C–H Borylation Reactions Hot Paper

International Edition: DOI: 10.1002/anie.201701238
German Edition: DOI: 10.1002/ange.201701238

para-Selective C–H Borylation of (Hetero)Arenes by Cooperative Iridium/Aluminum Catalysis

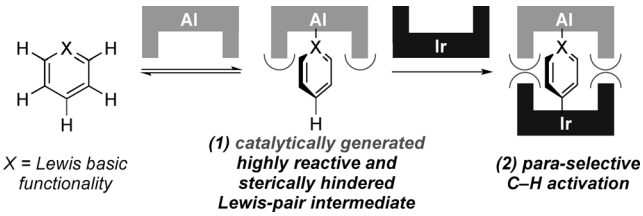
*Lichen Yang, Kazuhiko Semba, and Yoshiaki Nakao**

Abstract: *para-Selective C–H borylation of benzamides and pyridines has been achieved by cooperative iridium/aluminum catalysis. A combination of iridium catalysts commonly employed for arene C–H borylation and bulky aluminum-based Lewis acid catalysts provides an unprecedented strategy for controlling the regioselectivity of C–H borylation to give variously substituted (hetero)arylboronates, which are versatile synthetic intermediates for complex multi-substituted aromatic compounds.*

Selective C–H functionalization of readily available arene is the most atom- and step-economic method for building C–C and C-heteroatom bonds and, over the last decade, has become a powerful tool for constructing complex molecules.[1] One important issue of arene C–H functionalization is regioselectivity. *ortho*-Selective reactions are well-developed and incorporate various directing groups,[2] while remote C–H functionalization still remains a major challenge. Compared to recently developed *meta*-selective C–H functionalization,[3] *para*-selective C–H functionalization is less explored and is limited mainly to electron-rich arenes. Recent examples include electrophilic metalations,[4] hypervalent iodine-mediated reactions,[5] carbene insertions,[6] radical substitutions,[7] steric control strategies,[8,9] and template-directed metalations.[10]

Among various C–H functionalization reactions, iridium-catalyzed arene C–H borylation reactions[11] have received significant attentions because resulting arylboronate esters are versatile synthons of various derivatization reactions and are widely used in the synthesis of functional materials, natural products, and pharmaceuticals. Generally, steric hindrance governs the regioselectivity of C–H borylation, and the reaction often gives a mixture of regioisomers when sterically less biased mono- and 1,2-di-substituted benzenes are employed. Typically, regioselective arene C–H borylation is limited to 1,3-di-substituted benzenes, which give C5-selective C–H borylation products.[12] Several strategies have been developed to overcome this problem. *ortho*-Selective C–H borylation have been successful with nitrogen, carbonyl, and other directing groups.[13] Recently, secondary interactions have emerged as a powerful strategy to control *meta*-selective C–H borylation.[14] On the other hand, *para*-selective C–H borylation has lacked a general strategy. The examples thus far are limited to arenes bearing tertiary alkyl- and silyl-substituents, which induce steric repulsion between a bulky ligand[9] and electrophilic borylations.[15] Therefore, a catalyst-controlled strategy for *para*-selective C–H borylation of arenes is highly desired.

Cooperative nickel/aluminum catalysis is a powerful strategy for regioselective C–H alkylation and alkenylation.[16] We envisaged that cooperative catalysis could also overcome the regioselectivity issue and achieve *para*-selective arene C–H borylation. Our motivation was based on the following considerations (Scheme 1): 1) Complexation of an arene bearing a Lewis basic functionality with a Lewis acid (LA) results in charge transfer, making the arene core more electron-deficient and thus more reactive;[17] 2) steric repulsion between a ligand on iridium and LA would block the *ortho*- and *meta*-positions and force the C–H borylation to proceed at the *para*-position. Herein, we report the realization of this strategy to develop *para*-selective C–H borylation of benzamides and pyridines by cooperative iridium/aluminum catalysis.



