Selective *ortho* C–H activation of Pyridines Directed by Lewis Acidic Boron of PBP Pincer Iridium Complexes

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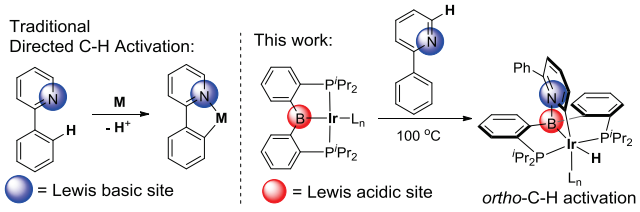
Supporting Information Placeholder

ABSTRACT: Transition-metal mediated C-H functionalization has emerged as a powerful method in the chemistry relevant to the synthesis of pharmaceuticals, agrochemicals, and advanced materials. Since organic molecules typically contain multiple types of C-H bonds, selective C-H functionalization is a major ongoing challenge. C-H activation of heteroatom-containing organics has often been approached via the use of the directing effect, whereby the coordination to the basic heteroatom directs the reactive metal center to a specific C-H bond. We now report a different approach where the nitrogen donor in pyridine derivatives coordinates to an ancillary Lewis-acidic boryl ligand directly attached to the metal (iridium) center, as opposed to the metal itself. This topology directs the iridium center to activate a different C-H bond than in the cases of directing donor coordination to the metal. Using this strategy, we demonstrate *ortho*-regiospecific C-H activation of pyridines and an example of the subsequent functionalization via C-C bond formation.

Selective transition-metal catalyzed C-H functionalization is a promising strategy for the expedient synthesis of complex organic molecules in service to biochemistry, medicinal chemistry, and materials science.[1] Selective C-H activation and functionalization of heterocycles, such as pyridine derivatives, presents special challenges and opportunities.[2] The pyridine nitrogen site is a generally good ligand with affinity for many types of transition metals. On the one hand, this presents a problem because coordination of the pyridine substrate can deactivate the metal center by blocking the coordination sites necessary for activating C-H bonds. This often means that C-H activation methods are only effective with pyridine derivatives in which the coordinating ability is diminished by *ortho*-substitution. On the other hand, the nitrogen coordination ability can be judiciously exploited to direct the metal center to specific C-H bonds in the pyridine-containing substrate. This approach generally relies on the formation of five- and sometimes six-membered rings as a result of the directed C-H activation,[3] and is common for many other heteroatom-containing directing groups besides pyridine.[4] Directed activation of the more distant C-H bonds has been tackled with more elaborate templating groups.[5] Such directed approaches generally only operate[6] when two coordination sites can be made available at the metal – one for the coordination of the directing group first and another for subsequent C-H activation. Selective C-H functionalization of certain pyridines has also been demonstrated based on the C-H bond acidity.[7]

We envisioned an alternative situation where the metal center intended to effect C-H activation would be complemented by a directly attached Lewis-acidic auxiliary ligand, such as a boryl (i.e., an sp^2-hybridized boron with the metal as one of its three substituents). We surmised that coordination of a pyridine nitrogen to the boron would lead to the direction of C-H activation to the *ortho*-position in pyridine, even when other C-H bonds are available (Chart 1).

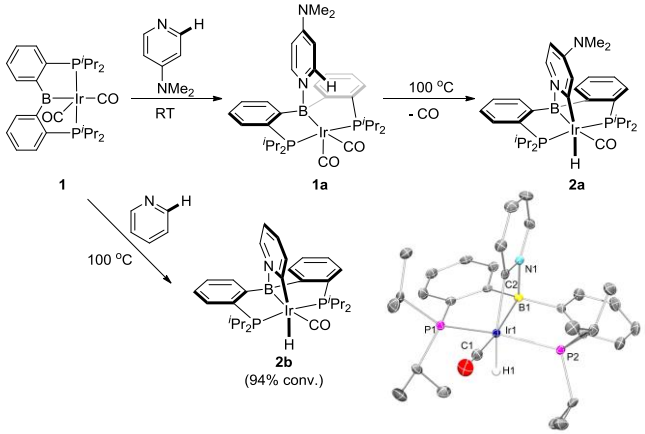
Chart 1. Contrast in C-H activation directed by binding of the directing group to the metal vs to the Lewis-acidic boron in the ligand.



