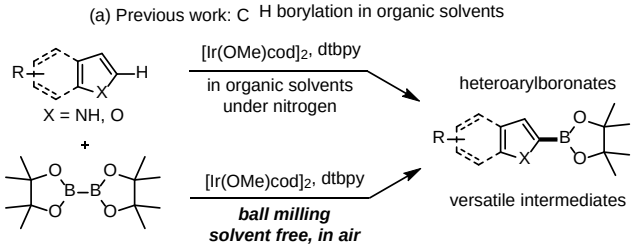
Iridium(I)-Catalyzed C–H Borylation in Air Using Mechanochemistry

Yadong Pang,[a] Tatsuo Ishiyama,[a] Koji Kubota,*[a] and Hajime Ito*[a,b]

Abstract: Mechanochemistry has been applied for the first time to an iridium(I)-catalyzed C–H borylation reaction. Using either none or just a catalytic amount of a liquid, the mechanochemical C–H borylation of a series of heteroaromatic compounds proceeded in air to afford the corresponding arylboronates in good to excellent yield. A one-pot mechanochemical C–H borylation/Suzuki–Miyaura cross-coupling sequence for the direct synthesis of 2-aryl indole derivatives is also described. The present study constitutes an important milestone toward the development of industrially attractive solvent-free C–H bond functionalization processes in air.

Organoboronic acids and their derivatives, especially arylboronate esters, are powerful and versatile reagents in synthetic chemistry, medicine, and materials science owing to their high stability, low toxicity, and synthetic utility in various transformations such as the Suzuki–Miyaura cross-coupling reaction.[1] C–H borylation reactions have become an especially important synthetic method since they provide straightforward access to 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, which is widely used in the synthesis of complex molecules (Scheme 1a).[2c,3] However, despite the significant progress, the exploration of new concepts and reaction media to improve the sustainability of such C–H borylation transformations remains crucial.[2c,3] In this context, the use of significant amounts of dry and degassed organic solvents and the need to operate under an atmosphere of inert gas are still important limiting factors.

In recent years, significant progress has been made concerning organic transformations that are carried out under mechanochemical conditions.[4,5] Compared to traditional solvent-based protocols, the advantages of conducting chemical transformations using mechanochemistry include the avoidance of harmful organic solvents, shorter reaction times, 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, 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. However, to the best of our 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. Herein, we report the first mechanochemical method for an iridium(I)-catalyzed C–H borylation using a diboron reagent (Scheme 1b). This reaction was applied to a variety of heteroaromatic compounds, furnishing the corresponding arylboronates in good to high yield 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.



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

Initially, we applied reaction conditions analogous to those used by Hartwig and Miyaura[8] for a solution process in the mechanochemical C–H borylation of indole **1a** with bis(pinacolato)diboron **2** in the presence of $[Ir(OMe)cod]_2$ and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) (Table 1). The reaction was 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 1.5 mL milling jar using a 3.0 mm ball was unsuccessful, and the desired product (**3a**) was not detected (entry 1). We found that a careful choice of the jar and ball dramatically improved the efficiency of the mechanochemical C–H borylation (entries 2–5). When using a 5.0 mL milling jar and a 7.5 mm ball, **3a** was obtained in 74% yield upon grinding for 99 min (entry 2). Upon increasing the loading of **2** from 0.5 mmol to 0.6 mmol, the yield of **3a** improved further (84%; entry 6), and is comparable to the yield obtained by the reported solvent-based protocol.[8] In conventional C–H borylation reactions in solution, one or two of the boryl groups in the diboron reagent **2** may be introduced into the substrates, depending on the conditions applied.[2,8] Interestingly, we found that both boryl groups in **2** were introduced into **1a** under the applied mechanochemical conditions. Next, we investigated other transition-metal complexes containing nickel and iron, which are effective catalysts for aromatic C–H borylation reactions in

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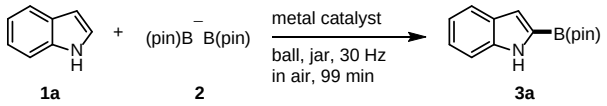
solution (entries 7 and 8).[9] However, no reaction was observed under the applied mechanochemical conditions.

