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meta-Selective C–H Borylation of Benzamides and Pyridines by an Iridium–Lewis Acid Bifunctional Catalyst

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ABSTRACT: We report herein the iridium-catalyzed *meta*-selective C–H borylation of benzamides by using a newly designed 2,2′-bipyridine (bpy) ligand bearing an alkylaluminum biphenoxide moiety. We also demonstrate the iridium-catalyzed C3-selective C–H borylation of pyridine with a 1,10-phenanthroline (Phen) ligand bearing an alkylborane moiety. It is proposed that the Lewis acid–base interaction between the Lewis acid moiety and the aminocarbonyl group or the sp^2-hybridized nitrogen atom accelerates the reaction and controls the site-selectivity.

INTRODUCTION

Transition metal (TM)-catalyzed C–H functionalization is one of the most efficient ways to construct C–C and C–heteroatom bonds and is now becoming a powerful tool for complex molecule synthesis.[1] To develop practical C–H functionalization methods, controlling the site-selectivity among similar C–H bonds is one of the key challenges.[2] In nature, enzymes functionalize certain C–H bonds with excellent site-selectivity through precise placing of substrates via non-covalent interactions.[3] Such an interaction[4] has inspired the development of artificial catalyst systems for site-selective C(sp^3)–H oxidation reactions, which are based on hydrophobic interaction,[5] Lewis acid–base interaction,[6] or hydrogen-bonding interaction.[7]

The non-covalent interaction strategies were extended to iridium-catalyzed arene C–H borylation reactions[8] in recent years because of the broad utilities of the resulting arylboronic esters.[8g,9] For example, hydrogen-bonding has been employed to control *ortho*-[10] and *meta*-selective[11] C–H borylation reactions. And ion-pair interaction has been used to control *ortho*-[12] and *meta*-selective[13] C–H borylation very recently.

Lewis acid (LA) catalysts,[14] as well as Lewis acid–Lewis base (LA–LB) bifunctional catalysts[15] have been widely used to control reaction selectivities. Recent researches of TM–LA bifunctional catalysts,[16] which contain TM and LA in one catalyst molecule, have shown its potential to control the site-selectivity of TM-catalyzed C–H functionalizations at the remote positions.[17] The application of TM–LA bifunctional catalysts in site-selective arene C–H borylation, however, was limited in a few reports, which included *ortho*-selective C–H borylation of aryl sulfides by an Ir–B catalyst (Figure 1a),[18] *meta*-selective C–H borylation of arylaldimines by an Ir–B catalyst (Figure 1b),[19] and *para*-selective C–H borylation of aryl esters by an Ir–K catalyst (Figure 1c).[20] Although great progresses have been made so far, this strategy is still in its infancy, and new TM–LA bimetallic catalyst systems are desired for other substrate classes and/or complementary site-selectivities.

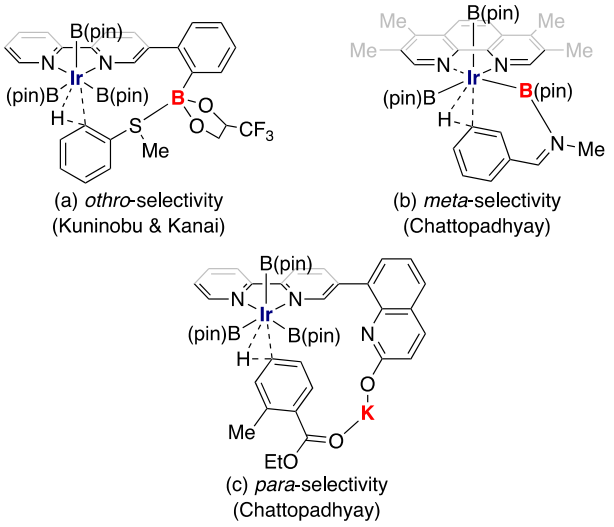


Figure 1. Site-control of arene C–H borylation reactions using TM–LA bimetallic catalysts.

