

Metal-Free Catalytic C-H Bond Activation and Borylation of Heteroarenes

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Abstract:

Transition metal complexes are efficient catalysts for the C-H bond functionalization of heteroarenes to generate useful products for the pharmaceutical and agricultural industries. However, the costly need to remove potentially toxic trace metals from the end products has prompted great interest in developing metal-free catalysts that can mimic metallic systems. We demonstrate here that the borane (1-TMP-2-BH₂-C₆H₄)₂ (TMP = 2,2,6,6-tetramethylpiperidine) can activate the C-H bonds of heteroarenes and catalyze the borylation of furans, pyrroles, and electron-rich thiophenes. The selectivities complement those observed with most transition metal catalysts reported for this transformation.

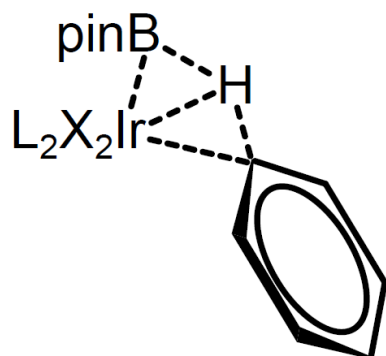
Transition-metal catalyzed reactions are ubiquitous tools in the pharmaceutical and agrochemical industries despite the costs associated with removing residual catalysts; trace metals in products for human consumption are heavily regulated by international bodies (*1*). Similar concerns exist in the modern electronic industry where metals need to be removed from organic electronic devices

to avoid loss of efficiency (2). Nevertheless, the importance of selectively forming bonds between carbon and other atoms using transition metals has been acknowledged by three Nobel Prizes in Chemistry in the past 15 years. More recently, the catalytic functionalization of C-H bonds using transition metals has emerged as an atom-economical way to generate new bonds without the need for activated precursors (3-4). Through such an activation process, the catalytic C_{sp2}-H borylation of aromatic molecules generates organoboronates, (5-7) which are important species for the pharmaceutical industry and in the field of modern organic materials, notably as building blocks for the creation of new bonds using the Suzuki-Miyaura cross-coupling reaction (8, 9). Although some base metal complexes have been used as catalysts for the borylation of arenes (10-12) the most efficient systems to date rely on noble metals, most notably iridium (6-7). Alternatively, borenium or boronium species generated by highly reactive precursors can promote the electrophilic borylation of arenes but stoichiometric quantities of amine derivatives are needed to generate the active boron reagents (13-15).

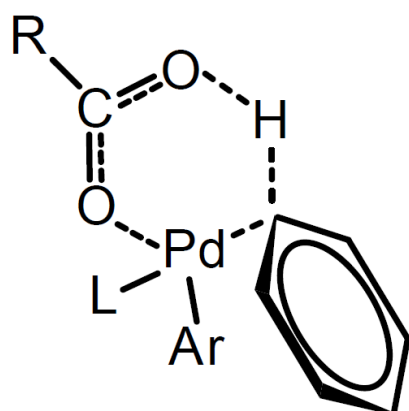
Noble metals are well suited to cleave aromatic C-H bonds in catalytic processes because they can easily mediate two-electron transfer processes. In the borylation reaction using iridium catalysts, this transformation is usually assisted by the boryl substituents present on the metal centre which facilitate the proton transfer (Fig. 1A) (16). An analogous process is the direct arylation through palladium carboxylate complexes in which the electron transfer is helped by the basic carboxylate group abstracting the proton on the aromatic molecule while the aryl group coordinates the metallic center (Fig. 1B) (17-18). Herein, we report that intramolecular “Frustrated Lewis Pairs” (FLPs) can be used as catalysts for the C-H bond cleavage and dehydrogenative borylation of heteroarenes. Replacing current metal-catalyzed technologies by FLP processes offers exciting possibilities because of the abundance, low cost and low toxicity of most organoboranes, especially

in comparison with noble metals (19). The metal-free activation of hydrogen reported in 2006 using the concept of FLPs (20-21) led to an important breakthrough in the metal-free hydrogenation reaction (22). In FLP processes, cleavage of H₂ occurs during the transition state via the cooperation of a Lewis acid and a Lewis base that are prevented from forming a Lewis adduct by steric or geometrical constraints. We now report the design of a FLP catalyst capable of cleaving and functionalizing C_{sp2}-H bonds. In this process, a Lewis basic amine putatively serves to abstract a proton while the electron density of the C_{sp2}-H bond is transferred to a Lewis acidic borane (Fig. 1C). This concept is thus reminiscent of the transformations observed with transition metal complexes.