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

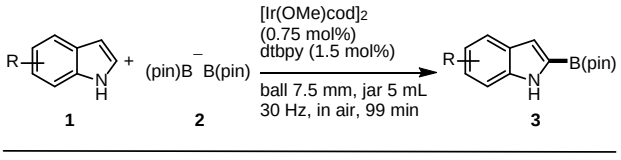


1a **2** **3a**

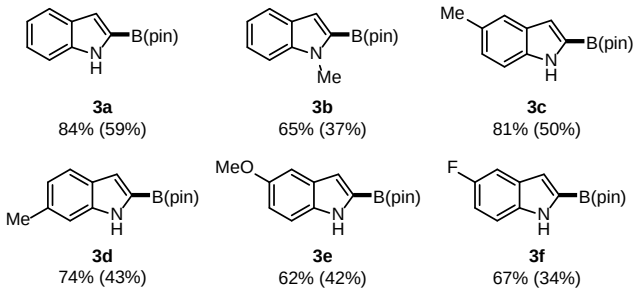
Entry	Catalyst	Ball (diameter, mm)	Milling jar (mL)	NMR yield (%)[b]
1	[Ir(OMe)cod]$_2$/dtbpy	3.0	1.5	0
2	[Ir(OMe)cod]$_2$/dtbpy	7.5	5.0	74
3	[Ir(OMe)cod]$_2$/dtbpy	7.5	25.0	0
4	[Ir(OMe)cod]$_2$/dtbpy	15.0	25.0	0
5	[Ir(OMe)cod]$_2$/dtbpy	3.0	5.0	68
6[c]	[Ir(OMe)cod]$_2$/dtbpy	7.5	5.0	84
7[d]	Ni(OAc)$_2$/ICy·HCl	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 are made of stainless steel. [b] Yields are based on the amount of **1a** and determined by ^{1}H 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.

Table 2. Substrate scope of the mechanochemical C–H borylation of indoles[a]



1 **2** **3**



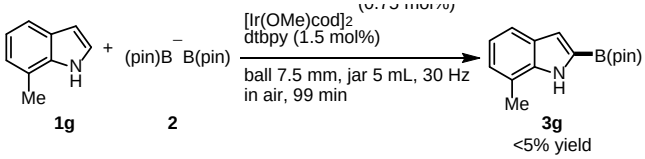
3a 84% (59%) **3b** 65% (37%) **3c** 81% (50%)

3d 74% (43%) **3e** 62% (42%) **3f** 67% (34%)

[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.

With the optimal reaction conditions in hand (Table 1, entry 6), a series of substituted indole substrates was tested in order to investigate the scope of the present mechanochemical iridium(I)-catalyzed C–H borylation in a ball mill (Table 2). The C–H borylation reactions proceeded efficiently to furnish the corresponding C2-borylated indoles in moderate to good yield. We found that the purification of the boronate esters without yield losses was difficult using conventional chromatography techniques, as these boronate esters are easily hydrolyzed and protonated on silica gel; thus, the isolated yields are generally lower than the corresponding NMR yields. Methyl-protected indole **1b** also reacted with **2** to afford borylation product **3b** in good yield (65% NMR yield; 37% isolated yield). The reaction of indoles bearing a methyl group at the 5- or 6-position (**1c** and **1d**) furnished the corresponding products (**3c** and **3d**) in good to excellent yield (81% and 74% NMR yield, respectively). In addition, methoxy (**1e**) and fluorine (**1f**) substituents did not hamper the mechanochemical C–H borylation, providing the corresponding products (**3e** and **3f**) in 62% and 67% NMR yield, respectively.

Unfortunately, no mechanochemical C–H borylation occurred when 7-methyl-substituted indole **1g** was used as the substrate (Scheme 2). We speculated that one possible reason behind the observed reactivity difference could be rheological changes in the reaction mixture upon mechanical grinding.[10] In the case of **1a**, the reaction mixture dramatically changes from a solid mixture to a viscous oil (Figure 1a, 1b, and S1). This drastic change in rheology could improve the mixing efficiency of the reactants and catalyst, thus facilitating the C–H borylation.[10] In contrast, the reaction mixture in the case of **1g**, which has a higher melting point (80 °C) than **1a** (55 °C), remained a heterogeneous solid mixture, even after grinding for 99 min (Figure 1c and 1d). These results suggest that the low yield of **3g** is likely due to poor mixing of the solid-state reaction mixture in the ball mill.



1g **2** **3g** <5% yield

Scheme 2. Mechanochemical C–H borylation of 7-methyl-substituted indole **1g**.

