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Remarkably Efficient Iridium Catalysts for Directed C(sp^2)−H and C(sp^3)−H Borylation of Diverse Classes of Substrates

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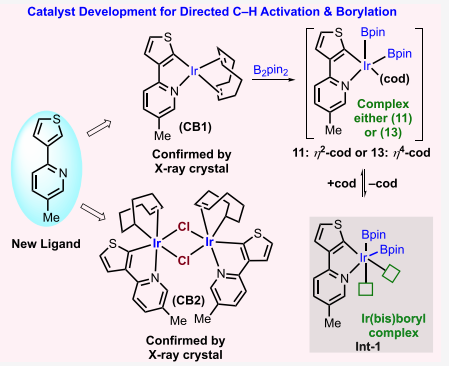
ABSTRACT: Here we describe the discovery of a new class of C−H borylation catalysts and their use for regioselective C−H borylation of aromatic, heteroaromatic, and aliphatic systems. The new catalysts have Ir−C(thienyl) or Ir−C(furyl) anionic ligands instead of the diamine-type neutral chelating ligands used in the standard C−H borylation conditions. It is reported that the employment of these newly discovered catalysts show excellent reactivity and *ortho*-selectivity for diverse classes of aromatic substrates with high isolated yields. Moreover, the catalysts proved to be efficient for a wide number of aliphatic substrates for selective C(sp^3)−H bond borylations. Heterocyclic molecules are selectively borylated using the inherently elevated reactivity of the C−H bonds. A number of late-stage C−H functionalization have been described using the same catalysts. Furthermore, we show that one of the catalysts could be used even in open air for the C(sp^2)−H and C(sp^3)−H borylations enabling the method more general. Preliminary mechanistic studies suggest that the active catalytic intermediate is the Ir(bis)boryl complex, and the attached ligand acts as bidentate ligand. Collectively, this study underlines the discovery of new class of C−H borylation catalysts that should find wide application in the context of C−H functionalization chemistry.



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INTRODUCTION

Direct C−H bond functionalization[1−10] using transition metal catalysts is one of the key emergent methods that is currently drawing remarkable attention owing to the rapidly expanding abundant chemical feedstocks to achieve higher-value materials.[11,12] Among them, the C−H bond borylation[3,13−15] is a unique functionalization reaction due to the versatile synthetic transformation of the C−B bond[16−19] and the key role of the organoboron reagents in the construction of natural products, pharmaceuticals, fine chemicals, and boron-bearing small drug molecules. In this context, among various transition-metal-mediated[20,21] C−H borylations, the use of iridium-based catalytic system is the major contributing factor compared to other transition metals. For example, the first iridium-catalyzed borylation of benzene was reported[22] by Smith and co-workers (Figure 1B), although scope and application was limited. Subsequently, a breakthrough discovery of iridium-catalyzed C−H borylations was reported[23,24] by Ishiyama, Takagi, Miyaura and Hartwig (the ITMH method) that provided a new dimension for the borylation of a wide number of arenes and heteroarenes (Figure 1C). At the same time, Smith and co-workers introduced[25] a new family of Ir-based catalyst ligated with the phosphine system for the C−H borylation of arenes (Figure 1D). While these were the pioneering reports of borylation reaction that followed the formation of the tris(boryl)Ir-complex, the first isolated tris(boryl)Ir complex was discovered[26] by Marder and co-workers (Figure 1A).

Importantly, since the discovery of the ITMH method,[23,24] numerous unique combinations of precatalyst, ligand, boron reagent and solvent have been reported in the literature. Subsequently, Hartwig and co-workers discovered[27−31] a series of powerful C−H borylations directed by hydrosilyl group via iridium catalysis (Figure 1E). On the other hand, Sawamura and co-workers introduced a new heterogeneous catalytic system[32] comprising silica-supported phosphine-bearing Ir catalyst that shows a board substrate scope (Figure 1F). Fernandez and Lassaletta subsequently reported[33] an elegant Ir-based catalytic system for borylation using hemilabile ligand (Figure 1G). In contrast to the above-mentioned Ir-based catalytic systems for the C−H borylation that undergo via the generation of the tris(boryl) complex (either isolated or proposed depending on the stability of the resulted complex), Smith and Maleczka reported a new catalytic system by the employment of phosphine−silyl and nitrogen−silyl ligand (Figure 1H)[34] for the borylation that proceeds via the generation of a bis(boryl)Ir complex. Moreover, a similar type of bis(boryl)Ir complex has been introduced by Li and co-

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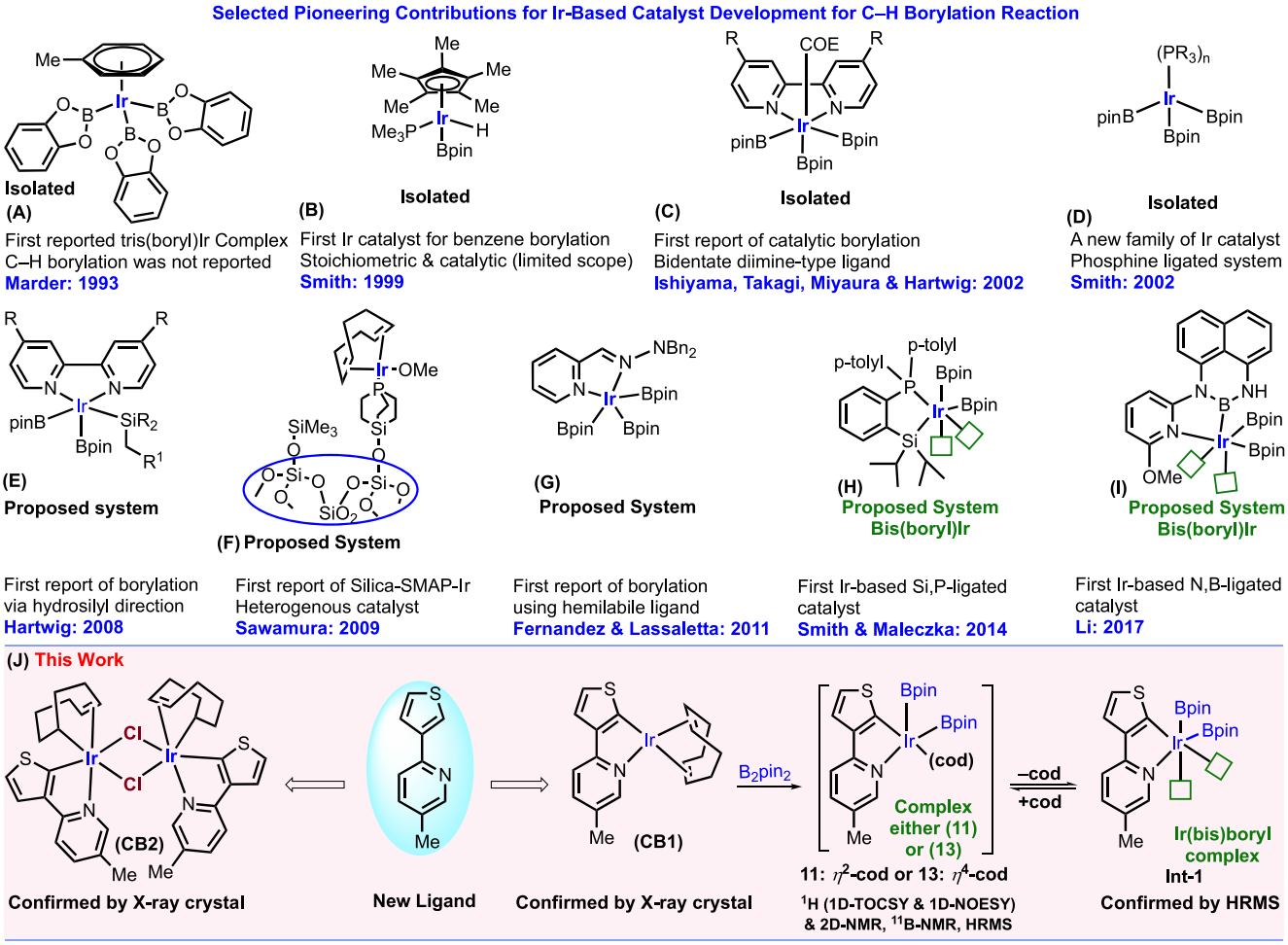

Figure 1. Iridium-based catalytic systems for C−H borylations: previous developments and present developments.[22,23,25−27,32−34]

workers with the help of the pyridine−boryl ligand framework (Figure 1I).[35] Although the catalyst and ligand systems reported by Smith, Maleczka, and Li are highly active, preparation of such a type of catalysts and ligands are not straightforward, in that they require air-sensitive reagents, multistep syntheses, and cryogenic reaction conditions, which make the methods challenging for the C−H borylation reactions. Thus, despite the discovery of all these catalysts, the utility and scope of the C−H borylation chemistry could be increased with further developments. Herein, we report the discovery of a new class of C−H borylation catalysts and their utility for the directed borylation of aromatic, heteroaromatic, and aliphatic systems. The newly developed catalysts have Ir−C(thienyl) or Ir−C(furyl) anionic ligands (Figure 1J) and mechanistically similar to those with the phosphine−silyl ligand and pyridine−boryl ligand introduced by Smith, Maleczka,[34] and Li.[35] For the first time, we have shown that one particular class of Ir-based catalyst can be utilized for the borylation of a wide range of aromatic substrates containing various functional groups (FG)/directing groups (DG) apart from the aliphatic and heterocyclic substrates. Moreover, we also demonstrate that some of the substrates that are either sensitive or unreactive under the reported borylation conditions that are also compatible under our developed conditions. Furthermore, we describe that one of the catalysts could be used even in open air for the C(sp^2)−H and C(sp^3)−H borylations. Mechanistic studies reveal that the active catalytic intermediate is the bis(boryl)Ir complex and the attached ligand acts as bidentate ligand. The simplicity and air stability of our developed catalysts or ligand system make either superior for catalysis.