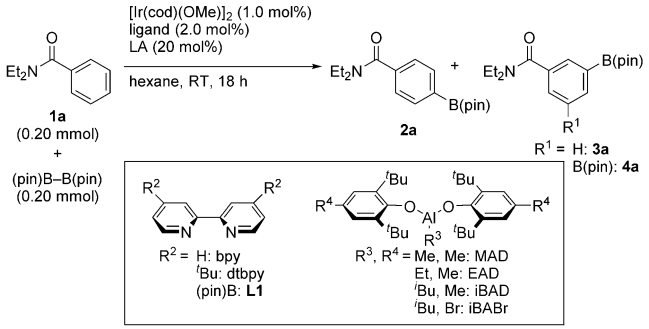
Scheme 1. Hypothesis of cooperative iridium/aluminum catalysis for *para*-selective C–H borylation.

From the outset, we chose the iridium-catalyzed C–H borylation of *N*,*N*-diethylbenzamide (**1a**) as a model reaction and sought proper conditions for *para*-selective reaction based on our hypothesis. The reaction of **1a** with bis(pinacolato)diboron ($B_2(pin)_2$) in the presence of $[Ir(cod)(OMe)]_2$ (cod = 1,5-cyclooctadiene) and 2,2′-bipyridyl (bpy) in hexane at room temperature gave a mixture of C–H borylation products derived from *para*-C–H borylation **2a**, *meta*-C–H borylation **3a**, and 3,5-di-borylation **4a** in 74% overall yield and with poor selectivity (Table 1, entry 1). The observed statistic ratio of the *meta*- and *para*-C–H borylation products indicated that the regioselectivity of the C–H borylation was governed purely by steric hindrance and no electronic bias affected the selectivity.[18] Adding 20 mol% methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD)[19] as a LA catalyst dramatically increased the yield (>99%) and

[*] L. Yang, Prof. Dr. K. Semba, Prof. Dr. Y. Nakao
Department of Material Chemistry, Graduate School of Engineering
Kyoto University
Katsura, Nishikyo-ku, Kyoto 615-8510 (Japan)
E-mail: nakao.yoshiaki.8n@kyoto-u.ac.jp

Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201701238.

Table 1: Optimization of *para*-selective C–H borylation of benzamide **1a**.[a]



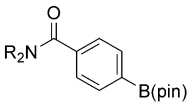
Entry	Ligand	LA	Ratio $\frac{2a}{3a+4a}$	Yield [%] 2a	3a	4a
1	bpy	none	0.4:1.0	22	45	7
2	bpy	MAD	3.3:1.0	82	17	7
3	dtbpy	MAD	0.9:1.0	44	41	12
4	**L1**	**MAD**	**6.9:1.0**	**92**	**8**	**6**
5	**L1**	none	0.6:1.0	25	41	2
6	**L1**	$AlMe_3$	–	–	–	–
7	**L1**	$Al(^tBu)_3$	0.5:1.0	11	22	1
8	**L1**	EAD	1.0:1.0	52	47	3
9	**L1**	$B(C_6F_5)_3$	0.5:1.0	18	35	4

[a] Yields and selectivities were calculated by crude ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