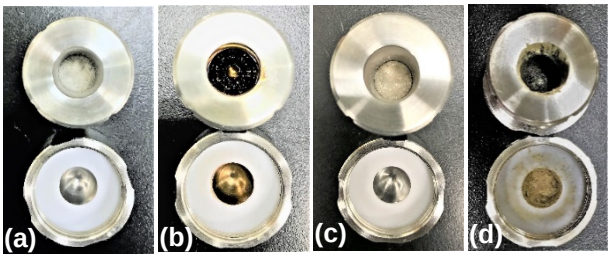
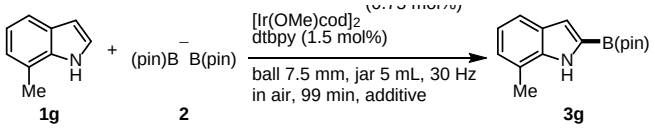


Figure 1. Reaction mixtures after grinding in a ball mill. Reaction mixture containing indole **1a** (a) before and (b) after grinding for 99 min, and that of 7-methyl indole **1g** (c) before and (d) after grinding for 99 min.

Therefore, we then attempted grinding in the presence of abrasive, inert, solid mechanochemical additives such as lubricants and inorganic salts in order to enhance the mixing efficiency (Table 3). First, we used common solid lubricants such as MoS_2, graphite, or polytetrafluoroethylene (PTFE) in the mechanochemical C–H borylation of **1g**. However, the desired product (**3g**) was not detected under these reaction conditions (entries 1–3). Reactions in the presence of inert solid auxiliaries (entries 4–5) or inorganic salts (entries 6–7) were also investigated, albeit that we did not observe any product formation. Next, we attempted liquid-assisted-grinding (LAG), which uses substoichiometric liquid additives, to improve the reactivity (entries 8–10).[11] These LAG reactions involved 0.25 μL of liquid per mg of reactants. Initially, hexane was tested since it is frequently employed in solvent-based iridium(I)-catalyzed C–H borylation reactions. Unfortunately, this reaction did not furnish **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 **3g** in high yield (87% yield; entry 10). We noted that the reaction mixture containing THF as the LAG additive changed from a solid-state mixture to a viscous oil.

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



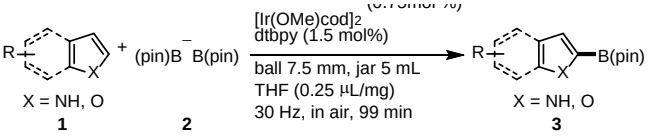
1g **2** **3g**

Entry	Additive	NMR yield (%)[b]
1	MoS_2 (80 mg)	0
2	Graphite (50 mg)	0
3	PTFE (50 mg)	0
4	4Å 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. [b] Yields are based on the amount of **1g** and were determined by ^{1}H NMR spectroscopy.

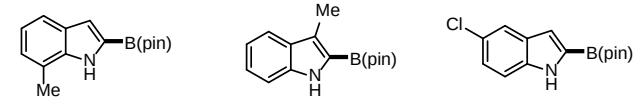
With the modified conditions in hand, a series of substituted indoles with relatively high melting points (>70 °C) were tested to investigate the scope of this mechanochemical iridium(I)-catalyzed C–H borylation enabled by LAG (Table 4a). Substrates bearing a methyl group at different positions on the aryl ring (**1g** and **1h**) efficiently reacted with **2** to provide the desired borylation products (**3g** and **3h**) in moderate to high yield (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 good yield (61–72%). When *N*-tosyl-protected indole **1l** was used as the substrate, the borylation selectively occurred at the 3-position of the indole to give **3l** as a result of the steric control of the bulky tosyl group.[12] It should be noted here that the substrates in Table 4a did not react in the absence of the LAG additive THF. Subsequently, we turned our attention to the scope of the heteroaryl substrates (Table 4b). Pyrroles bearing ester (**1m**) and ketone (**1n**) moieties, which are solid substrates with melting points > 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, which is probably due to poor mixing in the ball mill. Liquid furan derivatives (**1o**–**1q**) were efficiently borylated providing the corresponding products (**3o**–**3q**) in moderate to good yield without the LAG additive (33–71%). 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, while the desired product **3r** was obtained in high yield under LAG conditions (93%). The results shown in Tables 3 and 4 suggest that the LAG conditions are robust and can be applied to a wide range of heteroaryl compounds, while the borylation of solid substrates with relatively low melting points (< 70 °C) or liquid substrates proceeds efficiently even in the absence of a LAG additive.[13]

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



X = NH, O (**1**) (**2**) X = NH, O (**3**)

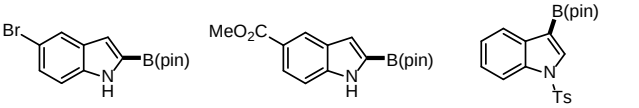
(a) Indoles with relatively high melting points (>70 °C)