Pioneering Previous Reports on *ortho*-Borylation. In contrast, there have been major developments in iridium-catalyzed C−H borylations of aromatic substrates to prepare *ortho*-substituted aryl boronic esters (a brief description is shown in Figure 2A). The first example of *ortho*-borylation using Ir-catalyzed homogeneous systems is the hydrosilyl-directed[27] borylation discovered by Hartwig. In contrast to Hartwig's homogeneous catalyst, the Ir-catalyzed borylations employing silica-supported phosphine ligands,[32] pioneered by Sawamura, demonstrate a broad scope for the directed *ortho*-borylations. Since these discoveries, many pioneering research groups developed powerful directed *ortho*-borylation methods for many substrates using a number of FG/DG such as ketones,[36] esters,[32,34,35,37] amides,[38] pyridines,[33,39] hydrazones,[33,40,41] imines,[42,43] ethers,[44] thioethers,[45,46] phenols,[47−49] anilines,[50−52] benzylamines,[53,54] phosphines,[55−57] boronyl,[58] and halides.[32,59] Notably, during submission of this manuscript, a paper describing Ir-catalyzed *ortho*-borylation of aryl phosphonates[60] appeared by Clark and Watson. Moreover, apart from the Ir-catalyzed directed arene borylations, the groups of Yu,[61] Chirik,[62] Nolan,[63] and Takaya[64] have discovered numerous powerful borylation methods using Pd, Co, and Ru, respectively. Collectively, it might be concluded

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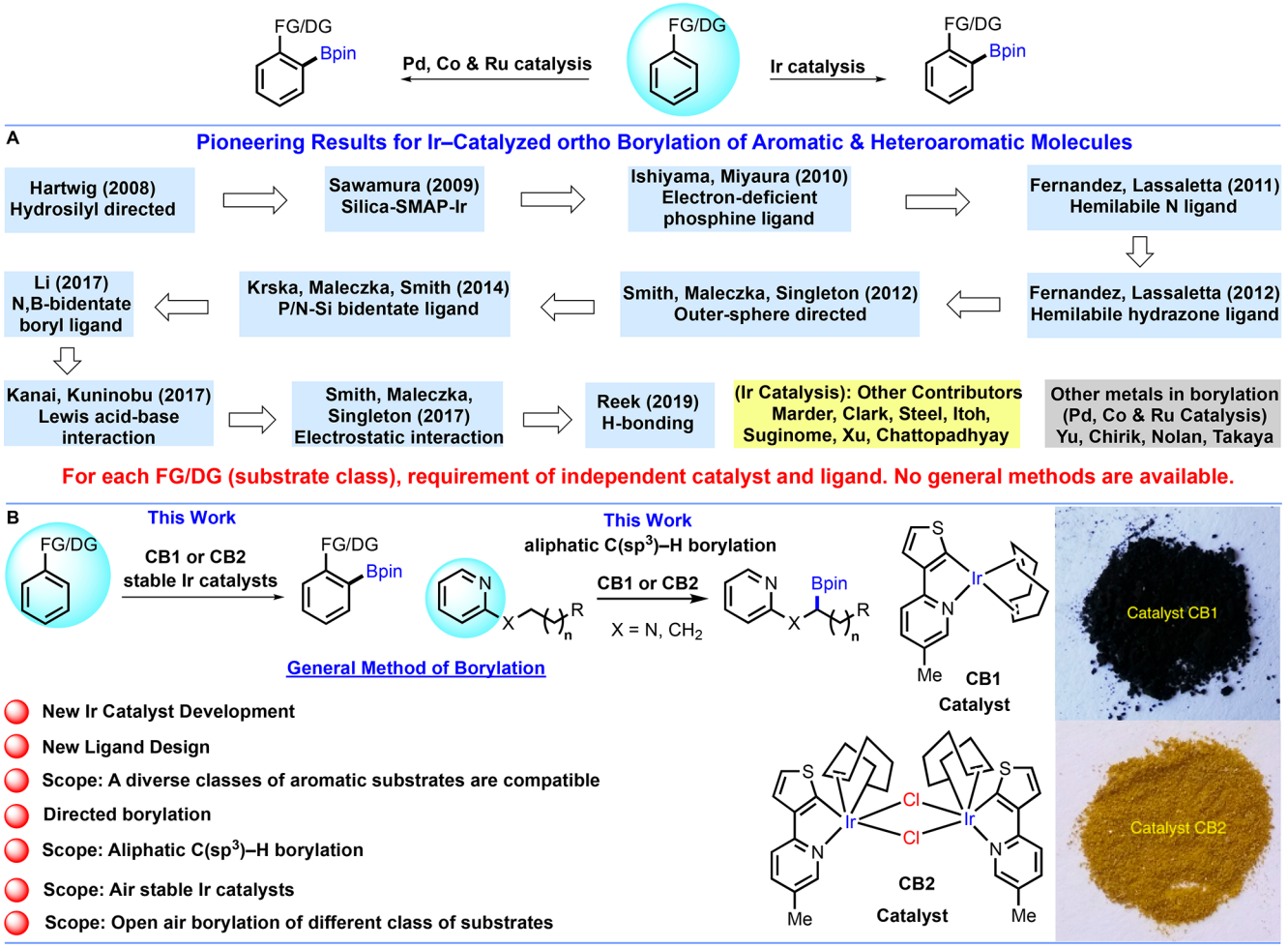

Figure 2. (A) Pioneering previous reports of directed *ortho*-borylation. (B) Present work: catalyst development and directed C(sp^2)–H and C(sp^3)–H borylation for diverse classes of substrates.[27−64]

that a variety of substrate classes using number of DGs have been demonstrated in the field of borylation chemistry employing various transition metals. Thus, while many methods have enabled highly efficient and site-selective C–H borylation of aromatic substrates using a variety of reaction conditions, employment of a particular set of reaction conditions for a diverse class of aromatic and heteroaromatic molecules remains an unmet challenge. For example, the coordinating efficiency of each FG/DG of the substrates is largely dependent on specific metal, ligands, and other parameters.[3,13−15,25−64] *Thus, each type of substrate (having a specific FG/DG) requires independent catalyst design and DG optimizations in each case, which is an extraordinary challenge.* Moreover, substrates that do not contain either proper functional groups or directing groups are extremely difficult for the site-selective[3,13,15,65] C–H borylation. Furthermore, the availability of stable Ir-based catalysts for C–H borylations that can cover a wide number of substrates is still rare. We envisioned that a general method can be developed through catalyst development[66−68] that can give a straightforward solution of this challenge. Here we report a general C–H borylation method for a diverse classes of aromatic substrates by developing iridium catalysts (Figure 2B, **CB1** and **CB2**) ligated by pyridyl-thiophene. We demonstrate that catalysts **CB1** and **CB2** are highly reactive and selective for both arenes and heteroarenes directed C–H borylation reactions. Moreover, we found that the developed catalytic system is highly competent for directed C(sp^3)–H borylations for several challenging substrates featuring *N*-adjacent C(sp^3)–H bonds[69−73] and nonactivated C(sp^3)–H bonds[29,74−78] (Figure 2B). Furthermore, we show that one of the catalysts (**CB2**) can be used even in open air for the borylations enabling the method more general. We characterize the structures of catalysts (catalyst **CB1** and catalyst **CB2**) using X-ray crystallography which give an insight into the coordination mode of these ligands with the Ir metal. We also employ these methods to the late-stage C–H borylation of important molecules.

RESULTS AND DISCUSSION

Ligand/Catalyst Development for Reaction Optimization. At the outset toward developing the catalyst, we first screened a number of ligands (Figure 3A). We started our initial investigation with substrate **1a-I** using conventional bipyridine type of ligands[24] (**dtbpy**, **L1**, **L2**, **L3**, and **L4**), which shows that none of these ligands are appropriate for the site-selective C–H borylations. The lack of selectivity under these conditions may be attributed to the fact that these ligands are strongly coordinating, the in situ generated Ir-trisboryl complex is unable to produce selective borylation for substrate **1a-I** and follows a routine catalytic cycle. On the contrary, employment of 2-phenylpyridine type of ligands