para-selectivity [**2a**/(**3a**+**4a**) = 3.3:1.0] (Table 1, entry 2), which was consistent with our hypothesis. Encouraged by this result, we decided to further optimize the conditions by screening various ligands. Conventionally used 4,4′-di-*tert*-butyl-2,2′-bipyridyl (dtbpy) gave good yield with decreased selectivity. (Table 1, entry 3). During the screening study, we noticed that the bpy ligand was converted to 4,4′-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,2′-bipyridine (**L1**) selectively under the reaction conditions. Therefore, we tested **L1**, which was obtained by our own method (see above), as a ligand. It gave improved *para*-selectivity (6.9:1.0; Table 1, entry 4). Notably, almost complete loss of regioselectivity was observed in the absence of MAD (Table 1, entry 5). We believed that the origin of the *para*-selectivity was from the geometry of **L1**, which afforded a proper steric repulsion with MAD (see Supporting Information). Subsequently, we screened various LA catalysts using **L1** as a ligand. Adding trialkylaluminum catalysts such as $AlMe_3$ and $Al(^tBu)_3$ resulted in sluggish reactions with no improvement of selectivity (Table 1, entries 6 and 7). We imagined that a larger LA would give further improved selectivity. However, ethylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (EAD) gave lower *para*-selectivity compared to MAD (Table 1, entry 8). Boron-based Lewis acid $B(C_6F_5)_3$ gave a moderate yield albeit with no selectivity (Table 1, entry 9). All these results indicated that both **L1** and MAD played a key role in induction of *para*-selectivity. Additionally, solvent effects were studied. The reaction in hexane solvent showed the highest reactivity and selectivity (see Supporting Information).

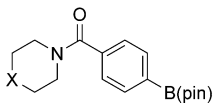
Using a combination of $[Ir(cod)(OMe)]_2$/**L1** and MAD as a catalyst, we subsequently examined the scope of benzamide products (Table 2). Firstly, a series of nonsubstituted benzamides with different *N*-substituents were examined (**1a**–**1g**). We found that the regioselectivity was influenced by the size of the *N*-substituents. *N*,*N*-Dimethylbenzamide (**1b**) afforded

Table 2: Scope of benzamide products.[a]



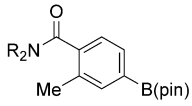
2a-2d

R =
Et: **2a**, 86%/2% (6.9:1.0)
Me: **2b**, 83%/9% (2.2:1.0)
^{i}Pr: **2c**,95%/0% (>20:1.0)
Hex: **2d**, 78%/0% (9.2:1.0)



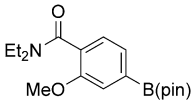
2e-2g

X =
CH_2: **2e**, 84%/0% (2.0:1.0)
O: **2f**, 71%/16% (1.7:1.0)
CH_2CH_2: **2g**, 95%/0% (5.3:1.0)[b]



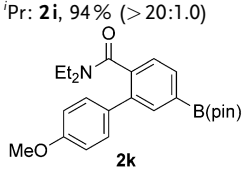
2h-2i

R =
Et: **2h**, 89% (10:1.0)
^{i}Pr: **2i**, 94% (>20:1.0)



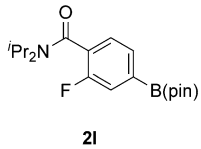
2j

2j, 90% (>20:1.0)



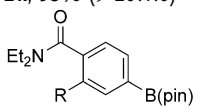
2k

2k, 98% (>20:1.0)[b]



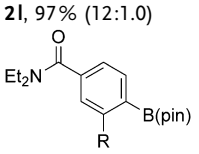
2l

2l, 97% (12:1.0)



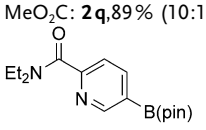
2m-2q

R =
Cl: **2m**,100% (>20:1.0)[b]
Br: **2n**,94% (>20:1.0)[b]
F_3C: **2o**, 89% (9.0:1.0)
CF_3O: **2p**,78% (>20:1.0)[b]
MeO_2C: **2q**,89% (10:1.0)



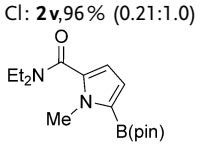
2r-2v

R =
F: **2r**, 93% (13:1.0)[b], (0.85:1.0)[b,c]
CN: **2s**, 96% (1.3:1.0)[b], (0.064:1.0)[b,c]
Me: **2t**,55% (0:1.0)
OMe: **2u**,77% (0.56:1.0)
Cl: **2v**,96% (0.21:1.0)



