hall, *J. Am. Chem. Soc.* **2004**, *126*, 4518; h) J. Yun, Asian *J. Org. Chem.* **2013**, *2*, 1016; i) K. Semba, T. Fujihara, J. Terao, Y. Tsuji, *Tetrahedron* **2015**, *71*, 2183, j) E. Yamamoto, S. Ukigai, H. Ito, *Chem. Sci.* **2015**, *6*, 2943; k) J. Schmidt, J. Choi, A. T. Liu, M. Slusarczyk, G. C. Fu, *Science* **2016**, *354*, 1265; l) A. B. Cuenca, R. Shishido, H. Ito, E. Fernández, *Chem. Soc. Rev.* **2017**, *46*, 415.
2. S. Xu, C. Lee, H. Rao, E. Negeshi, *Adv. Synth. Catal.* **2011**, *353*, 2981.
3. H. C. Brown, T. Imai, *Organometallics* **1984**, *3*, 1392.
4. H. C. Brown, T. Imai, N. G. Bhat, *J. Org. Chem.* **1986**, *51*, 5277.
5. H. C. Brown, R. Soundararajan, *Tetrahedron Lett.* **1994**, *35*, 6963.
6. N. G. Bhat, C. Martinez, J. De Los Santos, *Tetrahedron Lett.* **2000**, *41*, 6541.
7. N. G. Bhat, N. Varghese, *Synlett* **2007**, 2023.
8. F. Ramirez, N. B. Desai, N. McKelvie, *J. Am. Chem. Soc.* **1962**, *84*, 1745.
9. J. Takagi, K. Takahashi, T. Ishiyama, N. Miyaura, *J. Am. Chem. Soc.* **2002**, *124*, 8001.
10. J. Zhang, W. Dai, Q. Liu, S. Cao, *Org. Lett.* **2017**, *19*, 3283.
11. H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi, T. Hosoya, *J. Am. Chem. Soc.* **2017**, *139*, 12855.
12. D. Tan, E. Lin, W. Ji, Y. Zeng, W. Fan, Q. Li, H. Gao, H. Wang, *Adv. Synth. Catal.* **2018**, *360*, 1032.
13. R. Kojima, K. Kubota, H. Ito, *Chem. Commun.* **2017**, *53*, 10688.
14. J. Hu, X. Han, Y. Yuan, Z. Shi, *Angew. Chem. Int. Ed.* **2017**, *56*, 13342.
15. a) H. Ito, C. Kawakami, M. Sawamura, *J. Am. Chem. Soc.* **2005**, *127*, 16034; b) J. Lee, J. Kwon, J. Yun, *Chem. Commun.* **2008**, 733; c) K. B. Smith, K. M. Logan, W. You, M. K. Brown, *Chem. Eur. J.* **2014**, *20*, 12032; d) Z. Xu, Y. Jiang, W. Su, H. Yu, Y. Fu, *Chem. Eur. J.* **2016**, *22*, 14611.

List of Publications.

Chapter 1

Iridium(I)-Catalyzed C–H Borylation in Air by Using Mechanochemistry
Y. Pang, T. Ishiyama, K. Kubota, H. Ito
Chem. Eur. J. **2019**, *25*, 4654–4659.

Chapter 2

Redox Reactions of Small Organic Molecules Using Ball Milling and Piezoelectric Materials
K. Kubota, Y. Pang, A. Miura, H. Ito
Science **2019**, *366*, 1500–1504.

Chapter 3

Copper(I)-Catalysed Stereoselective Debromoborylation of Aliphatic 1,1-Dibromo-1-alkenes with Bis(pinacolato)diboron
Y. Pang, R. Kojima, H. Ito
Org. Biomol. Chem. **2018**, *16*, 6187–6190.

Other Publications.

1. Fe(III)-Catalyzed Trityl Benzyl Ether Formation and Disproportionation Cascade Reactions to Yield Benzaldehydes.
   X. Wang, C. Du, H. Shi, Y. Pang, S. Jin, Y. Hou, Y. Wang, X. Peng, J. Xiao, Y. Liu, Y. Liu, M. Cheng
   Tetrahedron **2015**, *71*, 6744–6748.
2. Investigation of Meyer-Schuster Rearrangement Promoted by a Samarium(III) Triflate/*N*-Fluorobenzenesulfonimide Lewis Acid System.
   C. Du, X. Wang, S. Jin, H. Shi, Y. Li, Y. Pang, Y. Liu, M. Cheng, C. Guo, Y. Liu
   Asian J. Org. Chem. **2016**, *5*, 755–762.
3. Lewis Acid-Assisted *N*-Fluorobenzenesulfonimide-Based Electrophilic Fluorine Catalysis in Beckmann Rearrangement.
   F. Xie, C. Du, Y. Pang, X. Lian, C. Xue, Y. Chen, X. Wang, M. Cheng, C. Guo, B. Lin, Y. Liu
   Tetrahedron Lett. **2016**, *57*, 5820–5824.
4. Access to Benzo[*a*]carbazoles and Indeno[1,2-*c*]quinolines by a Gold(I)-Catalyzed Tunable Domino Cyclization of Difunctional 1,2-Diphenylethynes.
   X. Peng, L. Zhu, Y. Hou, Y. Pang, Y. Li, J. Fu, L. Yang, B. Lin, Y. Liu, M. Cheng
   Org. Lett. **2017**, *19*, 3402–3405.
5. *N*-Fluorobenzenesulfonimide as a highly effective Ag(I)-Catalyst Attenuator for Tryptamine-Derived Ynesulfonamide Cycloisomerization.
   Y. Pang, G. Liang, F. Xie, H. Hu, C. Du, X. Zhang, M. Cheng, B. Lin, Y. Liu
   Org. Biomol. Chem. **2019**, *17*, 2247–2257.

Acknowledgements

The studies presented in this thesis have been carried out under the direction of Professor Doctor Hajime Ito at the Faculty of Engineering of Hokkaido University during 2017–2020. The studies are concerned with the development of new organic transformations using mechanochemistry.

At first and foremost the author would like to express his deepest gratitude to Prof. Hajime Ito and Prof. Koji Kubota, whose constant guidance, enormous supports, and sharp insight throughout this study. The author particularly indebted to Prof. Tatsuo Ishiyama for his helpful advice and stimulating discussions during this study. The author would like to thank Prof. Akira Miura for the gift of $BaTiO_3$ and helpful advice. The author would also like to thank Prof. Tomohiro Seki and Takaki Mashimo for their help analyzing the X-ray crystallography data. The author is grateful to thank other members of the Prof. Ito's research group for their good collaboration and for providing a good working atmosphere. In addition, the author would also like to thank the Otsuka Toshimi Scholarship Foundation for a scholarship.

Yadong Pang

Graduate school of chemical sciences and engineering
Hokkaido University
2020