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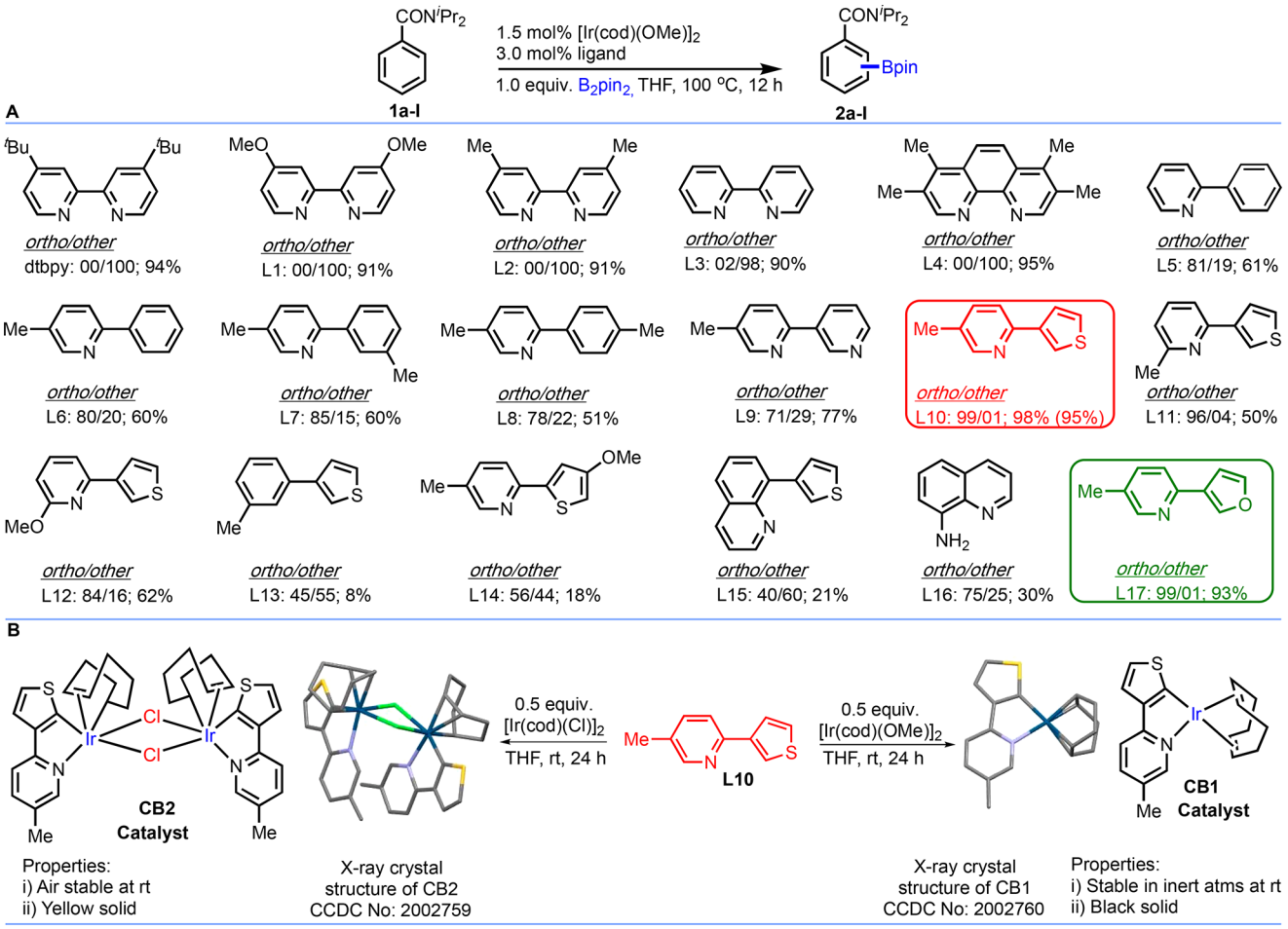

Figure 3. (A) Reaction optimization and evaluation of the reaction conditions. (B) Catalyst development (**CB1** and **CB2**).

(**L5**−**L8**) exhibited inspiring outcomes. Although we were not sure whether these ligands were acting as the bidentate ligands by generating the cyclometalated[79] complexes or monodentate ligands. Attempted synthesis of the cyclometalated complexes with these ligands was also unsuccessful. Moreover, replacing the phenyl ring by a 3-pyridyl unit (ligand **L9**) resulted similar type of outcomes. For these, we reasoned that the C−H bond's acidity of benzene (pK_a = 44.7)[80] and 3-pyridyl unit (pK_a = 43.6, C2−H)[80] are not sufficient enough to make cyclometalated complexes. Next, considering the relatively more C−H bond acidity of the thiophene heterocycle (pK_a = 33.5, C2−H),[80] we developed ligand system **L10**, a combination of two different heterocyclic units. We hypothesized that owing to the more reactivity of the thiophene's C2−H bond, it would generate a cyclometalated complex and will facilitate the C−H borylation. Following this hypothesis, borylation was performed using **L10** ligand, and to our delight, we observed almost a single isomer with quantitative conversion.[81] To see the effects of the substituents and other types of ligand frameworks, we performed borylations, and the results are summarized in Figure 3A. Toward this end, we were also curious about the ligand development using the furan unit, and thus accordingly when a reaction was conducted with **L17** ligand, we observed almost similar outcomes. Next, we attempted to characterize the actual catalyst structures. Thus, when a solution of **L10** and 0.5 equiv of [Ir(OMe)(cod)]$_2$ in THF was stirred at room temperature for 24 h, cyclometalated[82] complex **CB1** was formed quantitatively based on NMR spectroscopic analysis and isolated in 90% yield (Figure 3B). A single crystal was obtained in a THF−hexane solution. Using the same method we have prepared catalyst **CB2** using [Ir(cod)Cl]$_2$ instead of [Ir(OMe)(cod)]$_2$, but here a different type of complex formation[83,84] occurs which is probably due to the difference in reactivity of the two precatalysts, although in both cases the binding mode of the ligands are the same and cyclometalated complex formation occurs which is confirmed by single crystal.

Substrate Scope: C−H Borylation of Diverse Classes of Arenes. Encouraged by these results, we first examined the scope of these developed conditions toward the arene bearing different types of amide directing groups (monosubstituted aromatic amides, Figure 4A). To our delight, the developed catalytic conditions was appeared to be very general for a wide number of differently substituted amides regardless of the nature of the amide nitrogen substitutions affording high level of selectivity (*ortho*/other = 99/1) and isolated yields of the pure borylated products (entries **2a-II**−**2a-XVIII**). Next, to expand the scope of the borylation and to see the effect of the various substituents around the aromatic ring, we performed borylations for a series of aromatic amides bearing a *N*,*N*-diisopropyl group due to the relatively higher product conversion and ease of isolation of the borylated products (Figure 4B). We observed that a wide number of substituents (such as, methoxy, phenyl, chloro, fluoro, bromo, trifluoromethyl, butoxy, and methyl) at the *ortho*-, *meta*-, and *para*-positions gave high *ortho*-selectivity as well as high isolated

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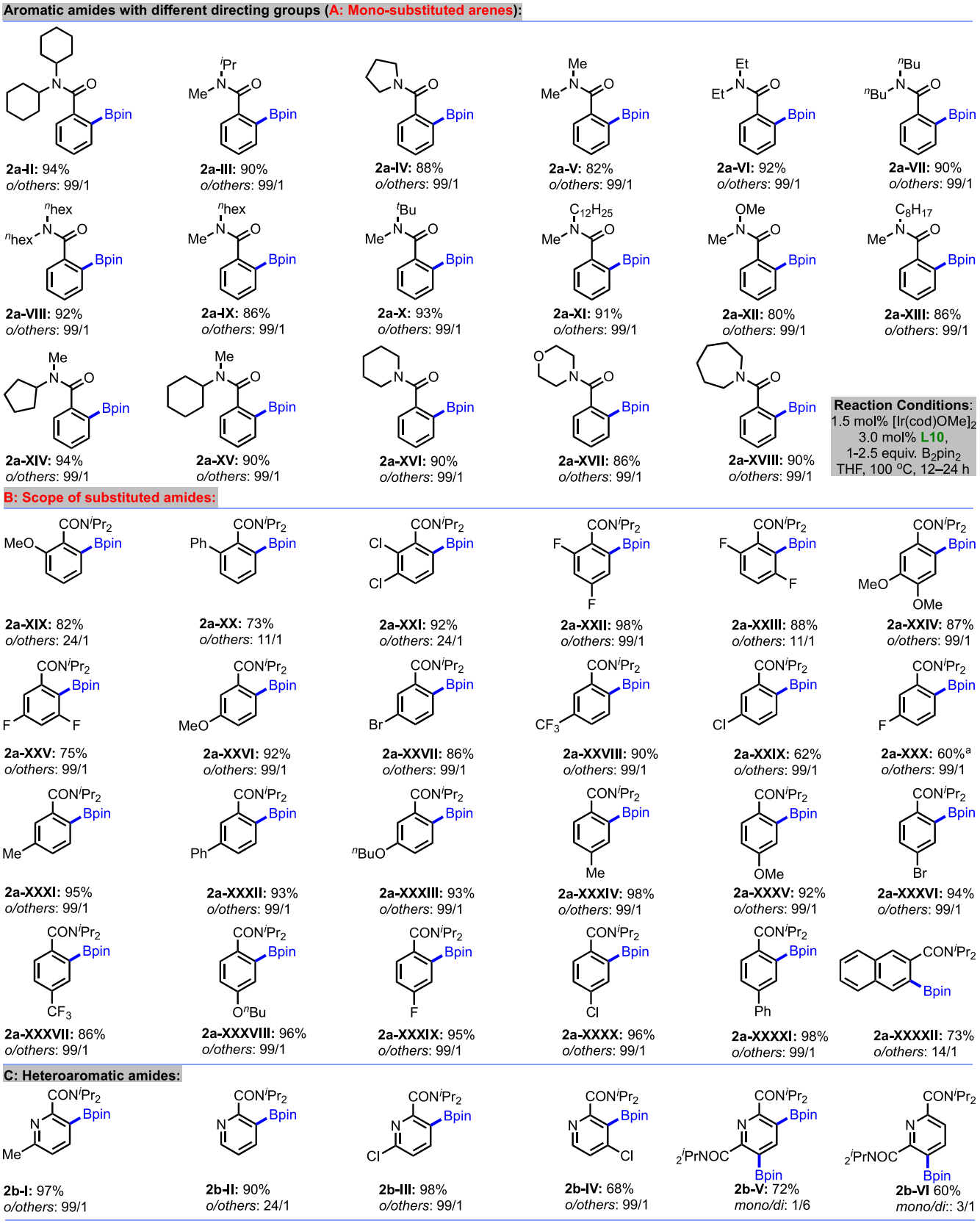