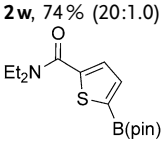
2w

2w, 74% (20:1.0)



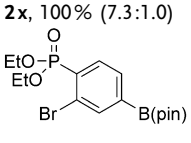
2x

2x, 100% (7.3:1.0)



2y

2y, 90% (1.0:0)



2z

2z, 92% (6.6:1.0)

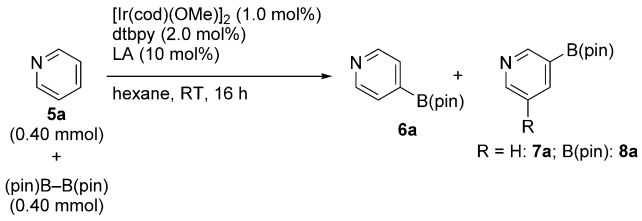
[a] Reactions were run with benzamide (0.20 mmol), $B_2(pin)_2$ (0.20 mmol), $[Ir(cod)(OMe)]_2$ (1.0 mol%), **L1** (2.0 mol%), and MAD (20 mol%) in hexane (2.0 mL) at room temperature for 18 h. Selectivities (*p*/*m*) were estimated by analysis of ^{1}H NMR spectra of the crude mixtures. Yields for the nonsubstituted benzamides are shown as mono-C–H borylation product/3,5-di-C–H borylation product, which were calculated based on an isolated mixture of mono- and di-C–H borylation products. [b] Selectivity was calculated based on GC analysis. [c] Selectivity of the control experiment without MAD.

para-selectivity lower than that of *N*,*N*-diethylbenzamide (**1a**) and the selectivity became even worse when bulkier Lewis acid was used instead of MAD (see Supporting Information). In contrast, *N*,*N*-diisopropylbenzamide (**1c**) and *N*,*N*-dihexylbenzamide (**1d**) showed selectivity higher than **1b**. The same trend was also found for benzamides derived from cyclic amines (**1e**–**1g**). Subsequently, the C–H borylation of *ortho*-monosubstituted benzamides was examined. Generally the reaction tolerated a wide range of functional groups at the *ortho*-position and afforded good yields and selectivities. *N*,*N*-Diethyl-2-methylbenzamide (**1h**) gave good yield and selectivity. Substrate bearing a bulkier amine moiety **1i** afforded improved selectivity. An electron-donating and Lewis basic methoxy group was tolerated by our method to give **2j**. A substituent on the aryl group of 2-arylbenzamide **1k** was essential to block the C–H borylation at its *para*-position. For **1l**, which has a small *ortho*-fluorine substituent, a bulky amine moiety was essential to achieve good selectivity. Our method could also tolerate other halogen functionalities to give **2m**–**2p**. An *ortho*-CF_3 group strongly activated the C5-position, which caused the moderate selectivity of **1o**. Notably, dicarbonyl substrate **1q** was exclusively borylated at the *para*-position of the aminocarbonyl group. On the other hand, substrate-control governs the regioselectivity with C3-substituted benzamides. While **1r** and **1s** bearing a small substituent still showed *para*-selectivity, other substrates directed C–H borylation at their *meta*-position. Heteroaromatic carboxamide **1w** afforded C5 C–H borylation product selectively. 5-Membered heteroarene substrates **1x** and **1y** also afforded C5 C–H borylation products. Our method could also be applied to arylphosphonate **1z**, which afforded a *para*-C–H borylation product with good yield and selectivity. However, other functionalized arenes, such as arylketones and benzoates, were not tolerated by our method (see Supporting Information).