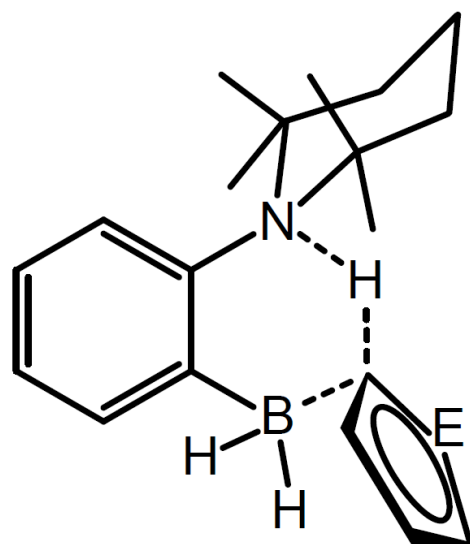
A) *Boryl assisted C-H bond activation*



B) *Concerted metalation deprotonation*



C) *Metal-free C-H bond activation*



E=O,S,N-R

Fig. 1. Representative transition states for the C-H activation of arenes. A) Activation of C-H bonds in borylation transformations using Ir catalysts. B) Carboxylate-assisted metalation deprotonation at palladium. C) Metal-free C-H activation of heteroarenes using FLP catalysts. The dashed lines represent bonds formed and cleaved during the electron transfer.

The catalyst presented in Figure 1C was designed to afford the nucleophilic carbon of the heterocyclic substrate close access to the Lewis acidic BH₂ moiety. In concert, the bulky amine moiety favors the abstraction of the proton from the C_{sp2} while preventing possible head-to-tail dimerization. The phenyl linker between the Lewis moieties has been shown to be quite durable in FLP catalysis (23-26). Compound **1** [(1-TMP-2-BH₂-C₆H₄)₂ (TMP = 2,2,6,6-tetramethylpiperidine)] was therefore a promising candidate for the metal-free C_{sp2}-H activation of aromatic molecules in addition to being synthetically easily accessible. While we were carrying out this work, compound **1** was shown to be in equilibrium with the monomeric form and was reported to be an active species for hydrogen activation (26).

¹H nuclear magnetic resonance (NMR) monitoring of the addition of 1-methylpyrrole to a solution of **1** in chloroform-*d* at 80 °C revealed the evolution of H₂ (δ = 4.63) and the formation of product **2** over a period of 5 hours, resulting from the C-H activation of 1-methylpyrrole at the 2 position (Fig. 2A). Conducting a similar reaction with 1-methylpyrrole-*d*₄ allowed the observation of HD and the unambiguous assignment of the resonances associated with the 1-Me-pyrrole activation products (Fig. 2C). Compound **2** was shown to react with HBpin (pin = pinacolato) in a chloroform-*d* solution over the course of 10 minutes at ambient temperature, regenerating **1** by releasing 1-Me-2-Bpin-pyrrole (**3a**) (Fig. 2B).