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%

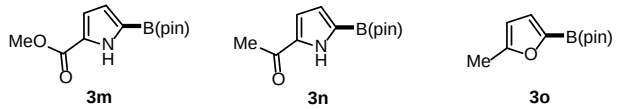


3j with LAG: 66% (38%)[b] without LAG: 0%

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

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

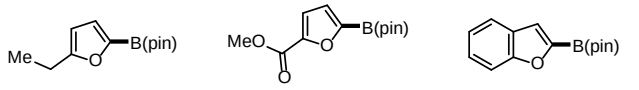
(b) Various heteroaryl substrates



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%)

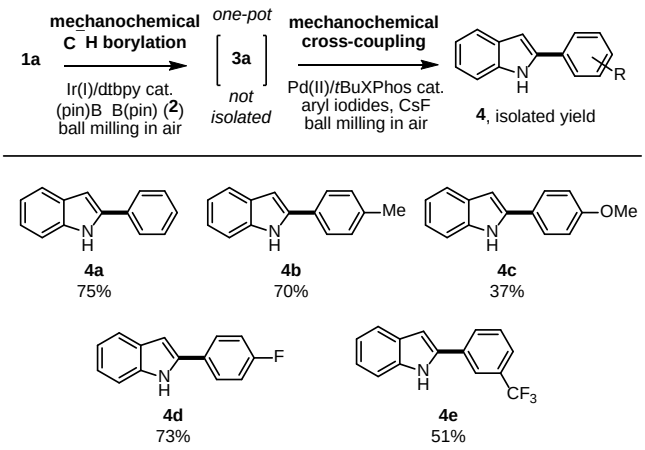
3r with LAG: 93% (60%) without LAG: 0%

[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 were determined by ^{1}H NMR spectroscopy; isolated yields are shown in parentheses. [b] 0.40 μL/mg THF were used as a LAG additive.

To demonstrate the synthetic utility of this method, we investigated a direct one-pot mechanochemical C–H borylation/Suzuki–Miyaura cross-coupling sequence in air for the synthesis of 2-aryl indole derivatives from indole **1a** (Scheme 3). The *in situ* obtained 2-borylated indole **3a** was directly subjected to a one-pot cross-coupling with aryl iodides using the Pd/*t*BuXPhos catalyst originally developed by Buchwald and co-workers.[14] Pleasingly, we found that the desired 2-aryl indoles (**4a**–**4e**) were successfully obtained *via* such a one-pot mechanochemical strategy in moderate to good yield (37–75%). This one-pot multi-step transition-metal-catalyzed transformation

using mechanochemistry represents a more sustainable synthetic alternative to conventional solution processes.[15]

Scheme 3. Mechanochemical one-pot C–H borylation/Suzuki–Miyaura cross-coupling sequence[a]



[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%), 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 mechanism of this mechanochemical C–H borylation reaction, preliminary mechanistic studies were carried out. First, we determined the kinetics of the reaction involving the solid indole substrate **1a** under different reaction conditions (Figure 2a). As periodic sampling of the mechanochemical reaction runs would require stopping the mill and opening the jar, each data point was obtained from an individual reaction. Under conventional solution conditions, the reaction rate is initially high and decreases after 20 min (Figure 2a, orange line). On the other hand, sigmoidal kinetics were observed under the developed mechanochemical conditions (Figure 2a, blue line). The reaction did not proceed in the first 60 min, but was rapidly completed between 60 and 70 min. We noted that the physical state of the reaction mixture dramatically changed from a solid to a viscous oil after 60–70 min (Figure 3). This dramatic change in rheology should improve the mixing efficiency of the reactants and catalyst, which would result in a rapid increase of the reaction rate.[10] Another possible reason for such sigmoidal kinetics would be an induction period (60 min) to generate the catalytically active trisboryl iridium complex from the iridium precursor under mechanochemical conditions.[16,17]

Subsequently, we investigated the kinetics of the reaction of the liquid benzofuran **1r** (Figure 2b). We found non-reactive periods of 90 and 50 min before the formation of the desired borylation product **3r** under both conventional solution conditions and the developed mechanochemical conditions, respectively (Figure 2b, orange and blue lines). Notably, the mechanochemical C–H borylation of **1r** showed a much shorter induction period than the reaction in solution. Given that no rheological changes in the reaction mixture of **1r** were observed under mechanochemical conditions (Figure S3), the main reason for the sigmoidal kinetics should be attributed to an induction period of 50 min to form the catalytically active trisboryl iridium complex from the iridium precursor.[16,17]