We recently reported on the synthesis of $(PBP)Ir(CO)_2$ (**1**)[8] and other complexes of a new diarylboryl/bis(phosphine) PBP pincer ligand[9] derived from a triarylboron/bis(phosphine) precursor.[10] Compound **1** appeared generally well-suited to the task, possessing an Ir center in a low oxidation state (+1) suitable for insertion into C-H bonds, and a trigonal planar boron center of the diarylboryl donor. The diarylboron center in this PBP ligand is likely to be more Lewis acidic than other literature examples of PBP pincer ligands, which are either derived from boron clusters or possess π-donating amino substituents on the boron.[11] We have also previously established that substituents can easily migrate between Ir and B in a variety of (PBP)Ir complexes, which was promising for accessing pyridine binding to boron even in potential intermediates with formally unsaturated Ir.[8,9a]

The addition of 1 or 2 equiv of pyridine to the C_6D_6 solution of **1** showed only small changes in the peak width and the chemical shifts of the $^{31}P\{^1H\}$, ^1H, and $^{11}B\{^1H\}$ NMR signals. However, the addition of the more basic 4-dimethylaminopyridine (DMAP) led to the observation of a dramatic upfield shift of the $^{11}B\{^1H\}$ NMR resonance from 99.4 to 15.7 ppm, indicative of the transformation of an sp^2-hybridized boron in **1** to an sp^3-hybridized boron in **1a** (Scheme 1). The observation of two CO stretching bands (ν_{CO} = 1937 and 1881 cm^{-1}) by IR spectroscopy was also consistent with the formulation of **1a**. Similar binding of pyridine to the boryl of the diphenylphosphino variant of the same type PBP ligand in a palladium complex was reported by the Tauchert group recently.[12]

Scheme 1. C-H activation reactions starting from the dicarbonyl complex **1**.[a]



[a] POV-Ray rendition of the ORTEP drawing (50% thermal ellipsoids) of **2b** showing selected atom labeling. Hydrogen atoms are omitted for clarity with the exception of the hydrogen bound to iridium. Selected bond distances (Å) and angles (°): Ir1–B1, 2.285(2); Ir1–C1, 1.920(2); Ir1–C2, 2.078(2); Ir1–P1, 2.2797(6); Ir1–P2, 2.2849(6); Ir1–H1, 1.50(3); B1–Ir1–C1, 168.22(8); P1–Ir1–P2, 152.371(18).

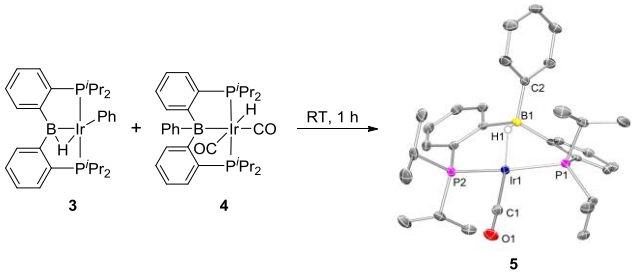
We were delighted to discover that thermolysis of compound **1a** at 100 °C for 18 h resulted in near-complete conversion to product **2a** (Scheme 1). The identification of compound **2a** was supported by the spectroscopic data. In the ^{1}H NMR spectrum, a single hydride resonance (δ -14.02 ppm, t, $^{3}J_{HP}$ = 19.3 Hz), and three aromatic resonances from the dimethylaminopyridyl group were observed. The ^{11}B{^{1}H} resonance at 1.0 ppm indicated a 4-coordinate, sp^{3}-hybridized boron center, while a single CO stretching band in the IR spectrum (ν_{CO} = 1924 cm^{-1}) was consistent with a single CO remaining in the complex.

Although complete formation of adducts similar to **1a** was not observed with pyridine itself,[13] a similar C-H activation product **2b** with strict selectivity for the 2-CH bond activation was obtained upon thermolysis of **1** at 100 °C with pyridine (Scheme 1). The same type of product was observed in the reactions with a variety of pyridine derivatives.[13] These reactions were more sluggish than with DMAP, and required days or weeks for high conversion, especially for pyridines with substituents in the 2-position. These products contained spectroscopic features similar to **2a**.