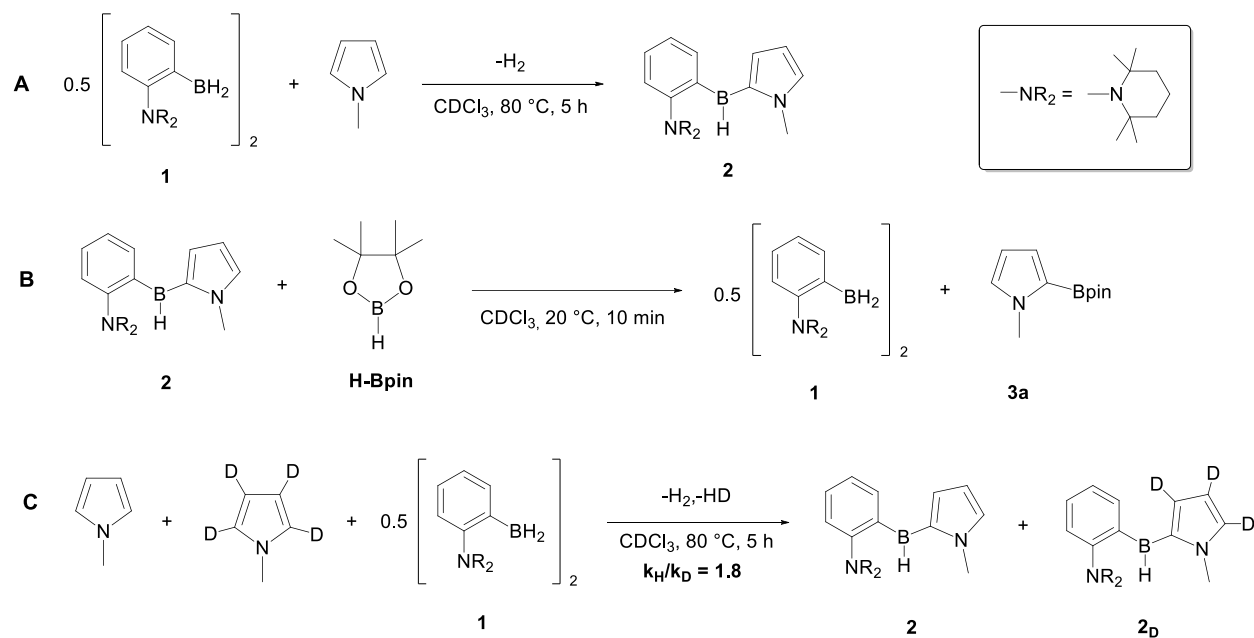


Fig. 2. Stoichiometric transformations observed in the course of this study using ^1H , ^{13}C , and ^{11}B NMR spectroscopy. A) Reaction of species **1** with 1-methylpyrrole generating **2**. B) Reaction of **2** with HBpin generating **1** and **3a**. C) Competitive experiment between 1-methylpyrrole and 1-methylpyrrole- d_4 allowing determination of the kinetic isotope effect for the generation of **2**.