The C–H borylation of some pyridine derivatives is reported to be sluggish and lacking in selectivity.[20] Thus, we wondered whether our method could also accelerate pyridine functionalization and control C4-selectivity. Initially, we chose pyridine (**5a**) as a substrate and examined ligands and LAs to achieve C4-selective C–H borylation (Table 3). The reaction of **5a** with $B_2(pin)_2$ in the presence of $[Ir(cod)(OMe)]_2$ and dtbpy in hexane at room temperature was indeed very slow, giving essentially no borylation products (Table 3, entry 1). However, adding 10 mol% MAD as a cocatalyst dramatically improved the yield and gave moderate C4-selectivity (Table 3, entry 2). Increasing the bulkiness of LA by introducing an isobutyl group instead of methyl on aluminum improved the C4-selectivity (Table 3, entry 3). Finally, iBABr[21] slightly improved the yield without any loss of selectivity (Table 3, entry 4).

With the optimized conditions in hand, we investigated the scope of substituted pyridines (Table 4). The C–H borylation of **5a** on a preparative scale gave mono-C–H borylation product **6a** in 76% isolated yield. C2-substituted pyridines were borylated at the C4-position exclusively because of steric repulsion between C2-substituents and iBABr, forcing LA to provide more severe steric hindrance at the C5-position. 2-Picoline (**5b**) reacted in moderate yield

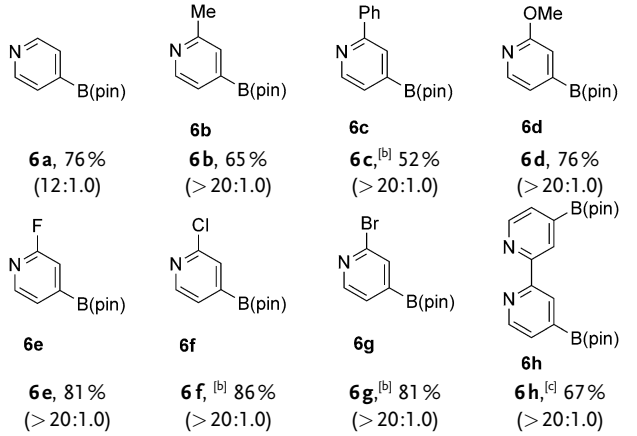
Table 3: Optimization of C4-selective C–H borylation of pyridine.[a]



Entry	LA	Ratio	Yield [%]		
		$\frac{6a}{7a+8a}$	**6a**	**7a**	**8a**
1	none	–	–	–	–
2	MAD	4.0:1.0	64	2	14
3	iBAD	12:1.0	75	1	4
4	**iBABr**	**12:1.0**	**79**	**2**	**5**

[a] Yields and selectivities were calculated by crude ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as an internal standard.

Table 4: Scope of pyridine products.[a]



[a] Reactions were run with pyridine (1.0 mmol), $B_2(pin)_2$ (1.0 mmol), $[Ir(cod)(OMe)]_2$ (1.0 mol%), dtbpy (2.0 mol%), and iBABr (10 mol%) in hexane (2.5 mL) at room temperature for 6 h. Selectivities (C4:C5) were estimated by ^{1}H NMR spectroscopy. [b] MAD (10 mol%) was used. [c] The reaction was performed with **5h** (1.0 mmol), $[Ir(cod)(OMe)]_2$ (0.30 mol%), bpy (0.60 mol%), MAD (20 mol%), and $B_2(pin)_2$ (2.0 mmol) in hexane (5.0 mL) at room temperature for 24 h.

but with complete C4-selectivity. 2-Phenylpyridine (**5c**), C–H functionalization of which often proceeds at the phenyl ring, afforded moderate yield and excellent C4-selectivity without any detectable C–H borylation on the phenyl group. In this case, iBABr gave good selectivity but low yield, probably because of steric repulsion by the C2 phenyl group. Ether and halogen functionalities were tolerated with excellent C4-selectivities to give **6d**–**6g**. Bpy could also serve as a substrate for our method, giving 4,4′-di-borylation product **6h** as the sole product, which was the ligand of choice (**L1**) for the *para*-selective C–H borylation of benzamides (see above). Our method failed for C3-substituted pyridines, which were governed by substrate control to give C5 C–H borylation products mainly.