The solid-state structure of **2b** was determined by single-crystal X-ray diffractometry (Scheme 1). The Ir1–B1 distance (2.285(2) Å) in **2b** is considerably longer than the distance between Ir and the sp^{2}-hybridized, trigonal-planar boryl center in **1** (ca 2.14 Å).[8] Elongation of the metal-boryl bond by ca. 0.2 Å upon coordination of pyridine has been reported by Braunschweig et al. for $(C_5H_5)Fe(CO)_2BCl_2$ and its pyridine adduct.[14] The structure of **2b** contains a four-membered metallacycle composed of Ir, B, N, and C atoms. Formation of four-membered rings is often disfavored for reasons of strain. However, in this case, the geometry of the four-membered ring is trapezoidal because the C-N bond (1.360(3) Å) is almost 1 Å shorter than the Ir-B bond (2.285(2) Å). This means that the angles at N and C do not have to deviate strongly from the expected sp^{2}-hybridized geometry in contrast to the deviations inherent to organic four-membered rings. The substantial elongation of the Ir-B distance upon binding of pyridine is likely what favors C-H activation in the *ortho*-position. This basis for selectivity is similar to the activations of pyridines by $Ru_3(CO)_{12}$, where two Ru centers connected by a direct bond perform the role of Ir (C-H activation) and B (binding of N).[15] It is also possible that coordination of the pyridine nitrogen to a Lewis acid favors *ortho*-CH activation electronically, as well.[16] On the other hand, coordination of pyridine to Lewis acids has also been used to direct C-H activation away from the *ortho*-position on steric grounds.[2c,17]

The Ir center in **1** is saturated, with an 18-electron valence shell count, and dissociation of CO would be required to enable it to undergo insertion into a C-H bond. Continuous production of **2** in a closed system generates free CO, which may act as an inhibitor partly responsible for the sluggishness of the reactions. Performing the reaction of **1** with pyridine under 1 atm of CO resulted in slower conversion to **2b** than under 1 atm of argon. To circumvent the inhibition problem, we synthesized complex **5** by comproportionation of **3** and **4** (Scheme 2). **5** can be viewed as an adduct of (PBP)Ir(CO) with benzene, and liberation of benzene was expected to lead to the *in situ* production of (PBP)Ir(CO), without generating a reaction inhibitor in the process. Structural and spectroscopic data indicated that **5** possesses a square-planar, monovalent Ir center that contains a hydride bridging Ir and B (Scheme 2). The Ir1···B1 distance of 2.621(3) Å is beyond the range of plausible Ir-B interactions and thus the central donor of the pincer can be viewed as a hydridotriarylborate. The upfield chemical shift (1.4 ppm) observed for **5** in the ^{11}B{^{1}H} NMR spectrum is consistent with an sp^{3}-hybridized boron in a borate and the broad hydride resonance at -4.09 ppm in the ^{1}H NMR spectrum is likewise consistent with a boron-bound hydride. This hydridoborate form of the PBP ligand has been previously described by the Peters group in Fe and Co complexes.[18] As our previous work,[8,9a] and the synthesis of **5** itself show, the migration of an aryl or a hydride between B and Ir in these systems is quite easily accessible, so rearrangement of **5** into an intermediate with both Ph and H on Ir in order for reductive elimination (RE) of benzene to proceed is a reasonable proposition.

Scheme 2. Synthesis of **5** by comproportionation of **3** with **4**.[a]



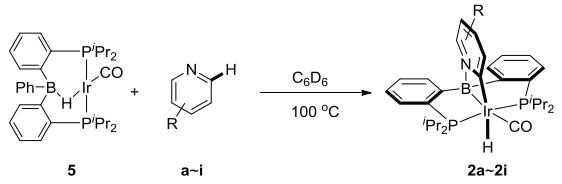
[a] POV-Ray rendition of the ORTEP drawing (50% thermal ellipsoids) of **5** showing selected atom labeling. Hydrogen atoms are omitted for clarity with the exception of the hydrogen bound to iridium. Selected bond distances (Å) and angles (°): Ir1–B1, 2.621(3); Ir1–C1, 1.824(3); Ir1–H1, 1.64(3); Ir1–P1, 2.2929(6); Ir1–P2, 2.2801(6); C1–Ir1–H1, 164.4(10); P1–Ir1–P2, 161.10(2).

Complex **5** proved to be a much more effective precursor for pyridine C-H activation reactions, as shown in Table 1. At 100 °C, the reactions were typically completed in 2 h, with only 2-arylpyridines (entries 8 and 9) requiring 6 h. No adduct formation was observed at RT between **5** and DMAP. Lesser differences between the reactions times with **5** (vs **1**) suggest that the rate-limiting step for many of them is not dependent on the basicity of the particular pyridine derivative, and is likely the elimination of benzene from **5**. The selectivity for the *ortho*-CH position is remarkable. 2-Picoline (entry 4) offers the potential to activate a C-H bond in the methyl group and form a five-membered metallacycle, but this is not observed. Quinoline (entry 7) offers an alternative C(sp^{2})-H bond in the 8-position to make a five-membered metallacycle, yet the 2-position (product **2g**, structure also deter-