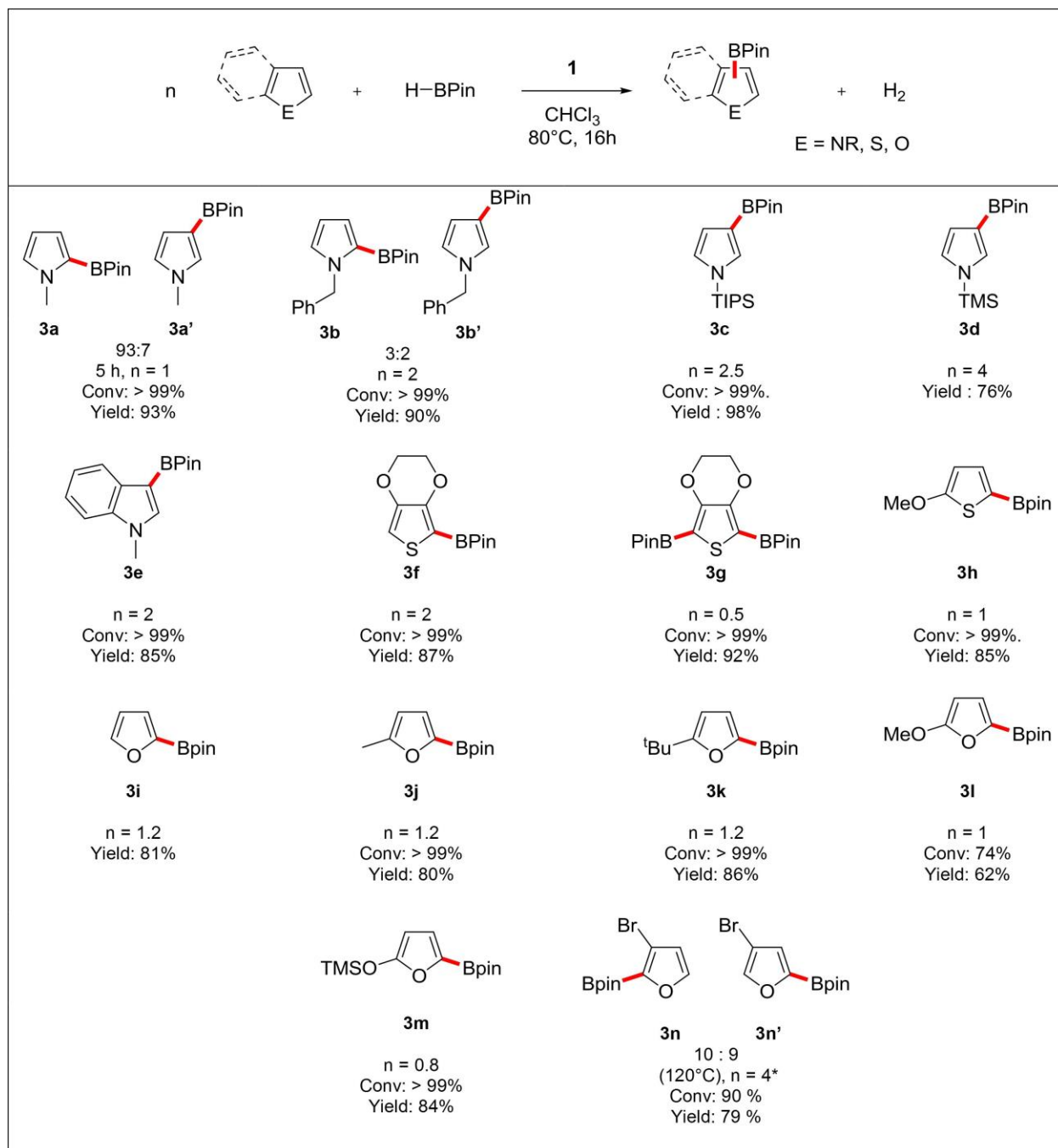


Fig. 3. Scope of the borylation reaction catalyzed by **1**. Unless specified otherwise, the reactions were run using **1** (14.0 mg, 0.0305 mmol, 2.5 mol. %), HBpin (156 mg, 1.22 mmol), and the substrate (n x 1.22 mmol) in 5 mL of CHCl₃ at 80 °C. The conversions (conv.) are given with respect to the transformation of the limiting reagent to the borylated product as measured by ¹H NMR spectroscopy at the end of the reaction. Yields and isomer ratios refer to isolated quantities.

Unless specified otherwise, a single isomer was isolated and detected. * **1** (2.1 mg, 0.045 mmol, 5 mol. %), 3-bromofuran (32.9 μ L, 53.9 mg, 0.367 mmol) and HBpin (12.8 μ L, 11.7 mg, 0.092 mmol), C₆D₆ (0.4 mL), 100 °C, 36 hours.

When equimolar amounts of 1-methylpyrrole and HBpin (1.22 mmol) were added to a 2.5 mol % solution of **1** in CHCl₃, we observed quantitative conversion of the reagents to a 93 : 7 ratio of **3a** and **3a'** by ¹H NMR spectroscopy, confirming that **1** is a catalyst for the borylation reaction. We obtained the isolated products in a yield of 93% by passing the reaction mixture over a short pad of silica to remove the catalyst. The same protocol was used on a multigram scale reaction (0.22 mol) to isolate 3.76 g of the desired product (yield = 81 %). With a catalytic loading as low as 0.5 mol %, we isolated species **3a** and **3a'** in an overall 72 % yield. The borylation of 1-methylpyrrole was also possible with catecholborane and 9-borabicyclo[3.3.1]nonane, but these gave yields of 42 and 60%, respectively. In addition, we tested functional group tolerance by conducting the borylation of 1-methylpyrrole in the presence of additives. The reaction was shown to be tolerant of aryl or alkyl halides, epoxides, ethers, hexamethylphosphoramide, and less basic amines, but inhibition was observed in the presence of basic amines, carbonyl groups, or unsaturated hydrocarbons (Table S2).

The scope of the borylation is displayed in Figure 3. The reaction does not proceed for the parent pyrrole because of the reactive N-H bond that presumably inhibits the catalyst. Protection of the pyrrole with the N-benzyl group allowed us to isolate a 3:2 mixture of **3b** and **3b'** in 90% yield. Not only are the TIPS (TIPS = triisopropylsilyl) and TMS protecting group also tolerated, but they allow the formation of the 3-substituted isomer, giving **3c** and **3d** in good yields. However, the presence of the electron-withdrawing *tert*butyloxycarbonyl group (BOC) inhibits the reaction

completely. The latter results suggest that the electronic parameters are critical for the reaction to proceed. Indeed, the quantitative borylation for 1-methylindole at the most electron-rich 3-position to generate **3e** rather than in the 2-position as observed for the iridium catalysts (**27**) is reminiscent of the regioselectivity observed in electrophilic borylations (*13,15*).