Figure 4. Substrates scope. (A) Monosubstituted aromatic amides with different *N*,*N*-di substitution. (B) differently substituted aromatic amides. (C) Scope of heteroaromatic substrates.

yield of the pure borylated products. The selectivity and yield of the products were not hampered by the electronic nature and position of the substituents. Moreover, we noticed that the C−H bonds of the phenyl ring attached at the *ortho*-, *meta*-, and *para*-position of amides were untouched under the employed borylation conditions (entries **2a-XX**, **2a-XXXII**,

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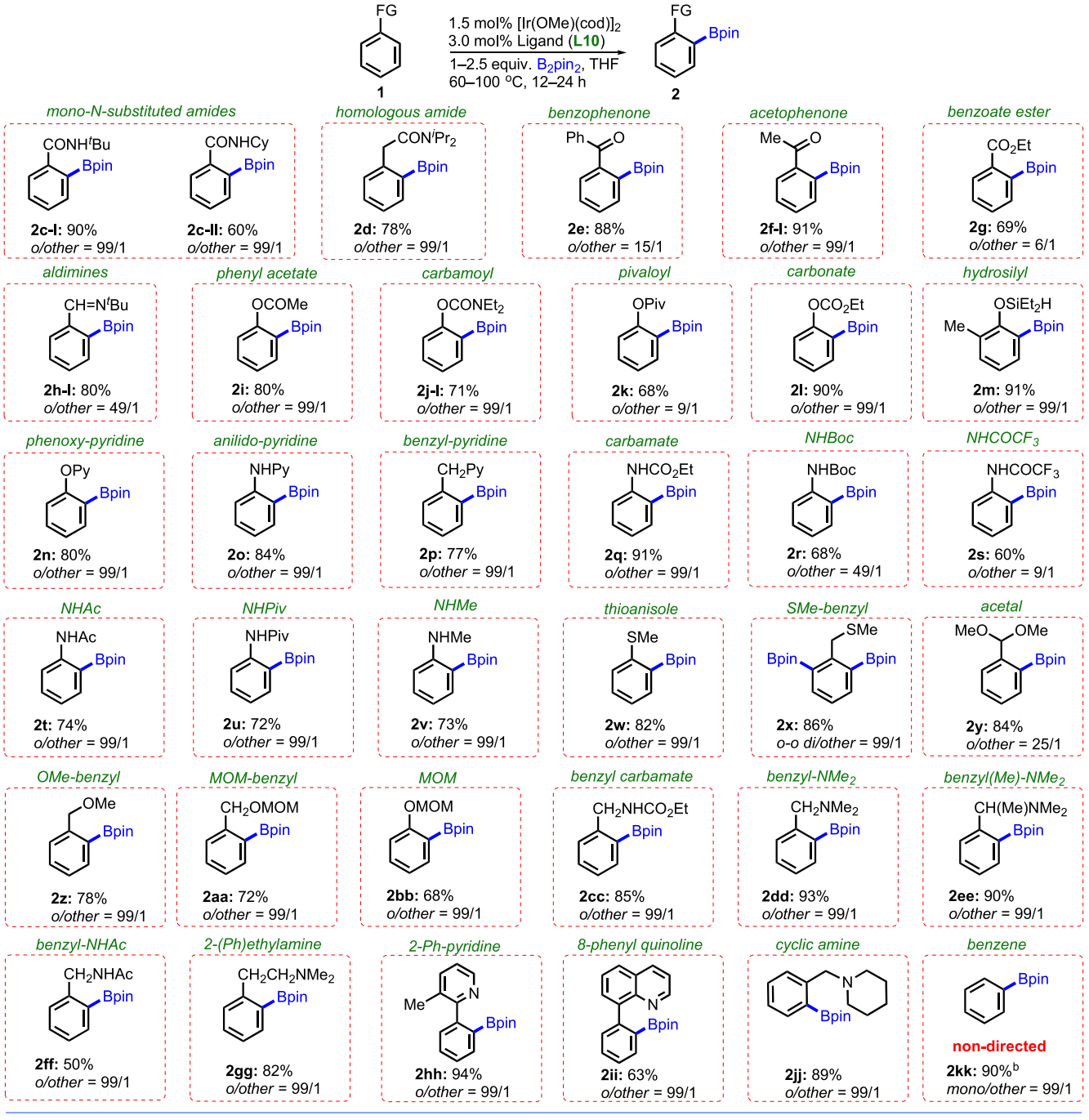

Figure 5. Substrates scope for the directed C−H borylation and nondirected benzene borylation. [a]Reaction scale = 0.2 mmol. GC/MS ratios are given using dodecane as internal standard. For detailed isolation of the products and isomer ratios; see the Supporting Information. [b]The reaction was performed using benzene as the substrate and solvent. The same reaction performed using 1.0 equiv of benzene as substrate in THF afforded 38% isolated mono-borylated product; see the Supporting Information for details.

and **2a-XXXXI**). Furthermore, several fluorinated amides were selectively borylated at the *ortho*-position with respect to the amide directing groups giving high yield of the products (entries **2a-XXII**, **2a-XXIII**, **2a-XXV**, **2a-XXX**, **2a-XXXIX**). Notably, all the borylated products are normally stable and can be stored at room temperature under air. Next, we performed borylations for several heterocyclic amides using *N*,*N*-diisopropyl group as the directing group (Figure 4C, **2b-I**–**2b-VI**). We observed that all the heterocyclic amides afforded high selectivity and yields of the pure products.

After successful borylation of a wide number of aromatic and heteroaromatic amides with varied directing groups using the developed catalytic conditions, we next decided to investigate other types of substrates class. Apart from the aforementioned aromatic and heteroaromatic amides, we found that the established method demonstrated remarkable efficiency with respect to the selectivity and reactivity for a vast number of substrate classes irrespective of various FG/DG gave good to excellent isolated yield of the borylated compounds. (Figure 5).

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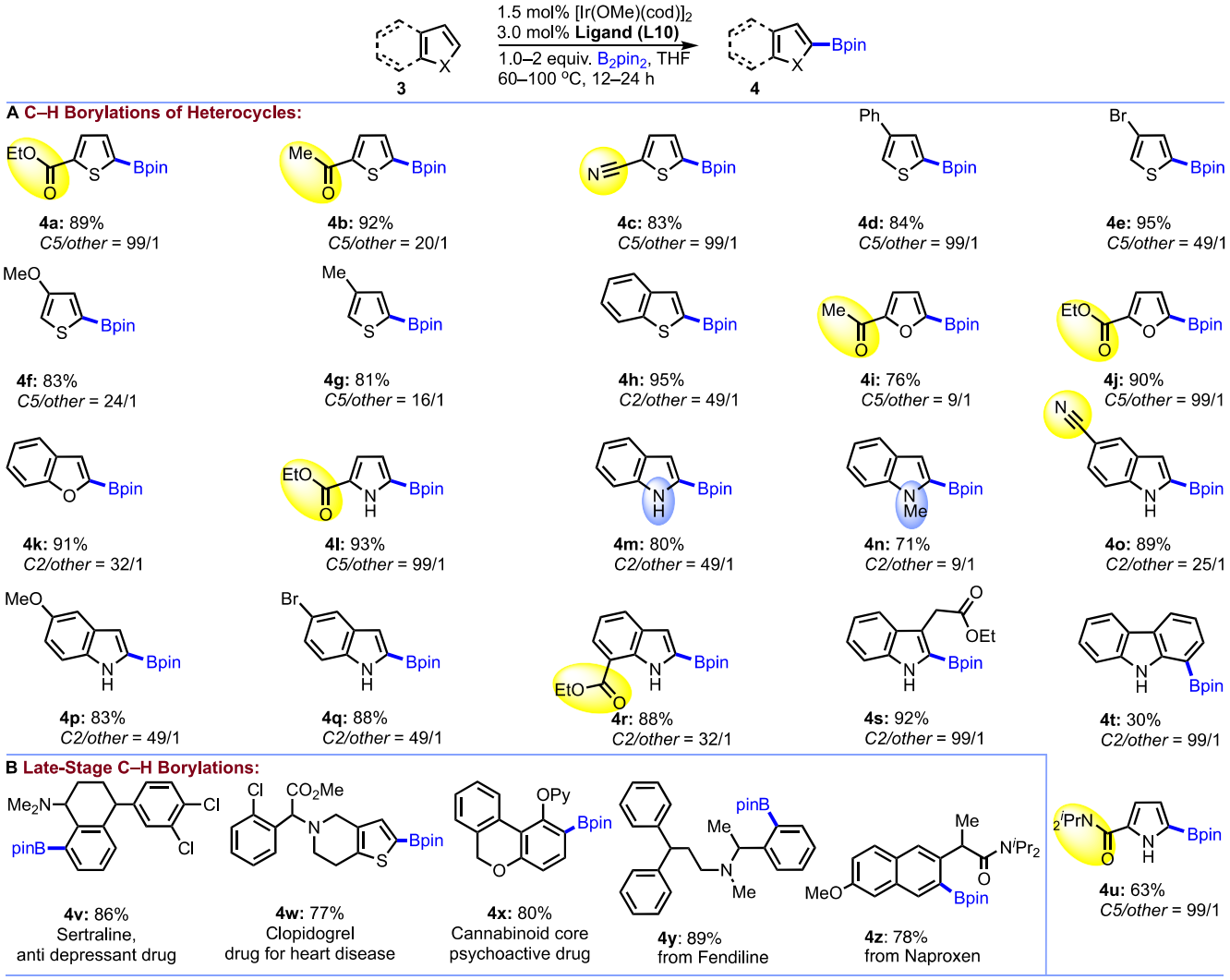

Figure 6. (A) Substrates scope for site-selective C−H borylation of heterocycles. (B) Late-stage C−H borylation of important molecules. Reaction scale = 0.2 mmol; GC/MS ratios are given using dodecane as internal standard. Isolated yields are given. See the Supporting Information for details.