We are interested in the site-control of C–H functionalization by cooperative TM/LA catalysis for a decade.[21] Recently, we have developed the *para*-selective C–H borylation of benzamides and pyridines by cooperative Ir/Al catalysis (Figure 2).[22] We found the aluminum LA catalysts dramatically accelerate the reaction by generating an LA–benzamide or –pyridine adduct. This fact inspired us to design an Ir–LA bifunctional catalyst for the *meta*-selective C–H borylation reaction of benzamides and pyridines. Herein, we report a newly designed LA-containing N-based bidentate ligands to realize these transformations.[24] The designed bifunctional catalyst includes: (1) A bpy or phenanthroline moiety for ligating Ir; (2) A linker which arranges the positions of the metal centers to control the site-selectivity[25]; (3) A Lewis acidic alkylaluminum- or alkylboron-based moiety to recognize aminocarbonyl groups or sp^2-hybridized nitrogen and accelerate the reactions through electronic activation of the (hetero)arene substrates (Figure 2).[22]

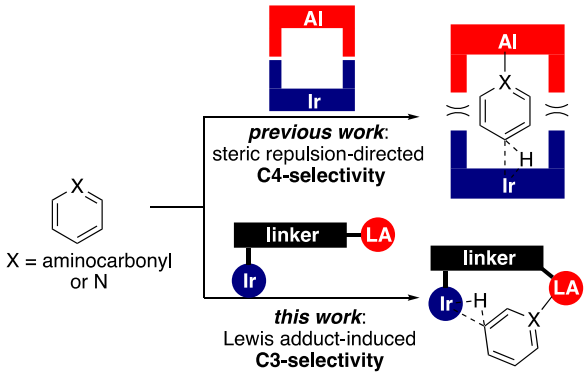


Figure 2. Design of Ir–LA bifunctional catalysts for meta-selective C–H borylation of benzamides.

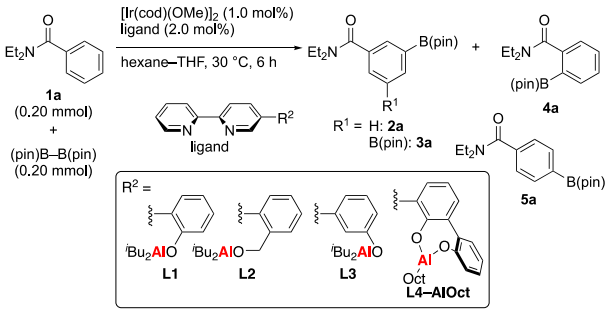
RESULTS AND DISCUSSION

In the beginning, we designed **L1**, which has a 2-hydroxyphenyl linker with a diisobutylaluminum LA moiety, as a ligand for the Ir-catalyzed C–H borylation of benzamides. The borylation reaction of **1a** using dtbpy as a ligand gave a mixture of *meta*- (**2a**) and *para*-borylation (**5a**) products including *m*,*m'*-double borylation (**3a**) in an almost statistic ratio, suggesting that the aminocarbonyl group served as an electronically neutral substituent (entry 1 of Table 1).[26] On the other hand, **L1** dramatically increased the *meta*-selectivity (entry 2) though a small amount of *ortho*-borylation product was also noted. **L2** which has a longer and more flexible linker gave lower *meta*-selectivity than **L1** (entry 3). **L3** bearing a 3-hydroxyphenyl linker gave a much lower yield without any enhancement of selectivity (entry 4). Finally, **L4–AlOct** was designed because we thought the rigid aluminum-biphenoxide moiety would limit the flexibility of the Al center and block the *ortho*-borylation. To our delight, the combination of an Ir pre-catalyst and **L4–AlOct** controlled the C–H borylation exclusively at the meta-position with good reactivity (entry 5). The reaction using a larger amount (0.30 mmol) of the borylating agent gave higher yields (entry 6).