Whereas our investigation revealed that thiophene is not reactive, the borylation proceeds rapidly for electron rich 3,4-ethylenedioxythiophene. By adding 0.5 or 2 equiv of HBpin, it was possible to observe quantitative conversion to the mono- (**3f**) or diborylated (**3g**) products. Similarly, 2-methoxythiophene was borylated successfully once more suggesting that electron-rich substrates are required for catalysis to occur.

Many furan derivatives are challenging to isolate since they tend to be light sensitive and degrade on silica but our simple purification methods allows rapid isolation of the products. Although furan gave only limited conversion to **3i** by NMR spectroscopy, we were able to isolate borylated 2-alkylfurans **3j** and **3k** in excellent yields. Once again, electron-rich substrates react readily, giving methoxide and siloxide species **3l** and **3m** in good yields and thus expanding the scope to the use of protected alcohol functionalities. **1** is tolerant of bromide-containing substrates and generates **3n** and **3n'** in a close to statistical 1:0.9 ratio.

Density functional theory (DFT) calculations were carried out at the ω B97xd/6-31+G** level (with the SMD solvation model to account for chloroform solvent) to propose a reliable mechanism for this transformation using 1-methylpyrrole as the model substrate, as shown in Figure 4. After dissociation of the dimer **1**, the rate-determining step was calculated to be the C-H activation of the substrate by **Int1**, generating the zwitterionic species **Int2**. Once **Int2** is generated, the calculations predict a rapid release of H₂ to generate **2** (*26*). The formation of **3a** in

the presence of HBpin was calculated to proceed via a four-centre sigma-bond metathesis, regenerating **1** in the process.