For example, we first investigated the scope of that type of arenes featuring CONHR (R = alkyl) FG/DG, which afforded excellent selectivity and good to high yields of the products (**2c-I** and **2c-II**). Substrate having an intervening methylene group in between arene and CON^{i}Pr$_2$ (**2d**) exhibited excellent *ortho*-selectivity (>99/1) providing 78% isolated yield. However, substrates bearing the ketone functionalities were also well-tolerated in our developed reaction conditions (**2e** and **2f-I**). For instance, benzophenone (**1e**), acetophenone (**1f-I**), and many other ketone-containing arenes smoothly underwent C−H borylation providing high selectivity and yields (see the Supporting Information for details). On the contrary, whereas substituted ethyl benzoate (see the Supporting Information for details) retains perfect *ortho*-selectivity (>99/1) with high yield of the borylated product, the simple ethyl benzoate (**2g**) afforded moderate *ortho*-selectivity (>6/1) with a slightly compromised yield of the borylated product (69%). Next, we targeted the substrate class featuring the imine functionality for the suitability toward the borylation conditions (**2h**). To our delight, a wide range of substrates were found to be compatible under the developed catalytic system, for example entry **1h-I** (see the Supporting Information for other substrate's scope). The use of acetate functionality on arene (**2i**) resulted in a high level of selectivity (>99/1) with good yield (80%). In contrast, while the arene having a carbamoyl directing group (**2j-I**) resulted in high *ortho*-selectivity (>99/1), the arene featuring a pivaloyl directing group (**2k**) afforded *ortho*-selectivity up to 9/1. A substrate containing a carbonate functionality (**2l**) exhibited excellent *ortho*-selectivity and reactivity, affording 90% of the *ortho*-borylated product. While the catalytic system of Hartwig's first Ir-catalyzed directed *ortho*-borylation of arene featuring a hydrosilyl group[27] is different to some degree from our developed catalyst system, we found that the same arene bearing a hydrosilyl group (**2m**) yielded 91% isolated pure product as well as 99/1 *ortho*-selectivity. Notably, by altering the functionality from hydrosilyl to phenoxy pyridine (**2n**), the developed catalytic conditions did not see any difference in *ortho*-selectivity (99/1). Replacing the phenoxy pyridine group to the anilido pyridine group gave 84% isolated of the *ortho*-borylated product (**2o**). Moreover, arene with a benzylpyridine (being electronically different) proceeded borylation under the same conditions providing 99/1 *ortho*-selectivity and 77% isolated yield of the borylated product (**2p**). Next, we explored the possibility of the borylation on arene featuring a carbamate

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directing group (**2q**), which resulted in 91% yield of the product with *ortho*-selectivity of 99/1.

While an unsubstituted arene with a NHBoc directing group is known to give nonselective borylation via an outer-sphere[50] mechanism (although substituted arenes with an NHBoc directing group afforded excellent *ortho*-selectivity), our developed conditions exhibited promising outcomes that afforded 49/1 *ortho*-selectivity (**2r**), but when the directing group of arene was changed from NHBoc to $NHCOCF_3$ (**2s**), the *ortho*-selectivity went down to 9/1, although the yield was comparable. The reason for the relatively low *ortho*-selectivity might be due to the different electronic nature of the directing groups. Importantly, these electronic differences were not observed for the arenes featuring the directing groups NHAc (**2t**), NHPiv (**2u**), and NHMe (**2v**). Both the substrate classes afforded the same *ortho*-selectivity (99/1) and yield of the pure isolated borylated products. The less reactive arenes having thiomethyl (**2w**) and benzylthiomethyl (**2x**) are also borylated selectively using this catalytic system, underlining the robustness of the method. Notably, despite of the different electronic nature of these two different directing groups, both the substrate classes resulted in complete *ortho*-selectivity (99/1), although, the benzyl thioanisole gave *ortho*-,*ortho*-diborylations. The efficiency of the catalytic system is also highlighted with the arenes bearing dimethyl acetal (**2y**), OMe-benzyl (**2z**), MOM-benzyl (**2aa**), and OMOM (**2bb**) functionalities, where the borylation occurred via coordination with the sp^3 oxygen atom. Moreover, arenes containing electron-deficient and electron-rich benzylamine functionalities (**2cc**, **2dd**, **2ee**, and **2ff**) appeared to be very general for the preparation of the synthetically useful borylation products in moderate to good yields. In sharp contrast, increasing the chain length from benzyl (**2dd**) to homobenzyl (**2gg**), the borylation also proceeded smoothly giving a high yield of the borylated product. The borylation of 2-phenylpyridine (**2hh**) and 8-phenylquinoline (**2ii**) also proceeded smoothly affording a single isomer. The borylation of arene featuring a cyclic amine as the directing group (**2jj**) also delivered the directed *ortho*-product with excellent selectivity (99/1). Thus, it is evident that arenes featuring numerous types of functionalities with different electronics and steric properties (**2a-I**–**2jj**) could successfully be borylated with high *ortho*-selectivity and yield using a single catalytic conditions.

Apart from these directed C–H borylation methods, we became interested in seeing what would happen for non-directed C–H borylation, especially for those substrates that do not have good directing groups. For that reason, we first performed a borylation of benzene and observed that borylation proceed smoothly and gave a monoborylated product (**2kk**) in 90% isolated yield (based on B_2pin_2 as limiting agent).

Site-Selective C–H Borylation of Heterocyclic Molecules. We then investigated various heterocyclic molecules under our developed conditions. Needless to mention, heterocyclic aromatics are commonly found in drug candidates because of their inherent properties to improve solubility and lower lipophilicity of drug molecules.[85] One of the key challenges[86−93] in the application of C–H borylation is realizing a method for controlling the positional selectivity of heterocyclic molecules. Thus, we focused on the positionally selective C–H borylation of the heterocyclic molecules using our developed catalytic system (Figure 6A). First, we tested the C–H borylation of various 2-substituted thiophenes and observed that these substrates (**3a**, **3b**, and **3c**) undergo regioselective C5 borylation with excellent yields. In this context, it deserves mentioning that the ester, ketone, and cyano groups attached with the five-membered heterocycles completely failed to show their directing effect as compared to the arenes bearing these groups. We did not observe any borylated products next to the ester, ketone, and cyano groups of these heterocycles. Importantly, this is also in sharp contrast to the results with the silica-supported phosphine ligands (Silica-SMAP-Ir),[88] which delivered the Bpin group at the position adjacent to the ester group. We then focused on borylations of C3-substituted thiophenes (**3d**–**3g**) that are known to give nonselective borylations.[94] To our delight, our developed conditions resulted in borylation exclusively at the C5 position (**4d**–**4g**). Moreover, we saw that benzothiophene (**3h**) afforded C2-selective borylation with high yield. Similarly, the borylation of the 2-substituted furans (**3i** and **3j**) and pyrrole (**3l**) occurred at the C5 position as the major products regardless of the existence of the ester and ketone directing groups. Similar to benzothiophene (**3h**), benzofuran (**3k**) undergoes borylation to deliver the corresponding C5 borylated products in good yields. Importantly, whereas traditional Ir-catalyzed borylation of simple indole (**3m**) and *N*-methylindole (**3n**) are known to undergo borylation at the C2 and C3 position, respectively, our method did not differentiate whether the indole *N*-atom is free or protected: Both resulted exclusively the C2 borylated products. Accordingly, other indoles with various substitutions (**3o**–**3s**) produce the C2-borylated products. The method is also compatible for the carbazole (**3t**) borylation. Notably, while arene-bearing amide directing groups direct borylation at the *ortho*-position (for example, **2a-I**–**2d**), a five-membered heteroarene having an amide directing group did not show any directing effect to give the borylation product next to the amide group. Instead, borylation occurred at the 5-position of the pyrrole ring via inherently directed fashion (Figure 6A, **4u**).[95]

Late-Stage Borylation. We next turned our attention toward the late-stage C–H bond borylation[96] of pharmaceutically and medicinally important molecules. While late-stage modification and functionalization are always important[97] for the discovery of new drugs and drug-like molecules, it is also difficult to selectively functionalize a particular C–H bond of a complex molecule. Delightfully, our developed catalytic system demonstrated that it could be successfully applied for the late stage borylation of various important molecules, and some of them are listed in Figure 6B. For example, even in the presence of so many similar C–H bonds, sertraline (**3v**, antidepressant agent), clopidogrel (**3w**, drug used for heart disease at high risk), cannabinoid core (**3x**, psychoactive drug), fendiline (**3y**, drug for calcium channel blocker, used as antihypertensive drug), and naproxen (**3z**, NSAIDs) are selectively borylated, which exclusively yielded one isomer with good yields.

Directed C(sp^3)–H Borylation. Next, we became interested to determine the efficiency of our developed catalytic system for the borylation of strong C(sp^3)–H bonds (Figure 7). Thus, when a reaction was performed with the substrate (**5a**) under the developed catalytic conditions, it afforded the corresponding C(sp^3)–H borylated product (**6a**) in 84% isolated yield. Employing the same set of reaction conditions, a number of six-membered nitrogen heterocycles were borylated that afforded the C(sp^3)–H borylated products with high isolated yield (entries **6b**–**6d**).