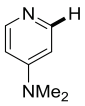
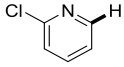
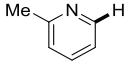
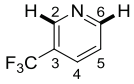
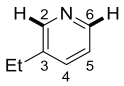
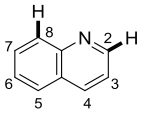
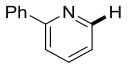
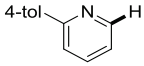
mined by X-ray diffractometry)[13] is preferred in a ca. 97:3 ratio. 2-Phenylpyridine is a classical substrate in traditional directed C-H activation,[4a] with the binding of the pyridine to the metal directing C-H activation to the *ortho*-CH bond of the phenyl group, however, only activation of the *ortho*-CH on the pyridine ring is observed in the reaction with **5** (entry 8, and entry 9 for 2-*p*-tolylpyridine). The *ortho*-C-Cl bond in 2-chloropyridine was untouched in the formation of **2c** (entry 3). In the case of *meta*-substituted pyridines (entries 5 and 6), activation of either C2 or C6 C-H bonds was recorded. Interestingly, the 90:10 mixture of **2e** and **2e'** obtained upon the initial 2 h of thermolysis evolved into an 81:19 mixture after heating for another 18 h, in the first indication of the reversibility of C-H activation. The CF_3 group in **2e**/**2e'** and the Et group in **2f**/**2f'** should be exerting quite different electronic influence on the C2 and C6 positions. The fact that the system does not definitively "choose" one of these *ortho*-positions over the other may signify that the selectivity is largely based on the topology and connectivity and not on the electronic factors or the steric pressure from the substituents.

We have also carried out the thermolysis of **5** with 2,6-lutidine (2 h at 100 °C in C_6D_6), which lacks *ortho*-CH bonds. A mixture of products resulted, including **1**, **3**, **5**, and others. The $^{31}P\{^1H\}$ spectrum of this mixture appeared to contain the same signals as observed upon thermolysis of **5** in C_6D_6 without any added substrate, suggesting that no 2,6-lutidine-derived Ir products had formed. The free 2,6-lutidine in the mixture after thermolysis had undergone partial deuteration of the *meta* (11%) and *para* (33%) positions, likely from reversible, non-directed C-H activation, followed by H/D exchange of the putative Ir-H with C_6D_6. However, when **5** was thermolyzed in the presence of 1 equiv of pyridine and 10 equiv of 2,6-lutidine, clean formation of **1b** was observed, with no evidence of the deuteration of 2,6-lutidine. This suggests that while activation of various C-H bonds is possible, it is not competitive with the activation of the *ortho*-CH bonds in pyridine.

Table 1. Selective C–H activation of pyridines using 5.[a]



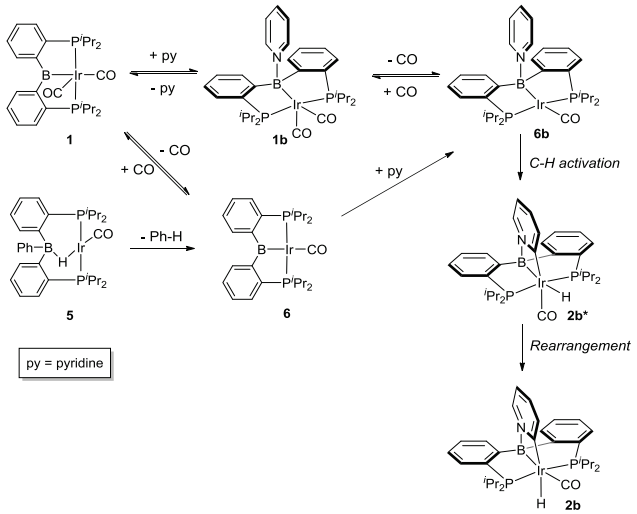
5 **a~i** **2a~2i**

entry	pyridines	product	time (h)	Yield (%)[b]
1		2a	2	95 (81)[c]
2		2b	2	99 (80)[c]
3		2c	2	79 (81)[c]
4		2d	2	93 (81)[c]
5		2e+2e'	2	98 [90:10][d]
6		2f+2f'	2	99 [56:44][d]
7		2g+2g'	2	99 [97:3][e]
8		2h	6	83
9		2i	6	92

[a] Reaction conditions: Ir complex **5** (0.020 mmol) and pyridine (0.020 mmol) in C_6D_6 at 100 °C. [b] Yields were determined by 1H NMR spectroscopy with hexamethyldisiloxane (0.010 mmol) as an internal standard. [c] Isolated yield (0.20 mmol scale). [d] The ratio of C6:C2 selectivity. [e] The ratio of C2:C8 selectivity.