By using **L4-AlOct** as a ligand, we applied our method to *ortho*-mono-substituted benzamides. Generally, the reaction proceeded at the C5 position. *N*,*N*-Diethyl-2-methylbenzamide (**1b**) gave good yield and selectivity at 60 °C. 2-Phenyl-substituted benzamide **1c** gave good selectivity notably without any borylation at the phenyl substituent. The catalyst-control overrode the observed electronically induced site-selectivity by a methoxy group, which accelerates the borylation at its *meta*-position,[26] to give **2d** with good selectivity. 2-Halogenated substrates **1e** and **1f** also gave good selectivity when hexane was used as a solvent. The low reactivity and/or selectivity of these reactions in THF/hexane could be ascribed to competitive coordination of THF to Al. Electron-withdrawing substituents like CF_3 and OCF_3 (**1g** and **1h**) were also tolerated and gave good yields and selectivities using hexane as a solvent. The reaction of dicarbonyl substrate **1i** exclusively proceeded at the position *meta* to the aminocarbonyl group.

For *meta*-substituted benzamides, 3-fluoro-substituted benzamide **1j**, which gave a mixture of isomers under conventional conditions, was borylated at the C5 position exclusively by our method. Picolinamide **1k** gave C4-borylation product with good selectivity. The reaction of **1l** proceeded at the more steric hindered C5 position selectively probably because of a more favored electronic property at the C(5)–H bond than the C(4)–H. Our method could also be applied to arylphosphonate **1m**, which afforded a *meta*-C–H borylation product with good yield and selectivity. Notably the hydrogen-bonding strategy was not effective to control the site-selectivity for **1m**.[11a] Sunifiram(**1n**), which is an experimental antiamnesic drug, was tested as a substrate. Our catalyst successfully achieved the *meta*-C–H borylation with moderate yield and high selectivity. Other functionalized arenes like arylketones, benzoates and sulfonamides were not tolerated under these conditions probably due presumably to their weaker Lewis basicity (see Supporting Information). We indeed failed to observe the interaction between **L4–AlOct** and **1a** in NMR experiments. We suggest that the alkylaluminum biphenoxide is a weak LA but it could accelerate the reaction by stabilizing the transition state of the *meta*-C–H activation.

Table 1. Ligand Optimization

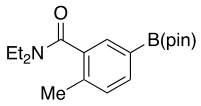
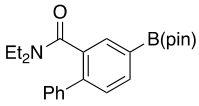
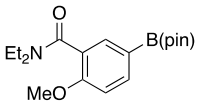
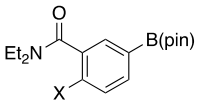
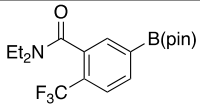
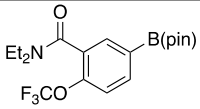
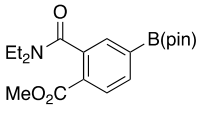
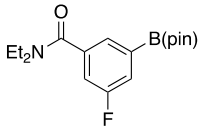
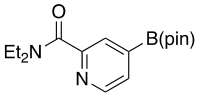
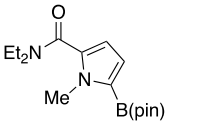
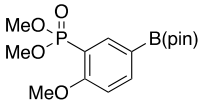
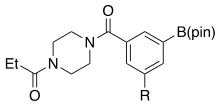


entry	ligand	selectivity[a]	yield (%)[a]			
		meta:*ortho*:*para*	**2a**	**3a**	**4a**	**5a**
1[b]	dtbpy	52:0:48	36	13	—	23
2[b]	**L1**	69:6:25	11	—	1	2
3[b]	**L2**	59:3:38	18	1	1	6
4[b]	**L3**	50:10:40	5	—	1	2
5	**L4–AlOct**	>99:0:0	36	3	—	—
6[c]	**L4–AlOct**	>99:0:0	46	49	—	—

[a] Estimated by GC analysis of the reaction mixtures using *n*-dodecane as an internal standard. Selectivity was calculated as following: *meta*:*ortho*:*para* = [(**2a**+**3a**)/2]:(**4a**/2):**5a**. [b] 4.0 mol% HB(pin) was used. [c] $B_2(pin)_2$ (0.30 mmol) was used under standard conditions.