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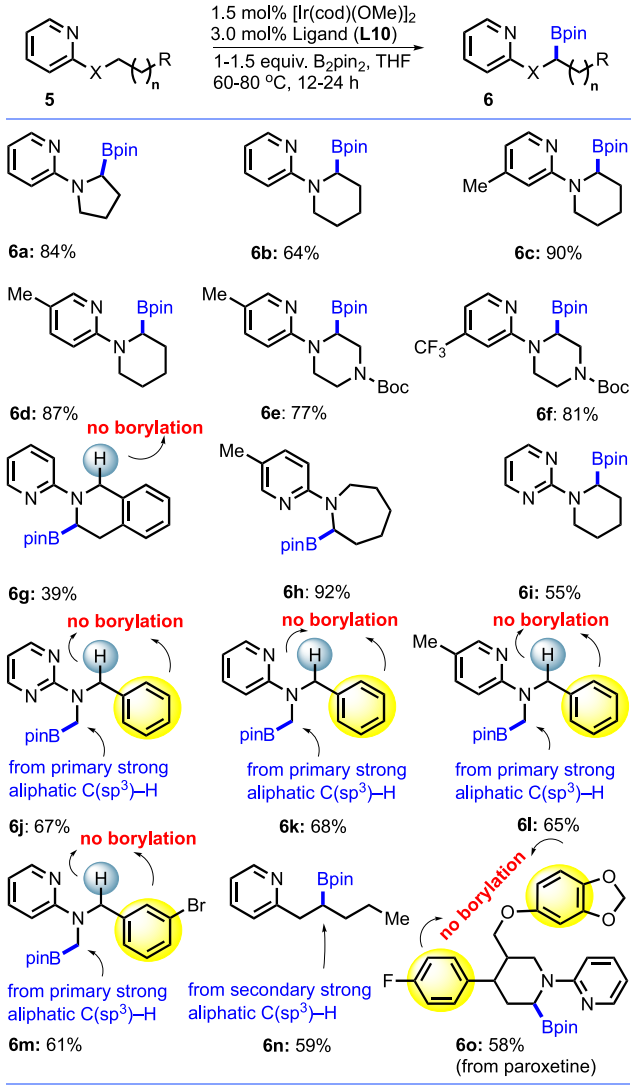

Figure 7. C(sp^3)–H borylations of aliphatic strong C(sp^3)–H bonds of challenging substrates. Reaction scale = 0.2 mmol. Isolated yields are given. See the Supporting Information for details.

In all cases, only a single isomer was observed that demonstrates the highly selective nature of the developed catalytic systems. Likewise, selective C(sp^3)–H borylations were performed with the complex substrates (**5e**) and (**5f**) that delivered a single isomer with high yield of the products. Substrate (**5g**) featuring two different aliphatic C(sp^3)–H bonds (that may afford mixture of products) also underwent selective C(sp^3)–H borylation delivering a single isomer (**6g**) in 39% yield. Interestingly, increasing the ring size of this C(sp^3)–H borylation from five- to six- to seven-membered, as in the case of the azepane ring system (**5h**), we achieved 92% isolated yield of the C(sp^3)–H borylated product (**6h**). Replacing the directing group of the substrate from pyridine to pyrimidine, the borylation also occurred successfully.

For example, substrate (**5i**) bearing a pyrimidine directing group smoothly underwent borylation that gave 55% borylated product (**6i**). Moreover, we found that with employment of the developed catalyst, substrates featuring several electronically distinct C–H bonds underwent C(sp^3)–H borylation in a highly selective fashion without touching the other C–H bonds of the substrates. For instance, a substrate (**5j**) having two electronically distinct aliphatic strong C(sp^3)–H bonds (primary C–H and secondary C–H bonds) and several C(sp^2)–H arene bonds, yet the developed catalyst exhibited excellent level of selectivity for aliphatic primary C(sp^3)–H bond (**6j**). Similarly, the catalytic activity of the developed system has been demonstrated with various other substrates (**5k**–**5m**) that selectively borylated at the primary C(sp^3)–H bonds gives good isolated yield of the products (**6k**–**6m**). However, using the developed catalyst, an alkyl chain featuring a nonactivated C(sp^3)–H bond was borylated that provided 59% isolated yield of the product as a single isomer (**6n**).

To showcase the utility and efficiency of the developed catalytic system, a marketed drug paroxetine (**5o**, antidepressant) was successfully borylated at the C(sp^3)–H bond with high selectivity (without affecting the other so many C–H bonds of the molecule including the reactive arene C–H bonds) using a pyridine as the directing group that afforded 58% isolated yield of the product (**6o**). We next intended to measure the performance in terms of selectivity and reactivity of the two newly developed catalysts (**CB1** and **CB2**) directly in the C(sp^2)–H and C(sp^3)–H borylations instead of mixing **L10** ligand with $[Ir(cod)(OMe)]_2$ and $[Ir(cod)Cl]_2$. Accordingly, borylations were performed with the substrates (**1a-l** and **5k**), and we observed that both the catalysts (**CB1** and **CB2**) yielded quantitative product formation without compromising the selectivity and reactivity (Figure 8).

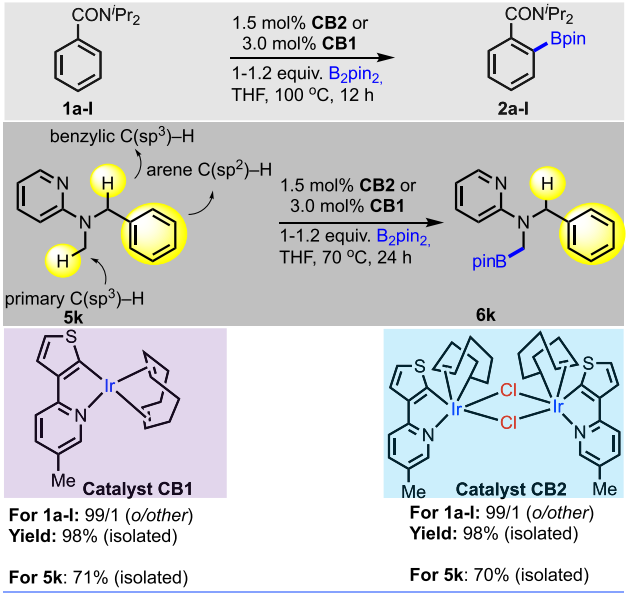

Figure 8. Comparative studies of C(sp^2)–H and C(sp^3)–H borylations by developed catalysts **CB1** and **CB2**.

C–H Borylation in Open Air Using CB2 Catalyst. Iridium-catalyzed C–H borylations are an extremely important synthetic method, but use of inert atmospheric conditions is necessary to perform these reactions. Thus, C–H borylation reactions without the presence of inert atmosphere is always a great challenge although extremely desirable.

Considering this challenge and difficulty, we next planned to use the developed air-stable catalyst (**CB2**) directly in the C(sp^2)–H and C(sp^3)–H borylation reactions in open air in absence of continuous use of inert gases. Accordingly, we performed the borylations in open air for several substrates (Figure 9) using catalyst **CB2**. Remarkably, we found that the

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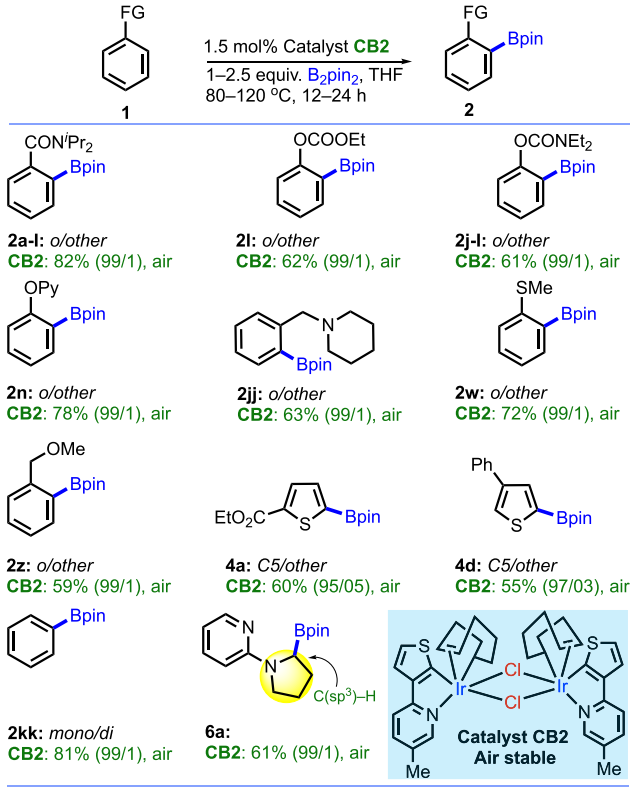

Figure 9. C(sp^2)−H and C(sp^3)−H borylations at open air using air-stable catalyst **CB2**.

tested substrates exhibited excellent selectivity and gave good isolated yields. Moreover, we have demonstrated that catalyst **CB2** can efficiently be employed for the C(sp^3)−H borylation such as that with substrate (**5a**) that afforded 61% isolated yield of the borylated product (**6a**). To demonstrate the scalability and practicality of the method using this air stable catalyst **CB2**, we performed a gram-scale reaction of substrate **1a-I**, which resulted in almost the same results (see the Supporting Information for details).