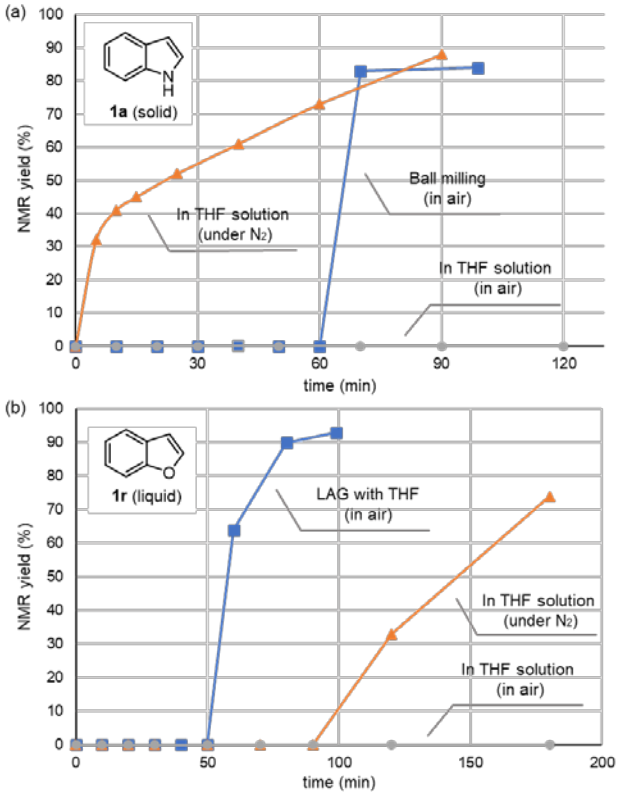


Figure 2. Reaction progress of the iridium(I)-catalyzed C–H borylation under conventional solution conditions or under the developed mechanochemical conditions: (a) indole **1a** (solid) and (b) benzofuran **1r** (liquid).

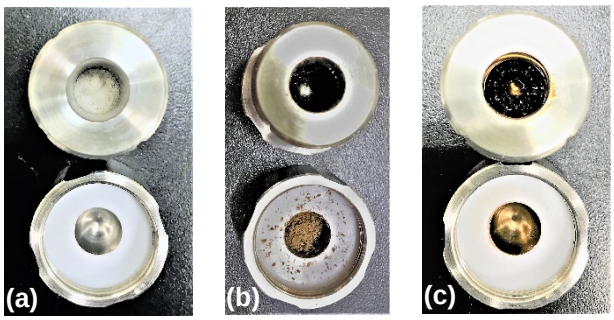


Figure 3. Reaction mixtures containing indole **1a** upon grinding after (a) 0, (b) 60, and (c) 70 min.

It should be noted that no reaction occurred when the C–H borylations were conducted in solution in air (Figure 2a and 2b, gray lines), while the mechanochemical reactions can be carried out in air (Figure 2a and 2b, blue lines). This is probably because the reaction between sensitive iridium species and gaseous oxygen or water in the ball mill is much slower than that with dissolved oxygen or water in organic solvents.[18] These results highlight the synthetic utility of the present C–H borylation protocol in terms of operational simplicity.

In conclusion, we have described the first application of mechanochemistry to catalytic C–H borylation reactions. Careful choice of the reaction milling jar, ball, and LAG additive enabled the development of a solvent-free C–H borylation reaction that proceeds efficiently in air. Considering the broad significance of C–H borylation processes and the industrial demand for sustainable synthetic methods, the present study constitutes an important milestone toward the development of industrially attractive C–H bond functionalization processes. Furthermore, we

expect that this study will open an unexplored area of C–H borylation reactions, where reactivity and selectivity different to those of conventional solution-based reactions may be realized. We are currently working on a new catalyst design for such mechanochemical C–H borylations with unique site-selectivity.

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Conflict of interest

The authors declare no conflict of interests.

Keywords: mechanochemistry • C–H borylation • iridium • boron • synthetic method

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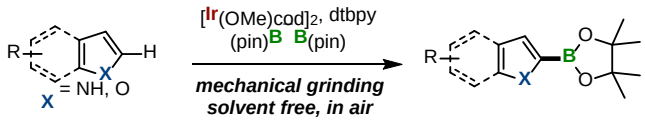
COMMUNICATION

The first C–H borylation using mechanochemistry



The first application of mechanochemistry to a catalytic C–H borylation reaction is described. Using either none or just a catalytic amount of a liquid, a series of heteroaromatic compounds was efficiently reacted with bis(pinacolato)diboron in the presence of an iridium(I)/dtbpy catalyst under mechanochemical conditions to afford the corresponding C–H borylation products in good to excellent yield.

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