To confirm the importance of the substrate–Al interaction for the observed high *meta*-selectivity and reactivity, we conducted the following experiments. The ligand **L4** and **L4-MOM**, which lack the Al moiety, gave a mixture of isomers as products without selectivity (Table 3, entry 1 vs. entries 2 and 3). Unlike the directed Ir–Al bifunctional catalyst (entry 1), the combination of Ir–**L1-MOM** catalyst and Al(^{n}Oct)$_3$ as LA increased the *ortho*-selectivity with much lower yield (entry 4). This result showed that the Al moiety located at an appropriate distance to the Ir center is crucial for the high site-selectivity as well as reactivity. Replacing the Al with K[20,27] resulted in lower selectivities and yields (entry 5). Finally, **L4–AlOct** showed the highest catalytic activity compared with other conditions, which indicated the acceleration effect of the Al LA catalyst (see Supporting Information).

Table 2. Scope of *meta*-Selective C–H Borylation[a]

 **2b**,[b] 97% (>99:1) (at 60 °C)	 **2c**, 77% (98:2)	 **2d**,[c] 98% (94:6)[d]; (68%, 22:78)[e]	 X = Cl[c]: **2e**, 99% (97:3) (at 50 °C); (96%, 40:60)[e] Br[c]: **2f**, 89% (>99:1) (at 80 °C); (93%, 37:63)[e]	 **2g**,[c] 97% (>99:1); (92%, 58:42)[e]	 **2h**,[c,f] 65% (90:10)
 **2i**, 98% (95:5); (94%, 72:28)[e]	 **2j**, 88% (>99:1); (56%, 56:44)[e]	 **2k**, 83% (85:15); (59%, 57:43)[e]	 **2l**, 95% (97:3); (>99%, 64:36)[e]	 **2m**, 84% (87:13)[d]; (87%, 18:82)	 **2n**, R = H, 24%; B(pin), 22% (93:7)[g]; (>99%, 56:44)[h]

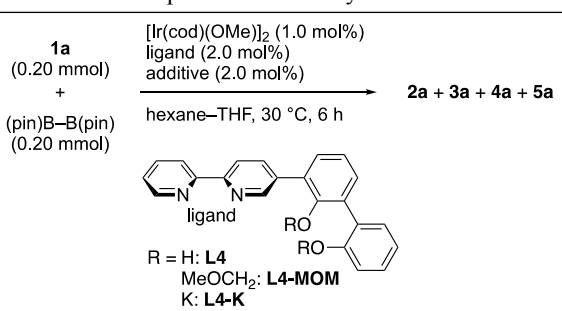
[a] Reactions were performed with an arene substrate (0.20 mmol), $B_2(pin)_2$ (0.20 mmol), $[Ir(cod)(OMe)]_2$ (1.0 mol%), and **L4-AlOct** (2.0 mol%) in THF (0.50 mL) and hexane (2.5 mL) at 30 °C for 18 h. Yields were calculated by crude ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. Isolated yields shown in Supporting Information are generally lower than the NMR yields due to loss and/or partial protodeboration of the products during purification. [b] Reaction run at 60 °C. [c] Reaction run using hexane (3.0 mL) as a solvent. [d] Selectivity was estimated based on ^{1}H NMR analysis of a crude product. [e] Reaction was performed under standard condition using dtbpy as ligand. Yields and selectivities were calculated by crude ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard. [f] Reaction run at 50 °C. [g] Reactions were performed with an arene substrate (1.0 mmol), $B_2(pin)_2$ (1.5 mmol), $[Ir(cod)(OMe)]_2$ (1.0 mol%), and **L4-AlOct** (2.0 mol%) in THF (13 mL) at 60 °C for 18 h. isolated yield. Selectivity was based on ^{1}H NMR. [h] Reactions were performed with an arene substrate (0.20 mmol), $B_2(pin)_2$ (0.30 mmol), $[Ir(cod)(OMe)]_2$ (1.0 mol%), and dtbpy (2.0 mol%) in THF (2.5 mL) at 60 °C for 18 h. Yield and selectivity were based on ^{1}H NMR with 1,3,5-trimethoxybenzene as an internal standard.

We then turned our attention to the C3-selective borylation of pyridine. Substituted pyridines play an important role in pharmaceuticals, natural products and functional materials. Among various methods for their syntheses, direct functionalization of a preformed pyridine core has an advantage in terms of step- and atom-economy.[28] C2-[29] and C4-selective[30] functionalization of pyridines has been studied extensively. However, C3-selective functionalization of pyridines remains challenging.