Mechanistic Studies. Next, we studied the reaction mechanism, and for that reason, we performed some preliminary experiments. On the basis of the crystal structures of the developed catalysts (**CB1** and **CB2**), we hypothesized that the **L10** ligand we employed acts as a bidentate ligand. Notably, a similar type of bidentate coordination between iridium and either a phosphine-silyl ligand or a pyridine-boryl ligand is described by Smith and Maleczka[34] and Li,[35] respectively. Despite these literature precedents, we envisioned that it would be interesting to verify whether **L10** ligand acts as a bidentate ligand or monodentate ligand owing to the two different types of coordination ability of **L10** ligand. Thus, we first intended to confirm whether an Ir(thienyl) bond in the catalysts remain intact during the course of the reaction.

The idea behind the hypothesis of ligand **L10** might act as a monodentate ligand lying on the basis that during the borylation the ligand may first undergo borylation[98] to generate another potential borylation ligand (**L18**), which eventually might serve as the ligand (Figure 10A). Following this hypothesis, borylation was performed with a designed ligand (**L19**) having a methyl group at the C2 position with substrate (**1a-I**), and we found that the reaction is completely nonselective, resulting in less than 10% conversion, which

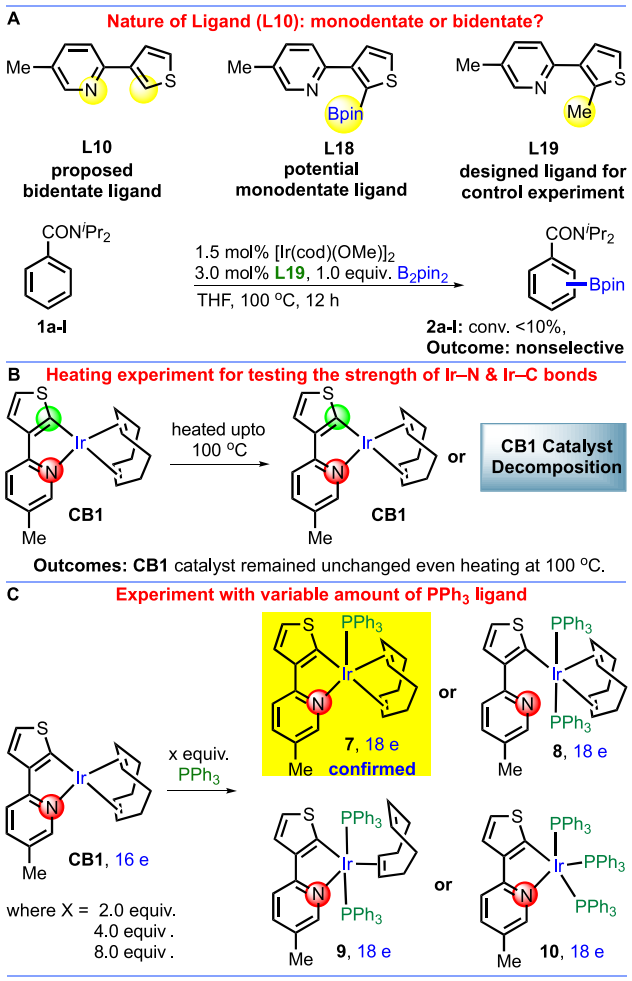

Figure 10. Control experiments for mechanistic studies.

confirms the Ir(thienyl) coordination of **L10** ligand. However, it does not provide conclusive evidence whether **L10** ligand acts as a bidentate or monodentate (hemilabile), since the weaker coordination site of the **L10** ligand is the pyridine fragment not the thienyl fragment. Thus, in order to get some idea about the metal−ligand bonds (hemilabile nature of **L10** ligand), we performed a heating experiment[99] with catalyst **CB1** hypothesizing that stable four-coordinated 16-electron catalyst **CB1** will either generate an unstable three-coordinated 14-electron species resulting the decomposition of **CB1** catalyst at high temperature (if the weaker N−Ir bond dissociates) or would be intact as it is (Figure 10B).

Following this hypothesis, we heated **CB1** catalyst at various temperatures up to 100 °C in C_6D_6 solution and recorded the NMR (Figure 11). We found that catalyst **CB1** remained unchanged even at 100 °C temperature. On the basis of these experimental findings, it may be concluded that the equilibrium favors the binding over the ligand dissociation of the pyridyl fragment. As a result, the binding over ligand dissociation at higher temperature indicates that the ligand might be acting as a bidentate type of ligand.

For further confirmation of the hemilabity of the Ir−N(pyridyl) coordination, we performed a ligand titration[100,101] experiment by adding external ligand (PPh_3) to catalyst **CB1** assuming that the hemilabile part of the ligand would undergo dissociation resulting several possible stable 18-electron complexes, such as 7−**10**, depending on the amount of

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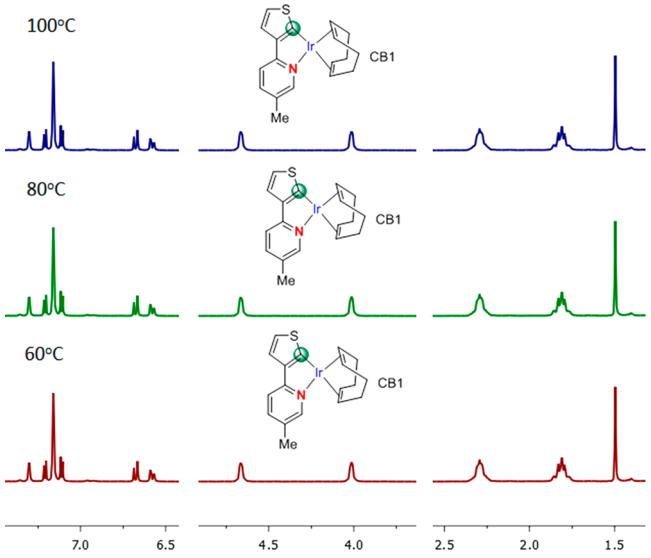

Figure 11. Stability of **CB1** catalyst in C_6D_6 at various temperatures.

externally added ligand (Figure 10C).We observed only the formation of complex **7** that was isolated and characterized by spectroscopic data. Moreover, we also observed that there is no change even after subsequent addition of PPh_3 (Figure 12, up

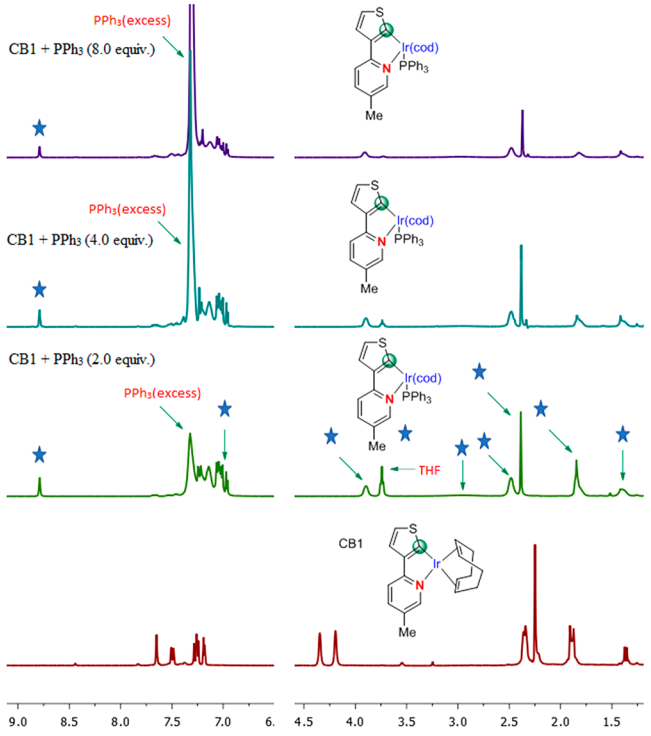

Figure 12. Control experiment of **CB1** catalyst with increasing amount of external ligand (PPh_3).

to 8.0 equiv of PPh_3). Thus, from all these experimental findings, it is evident that the developed (**L10**) ligand acts as a bidentate ligand and does not show hemilabile character.

Having identified the differential aspects of the ligand in the catalytic system (either monodentate or bidentate), we became interested to get more information about the catalytic intermediates. Accordingly, we performed an experiment between **CB1** catalyst and B_2pin_2 in C_6D_6 solution at room temperature for 48 h (Figure 13A) assuming that the reaction might generate four probable complexes, such as bis(boryl)Ir

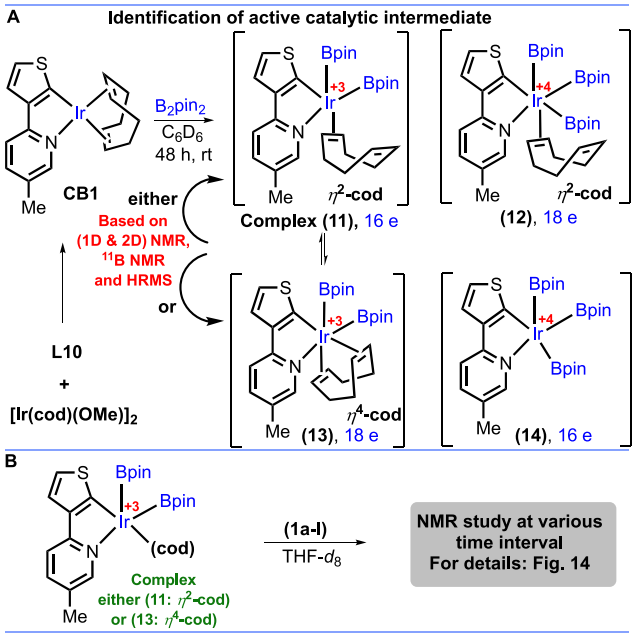

Figure 13. Mechanistic studies for active catalytic species. See Figure 14 for details.

complexes (**11**) and (**13**) and tris(boryl)Ir complexes (**12**) and (**14**). The possibility for the generation of the tris(boryl)Ir complexes (**12** and **14**) was ruled out considering the +4-oxidation state of the iridium metal in these complexes, which are uncommon in Ir-catalyzed C−H borylation. On the basis of the high-resolution mass spectrometry (HRMS) data,[102] it can be confirmed that the complex might be either a five-coordinated 16-electron bis(boryl)Ir species (**11**) or a six-coordinated 18-electron bis(boryl)Ir species (**13**). While the ^{11}B NMR data says the presence of the Ir−B bond, HRMS data confirms the presence of the bis(boryl)Ir complex; nevertheless, it was inconclusive whether the complex was either **11** or **13**. Moreover, it may also be assumed that the two complexes (**11** and **13**) might be in equilibrium, and if so, then it would be extremely difficult to identify (Figure 13A). Thus, in order to get some insight about these two complexes (**11** and **13**), we performed ^1H (1D selective gradient TOCSY and 1D selective gradient NOESY) and 2D NMR experiments in benzene-d_6 solvent and compared them with the reported data for a similar type of Ir complexes (see the Supporting Information for details). While the collective spectroscopic data and comparative ^1H NMR shift of the previously reported data (see the Supporting Information for details) indicate the possibility of the five-coordinated 16-electron bis(boryl)Ir complex (**11**), nevertheless, generation of the six-coordinated 18-electron bis(boryl)Ir complex (**13**) cannot be ruled out completely, and it may remain in equilibrium with complex **11**.