Scheme 3 depicts a proposed mechanism for the *ortho*-CH activation based on our observations so far, illustrated for the parent pyridine. We propose that pyridine binding might occur before or after CO dissociation from **1**, possibly depending on how strongly basic the pyridine substrate is. Starting with **5**, pyridine binding most likely occurs after loss of benzene from **5**, presumed to be favorable, unlike the loss of CO from **1**. After the formation of the common intermediate **6b** (not observed), insertion of the Ir center into the *ortho* C–H bond of pyridine should produce isomer **2b*** with a *cis*-disposition of the H and $C_{pyridyl}$ ligands about Ir. The formation of the observed product **2b** therefore must require an additional isomerization taking place after insertion of Ir into the C-H bond. The mechanism of such isomerization is not presently known, but may involve reversible dissociation of CO or one of the phosphine arms.

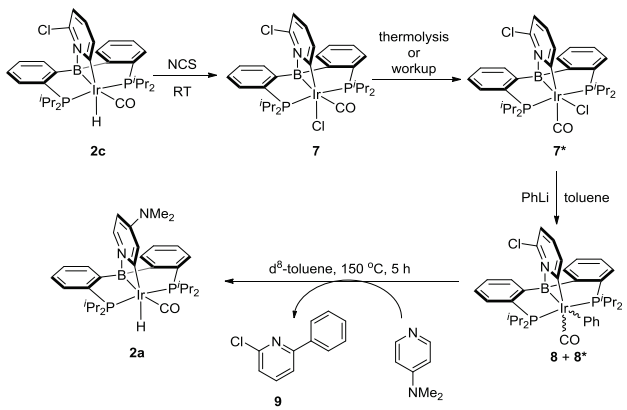
Scheme 3. Proposed C-H activation mechanism.



Square-planar, four coordinate complexes of Ir, and in particular (pincer)Ir(CO) complexes are generally not kinetically well-suited for the participation in concerted OA of C-H bonds.[19] From this perspective, the implied insertion of Ir into a C-H bond (**6b**-**2b***) may appear debatable, however, a few factors may be in play. Firstly, this is an intramolecular reaction with a great degree of prearrangement in the molecule. Secondly, the sp^3 hybridization of the boron center in **6b** should enable a more facile distortion away from perfect square-planar geometry about Ir. Thirdly, it is possible that the highly electron-releasing nature of the pyridine-bound boryl ligand in **6b** makes the Ir center in **6b** sufficiently electronically different from square-planar Ir centers bound to the more electronegative elements in place of boron. Lastly, we cannot rule out dissociation of one of the ligands in **6b**.

In order to demonstrate the potential of this approach in synthesis, we set out to carry out a functionalization of the initially activated substrate. Compound **2** was quantitatively converted to **7** (Scheme 4) by the action of N-chlorosuccinimide (NCS). The initially formed **7** isomerized into **7*** upon workup. The chloride in **7*** was then replaced by a phenyl group in a reaction with PhLi, producing a mixture of isomers **8** and **8***. Thermolysis of the mixture of **8** and **8*** in the presence of added DMAP (for trapping the Ir by-product) for 5 h at 150 °C resulted in the production of free 2-chloro-6-phenylpyridine (97%), and **2a** (96%), as determined *in situ* by NMR integration vs a standard.

Scheme 4. Synthesis of 2-Chloro-6-phenylpyriddine (9) via C-H Activation Followed by Arylation



Ortho C–H arylation of pyridine derivatives has been described previously using Cu,[7] Rh,[20] Au,[21] Ag,[22] Fe,[23] and Ni.[24] However, the method we report here is distinguished by that it possesses both the regiospecificity for the *ortho*-position and the consistent performance with differently substituted pyridines, especially with regard to the nature and the presence of the substituent in the other *ortho*-position. In addition, iridium may be advantageous for C-H activation in the presence of carbon-halogen bonds,[25] as demonstrated here in the C-H functionalization of 2-chloropyridine. While the exact system in this work is not capable of catalytic turnover, it showcases a new approach to the selective activation of pyridine derivatives that is not guided by the nature of the substrate but by the use of a Lewis-acidic supporting ligand.

ASSOCIATED CONTENT

Supporting Information

Details of experiments, characterization data, X-ray diffraction studies, and pictorial NMR and IR spectra. The supporting information is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interests.

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