C3-Selective C–H functionalization of pyridine has been achieved by the aid of directed C–H metalation of pyridines.[31] Only a few ideal catalyst-controlled C3-selective C–H functionalization of pyridine have been developed. Yu and co-workers reported Pd-catalyzed olefination[32] and arylation.[33] Itami and co-workers reported Pd-catalyzed oxidative cross-coupling of pyridines with heteroarenes.[29m] Shi and Li reported Ir-catalyzed carbonyl addition.[34] Oestreich reported Ru-catalyzed C5-selective silylation of 2-arylpyridine.[35] Oro reported NHC–Ir(III)-catalyzed C5-selective silylation of 2-arylpyridine.[36]Although these reactions show good yield and site-selectivity, they suffer from a limited scope of pyridine substrates and lack versatility.

Pyridylboronic esters have served as useful building blocks in natural product synthesis.[37] Nevertheless, the C–H borylation of pyridine often suffers from poor site-selectivity,[38] when sterically less biased, and lower reactivity compared with arenes.[38a,b] Although we have developed the C4-selective borylation of pyridines recently by cooperative Ir/Al catalysis,[22] a C3-selective variant has been elusive.

Table 3. Control Experiments to Study the Mechanism



entry	ligand	additive	selectivity[a] (2a+3a)/4a/5a	yield (%)[a] 2a	3a
1	**L4–AlOct**	—	>99:0:0	36	3
2	**L4**	—	56:0:44	14	—
3	**L4–MOM**	—	63:3:34	23	<1
4	**L4–MOM**	$AlOct_3$	7:89:4	9	—
5	**L4–K**[b]	—	82:0:18	6	—

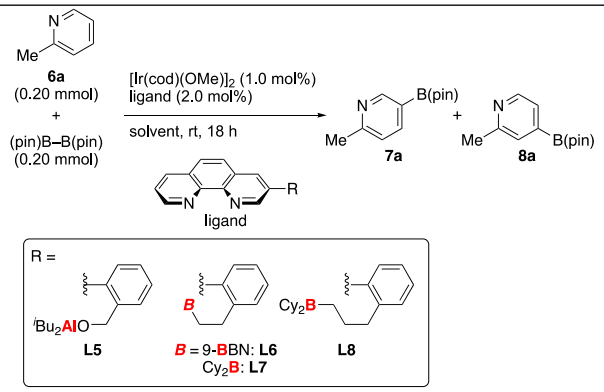
[a] Estimated by GC analysis of the reaction mixtures using *n*-dodecane as an internal standard. [b] **L4-K** was synthesized by

mixing **L4** with the same amount of KO^{t}Bu in THF at rt for 10 min and used as a solution.

At the onset, we studied the Ir-catalyzed borylation reaction of 2-picoline. The reactions using conventional ligands such as dtbpy or TMPhen gave a mixture of 4- and 5-boryl-2-picolines (Table 4, entries 1 and 2). We thus examined **L4-AlOct** but poor yield and site-selectivity resulted (entry 3). Al-tethered phenanthroline ligand **L5** gave a mixture in slightly higher yield (entry 4). We reasoned that the low conversion and site-selectivity with Al-tethered ligands might be ascribed to the weak Lewis acidity and thus prepared **L6**, the B-based LA moiety of which was introduced through hydroboration in situ. Gratifyingly, **L6** dramatically increased the C5-selectivity to 76% with a good yield (entry 5). Modification of the ligand by introducing BCy_2 as a LA unit further increased the selectivity to 97% (entry 6). **L8** bearing a BCy_2-substituted 2-propylphenyl side chain gave lower C5-selectivity compared with **L7** (entry 7). After a series of further screenings of reaction solvents and additives (see Supporting Information), we found that the combination of $[Ir(cod)(OMe)]_2$, **L7**, HB(pin) in a 1,4-dioxane solvent gave the highest C5-selectivity as well as yield (entry 8).