Finally, a stoichiometric C−H borylation was performed to see the complete reaction profile (Figures 13B and 14). In a J. Young NMR tube, a mixture of **CB1** catalyst and B_2pin_2 was stirred at room temperature for 5 min in THF-d_8, and ^1H NMR was recorded (Figure 14B), which was compared with the ^1H NMR data of **CB1** catalyst (Figure 14A). However, we did not see any progress of the reaction after 5 min.

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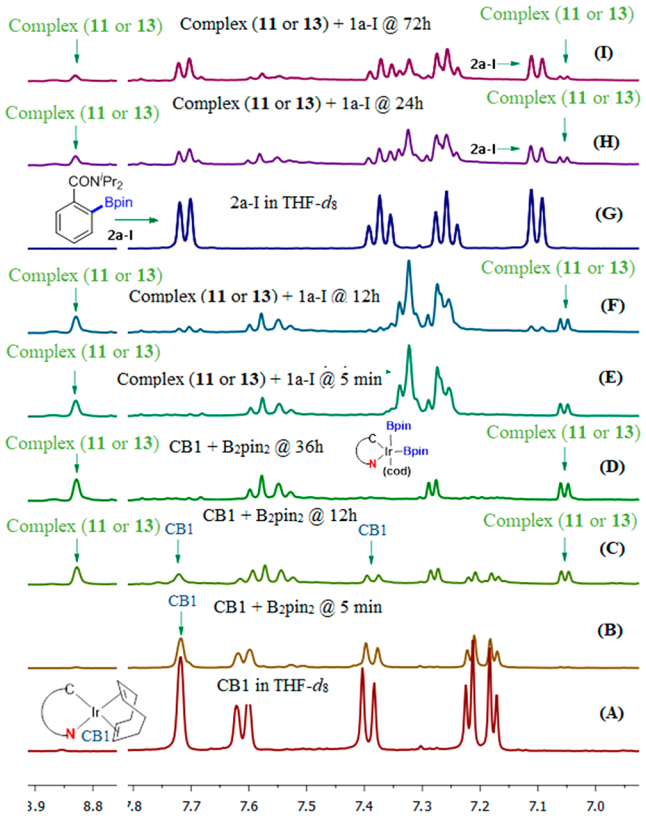

Figure 14. Detailed investigation of borylation with **CB1** catalyst.

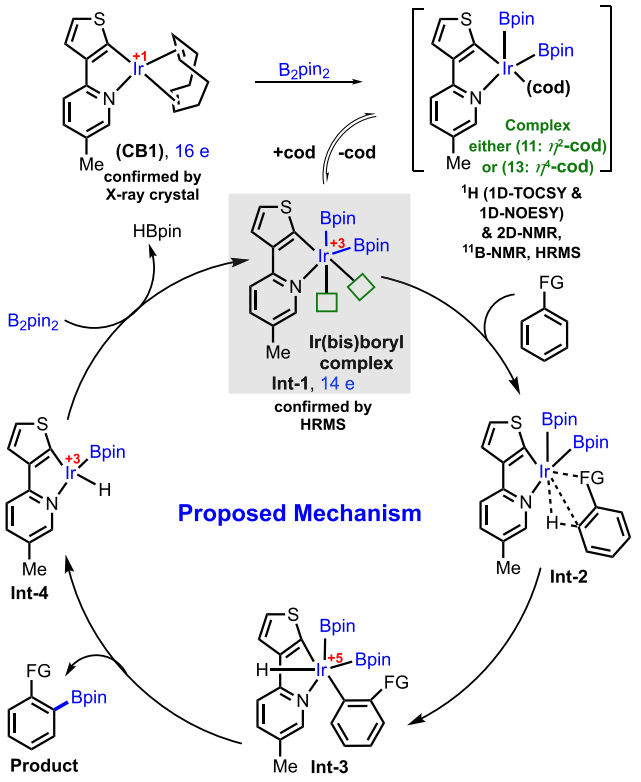

Figure 15. Proposed reaction mechanism.

Interestingly, after 12 h, we observed the generation of complex **11** or **13** (Figure 14C) at the expense of **CB1** catalyst, and full conversion was found after 36 h (Figure 14D). Next, in order to find out whether in situ generated complex **11** or **13** is the active catalyst or not, substrate (**1a-I**) was added into the NMR tube, and ^{1}H NMR was recorded at various time intervals (Figure 14F,H,I) and was again compared with the authentic ^{1}H NMR data of the pure product (**2a-I**, Figure 14G). We observed the formation of the borylated product (**2a-I**) gradually at the expense of the starting material. Moreover, we also noticed that even after 72 h, complex **11** or **13** did not decompose. Thus, from all these control experimental results, it may be concluded that **L10** ligand does not act as the hemilabile ligand (rather, it acts as a bidendate ligand) and that complex **11** or **13** is the key species for the in situ generation of the active catalytic species.

Thus, based on these experimental evidence and previous reported mechanism,[103] the proposed reaction mechanism is depicted in Figure 15. **CB1** catalyst undergoes oxidative addition of B_2pin_2 to generate complex **11** or **13**, which was identified by ^{1}H (1D-TOCSY, 1D-NOESY), 2D NMR, ^{11}B NMR, and HRMS data. Complex **11** or **13** may undergo a reversible COD dissociation to generate the Ir(bis)boryl complex (**Int-1**),[104] which was detected by the HRMS.[102] Next, the arene enter into the catalytic cycle by the coordination with its functional group and C−H bond activation occur (**Int-2**). Subsequently, following a routine reductive elimination to deliver the product and activation of the B_2pin_2 closes the catalytic cycle.

CONCLUSION

In conclusion, we have discovered a new class of C−H activation and borylation catalysts that show remarkable efficiency for the directed site-selective C(sp^2)−H and C(sp^3)−H borylation of diverse classes of substrates, such as a wide number of arenes featuring numerous FG/DG, heteroaromatic molecules with various FG, aliphatic substrates, and important molecules for late-stage borylation. The developed catalysts contain Ir−C(thienyl) or Ir−C(furyl) anionic ligands instead of the diimine containing neutral ligands that are normally used in the standard C−H borylation conditions. These catalysts are synthesized in one step, scalable, and exhibited excellent reactivity as well as selectivity. It has been shown that the use of these catalysts show excellent reactivity and selectivity for diverse classes of aromatic substrates, a number of heterocyclic systems with different ring size and functionality. In contrast, the developed catalysts proved to be efficient for a large number of aliphatic substrates for selective C(sp^3)−H bond borylations. Moreover, a number of late-stage C−H functionalizations have been described for various important molecules using the same catalysts. While both catalysts **CB1** and **CB2** are extremely useful for borylation, catalyst **CB2** is stable even under open air for the C(sp^2)−H and C(sp^3)−H borylations under atmospheric conditions (without the need of inert conditions) without the loss of any selectivity. We envision that this developed method will give a general solution for selective functionalization of arenes, heteroarnes, aliphatic systems and will be useful for the industrial deployment. Mechanistic investigations indicate that the active catalytic intermediate is the in situ generated Ir(bis)boryl complex, and the attached ligand acts as bidentate ligand. Collectively, the developed method underlines the discovery of a new class of C−H borylation catalysts, and we

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do believe that this should find wide application in the context of C−H functionalization chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c13415.

Experimental details, characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 2002759 and 2002760 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

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Notes

The authors declare the following competing financial interest(s): We have filed a patent for this work including the ligands and catalysts.

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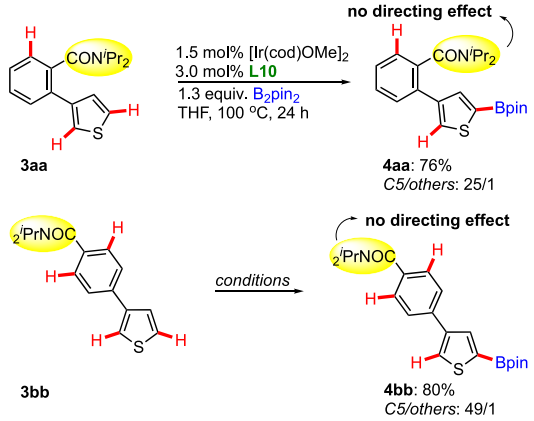

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