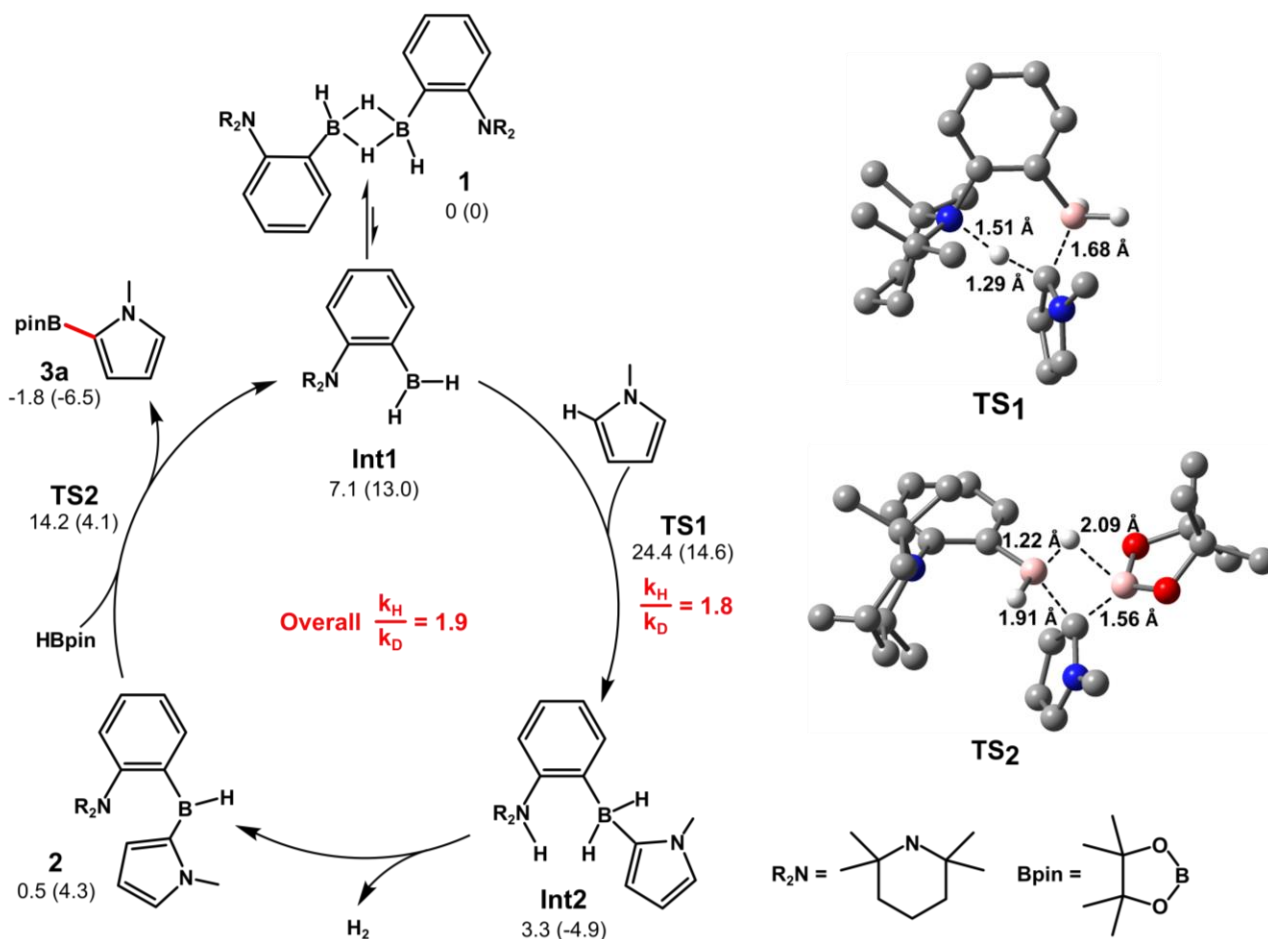


Fig. 4. Proposed mechanism of the borylation of 1-methylpyrrole using catalyst **1**, with calculated (ω B97xd/6-31+G**) energies ΔG^{273K} (ΔH^{273K}) given for each structure in kcal.mol⁻¹ in chloroform phase. The formation of **2** from **1** (KIE of 1.8 when was obtained using 1-methylpyrrole-*d*₄) and **3a** from **2** were observed using NMR spectroscopy, with an overall KIE of 1.9 for the catalytic transformation. **Int1** and **Int2** were not observed and transition states **TS1** and **TS2** are represented, based on DFT calculations.

Whereas the 24.4 kcal.mol⁻¹ barrier for C-H activation of the proton in the 2-position of the pyrrole is favored, the activation on the 3-position is also possible, requiring only 0.4 kcal.mol⁻¹ of additional activation energy, justifying the minor amount of **3a'** produced during catalysis. These barriers are consistent with catalysis operating at 80 °C. We performed competition experiments at 80 °C between 1-methylpyrrole and 1-methylpyrrole-*d*₄ to measure a kinetic isotope effect (KIE) of 1.8 for the stoichiometric C-H activation with formation of **2** and of 1.9 for the catalytic borylation. The relatively low KIE value of 1.8 to 1.9 is similar to that observed for the concerted metalation-deprotonation of the palladium-catalyzed arylation reaction with similar substrates (KIE of 2.1 at 100 °C) (28-29).

It is well established that the C-H activation processes using iridium catalysts correlate well with the acidity of the proton (30-31). In contrast, the ease of activation of C-H bonds using carboxylate-assisted palladium catalysts can be attributed to both the acidity of the proton and the nucleophilicity of the carbon (32-33). The regioselectivity observed for the borylated indole **3e** and the KIE values support the transition-state calculations indicating that the C-H bond activation by catalyst **1** is directed by the most nucleophilic carbon, therefore acting in a complementary fashion when compared to transition metal systems. Although thiophene and 1,3,5-trimethoxybenzene are more difficult to activate since these molecules have higher aromatic stabilization and hence lower nucleophilicity than pyrroles, the DFT results suggest that the C-H activation transition state energies of these molecules are, respectively, only 3.3 and 6.7 kcal.mol⁻¹ higher than for the activation of 1-methylpyrrole, suggesting that the borylation of these substrates might be accessible with further catalyst optimization. Furthermore, it is expected that the FLP

mediated activation of C-H bonds could be exploited for a plethora of C-H functionalization reactions.

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Supplementary Materials:

Materials and Methods

Supplementary text

Figures S1-S59

Tables S1-S3