By using **L7** as a ligand, we investigated other pyridine derivatives (Table 5). Pyridine gave a mixture of C3-borylation and C3,C5-diborylation products with excellent overall C3-selectivity (**7b**). 2-Ethylpyridine **6c** also gave excellent site-selectivity and high yield. While compatibility of Lewis basic functionality with the LA co-catalysis was concerned, oxygen and nitrogen-containing substituents as well as carbonyl, ether, and amine functionalities were all tolerated to give the respective functionalized pyridylboronates (**7d**–**7i**). 2-Benzylpyridine (**6j**) gave C5-borylated product selectively by using **L7** without any borylation on the benzyl group. *ortho*-Silyl group was also tolerated (**7k**). Our catalyst could also borylate nicotine at the C5 position with a reaction rate much faster than with dtpby (**7l**). Our method, however, failed to control the site-selectivity of C2-halogen-, methoxy- or carbonyl-substituted pyridines possibly because the competitive non-selective undirected reaction pathway (see Supporting Information).

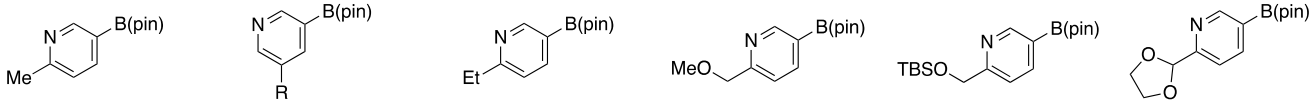
Table 4. Ligand Optimization



entry	ligand	solvent	**7a**/**8a**[a]	yield (%)[a]
1	dtbpy	hexane	27:73	71
2	TMPhen	hexane	42:58	88
3	**L4-AlOct**	1,4-dioxane	35:65	8
4	**L5**	1,4-dioxane	46:54	29
5	**L6**	hexane	76:24	83
6	**L7**	hexane	97:3	55
7	**L8**	hexane	71:29	82
8[b]	**L7**	1,4-dioxane	98:2	>99

[a] Estimated by GC analysis of the reaction mixtures using *n*-dodecane as an internal standard. [b] Reaction run in the presence of 4.0 mol% HB(pin) at rt for 2 h.

Table 5. Scope of C5(C3)-selective C–H Borylation of Pyridines[a]



7a, 89% (97:3)

7b,[b] R = H, 60%; B(pin), 16% (94:6)

7c, 96% (97:3)

7d, 98% (96:4)

7e, 99% (94:6)

7f, 97% (93:7)

7g, 99% (94:6)

7h, 92% (95:5)

7i, 99% (94:6)

7j, 99% (92:8); (87%, 27:73)[d,e]

7k, 99% (73:27)

7l, 99% (>99:1); (1%)[d,e]

7m,[c] R = H, 26%; B(pin), 24% (>99:1)

7n, >99% (60:40); (>99%, 2:98)[d,e]

7o, 99% (76:24); (48%, 46:54)[d,e]

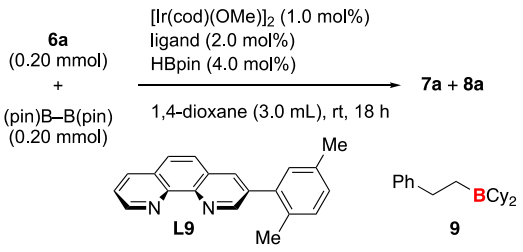
7p, 62% (>99:1)[f]

7q, 83% (71:29)[e]; (95%, 26:74)[d,e]

[a] Reactions were performed with a pyridine substrate (1.0 mmol), $B_2(pin)_2$ (1.0 mmol), $[Ir(OMe)(cod)]_2$ (1.0 mol%), HB(pin) (4.0 mol%) and **L7** (2.0 mol%) in dioxane (15 mL) at 25 °C for 18 h. Yields and site-selectivities were estimated by ^1H NMR analysis of crude products using dibromomethane as an internal standard. Isolated yields shown in Supporting Information are generally lower than the NMR yields due to loss and/or partial protodeboration of the products during purification. [b] Reaction run with 0.50 mmol $B_2(pin)_2$. [c] Reaction for 70 hours. [d] Reaction was performed under standard condition using dtbpy as a ligand. Yields and selectivities were calculated by crude ^1H NMR with 1,3,5-trimethoxybenzene as an internal standard. [e] Reaction run on a 0.20 mmol scale. [f] Reactions were performed with the substrate (1.0 mmol), $B_2(pin)_2$ (3.0 mmol), $[Ir(OMe)(cod)]_2$ (3.0 mol%), HB(pin) (12.0 mol%) and **L7** (6.0 mol%) in dioxane (45 mL) at 60 °C for 18 h. Isolated yield is shown.

For 4-substituted pyridines, the reaction of 4-picoline (**6m**) took place with excellent C3-selectivity, while no reaction proceeded when dtbpy was used as a ligand. This result demonstrated a significant rate-acceleration induced by our bifunctional Ir–B catalysis. Our catalyst could also direct the borylation of **6n** at the C6 position, while dtpby showed C7-selectivity. The method could be used to functionalize the pyridine-based polydentate ligands selectively at the C5 positions (**7o** and **7p**). The novel C5-selective C–H borylation reaction has been used to the late-stage functionalization of brompheniramine **7q**, which is an antihistamine drug. In sharp contrast to the conventional dtbpy ligand (95%, C5:C4 = 26:74), **L7** showed the C5-selectivity (83%, C5:C4 = 71:29).

Table 6. Control Experiments to Study the Mechanism



entry	ligand	additive	**7a**/**8a**[a]	yield (%)[a]
standard	**L7**	—	98:2	>99
1	**L9**	—	50:50	49
2	**L7**	DMAP (2.0 mol%)	47:53	77
3[b]	**L7**	—	94:6	92
4[c]	**L7**	—	93:7	91
5	**L7**	BEt_3 (0.20 mmol)	84:16	82
6	**L9**	**9** (2.0 mol%)	36:64	98

[a] Estimated by GC analysis of the reaction mixtures using *n*-dodecane as an internal standard. [b] Reaction run using 1.0 mL of 1,4-dioxane. [c] Reaction run at 60 °C.

We performed the following control experiments to confirm the designed directed pathway and the importance of Lewis acid-base interaction (Table 6). We revealed the following points: (1) Lewis acid-base interaction was essential for the site-selectivity because ligand **L9**, which was similar to **L7** in terms of its bulkiness but lacking the B moiety, gave a mixture of isomers as products (entry 1). The presence of a strong Lewis base such as DMAP hampered the LA function that dramatically decrease the site-selectivity and reactivity (entry 2 and Supporting Information); (2) Non-selective undirected reaction might compete with the desired site-selective pathway since increased concentration (entry 3) and/or increased reaction temperature (entry 4), as well as Et_3B as an additional LA reagent (entry 5), which could accelerate the undirected process, all decreased the site-selectivity; (3) The directed reaction was important for selectivity control because the combined use of **L9** and **9** did not improve the site-selectivity (entry 6). Finally, the interaction between pyridine or 3-borylpyridine with **L7** was confirmed by ^1H NMR analysis (see Supporting Information). We observed ligand exchange on the B moiety of **L7**, which was more rapid than a ^1H NMR time-scale, suggesting that the turnover of LA catalysis was not the rate-determine step of the reaction.

CONCLUSIONS

In summary, we have developed a new Ir–LA bifunctional catalyst for the *meta*-selective C–H borylation of benzamides and pyridines. The well-positioned Al or B recognizes the Lewis basic aminocarbonyl or sp^2-hybridized nitrogen to likely place the Ir catalyst center close to the reacting C3-position. Our method shows good tolerance toward a range of functional groups including Lewis basic ones without loss of site-selectivity. The unprecedented ligand design demonstrates the potential of the Lewis acid–base interaction as a powerful tool to control the site-selectivities of catalytic C–H functionalization reactions at the remote positions, which is potentially useful in other transition metal-catalyzed C–H functionalizations.

ASSOCIATED CONTENT

Supporting Information. Detailed experimental procedures including spectroscopic and analytical data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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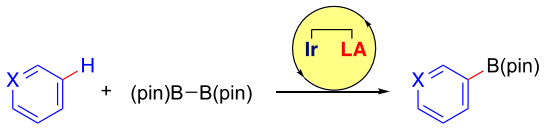

X = $R_2NC(=O)C$, $(MeO)_2P(=O)C$, or N