The origin of the *para*-selectivity is likely steric repulsion between the iridium catalysts and MAD-substrate adducts, which participate in the originally proposed catalytic

cycle.[17,22] We studied the interaction between MAD and **1a** by ^{1}H NMR spectroscopy, which showed a 1:1 adduct formed spontaneously after mixing the two compounds (see Supporting Information). Under otherwise identical conditions, the addition of MAD to **1a** greatly accelerated its conversion to product, consistent with activation of the substrate by MAD. (see Supporting Information). Finally, the turnover of the MAD Lewis acid catalysis was also confirmed by observing equilibrium quickly established between MAD-**1a** adduct and MAD-**2a** adduct at room temperature (see Supporting Information).

In summary, we have successfully achieved *para*-selective C–H borylation of benzamides and pyridines by cooperative iridium/aluminum catalysis. The aluminum Lewis acid catalysts likely accelerate the reaction by generating highly reactive Lewis-pair adducts. Moreover, the regioselectivity is controlled by the steric repulsion between the substrates coordinating to the bulky aluminum catalysts and the iridium catalyst. In spite of the use of the strong Lewis acid cocatalysts, our method shows good tolerance toward a range of functional groups, including Lewis basic groups, without loss of regioselectivity. This work demonstrates the potential of cooperative iridium/aluminum catalysis as a powerful tool to control the regioselectivity of otherwise nonselective C–H functionalization reactions.

Experimental Section

A 4 mL vial was charged with **L1** (1.60 mg, 4.0 μmol), $B_2(pin)_2$ (50.8 mg, 0.20 mmol) and brought into a nitrogen-filled glovebox. In the glovebox, the vial was charged with a solution of $[Ir(cod)(OMe)]_2$ (1.3 mg, 2.0 μmol) in hexane (1.0 mL) and a stir bar and it was sealed with a Teflon screw cap. The resulting solution was stirred for 30 min at 60 °C. After the mixture was cooled down to room temperature, it was mixed with another mixture of **1** (0.20 mmol), MAD (19.2 mg, 0.040 mmol), and hexane (1.0 mL). The vial was sealed with a Teflon screw cap again and taken out of the glovebox. The resulting mixture was stirred for 18 h at room temperature. After stirring for 18 h it was quenched with ethyl acetate. The regioselectivity was determined by ^{1}H NMR spectroscopic analysis with $CDCl_3$ as a solvent and 1,3,5-trimethoxybenzene as an internal standard, or by GC analysis of the crude product. All of the volatiles were removed in vacuo and the residue was purified by medium pressure liquid chromatography (MPLC) with a silica gel column (40–50 μm, $D = 2.0$ cm, $V = 15$ mL) to give the corresponding products.

Acknowledgements

This work was supported by the CREST program "Establishment of Molecular Technology towards the Creation of New Functions" Area from JST, "JSPS KAKENHI Grant Number 22105003 in Molecular Activation Directed toward Straightforward Synthesis", and "JSPS KAKENHI Grant Number JP15H05799 in Precisely Designed Catalysts with Customized Scaffolding".

Conflict of interest

The authors declare no conflict of interest.

Keywords: boronate esters · C-H activation · iridium · Lewis acids · regioselectivity

[1] For recent reviews, see: a) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960 – 9009; *Angew. Chem.* **2012**, *124*, 9092 – 9142; b) Y. Kuninobu, S. Sueki, *Synthesis* **2015**, 3823 – 3845.

[2] For a recent review, see: Z. Chen, B. Wang, J. Zhang, W. Yu, Z. Liu, Y. Zhang, *Org. Chem. Front.* **2015**, *2*, 1107 – 1295.

[3] For recent reviews, see: a) J. Yang, *Org. Biomol. Chem.* **2015**, *13*, 1930 – 1941; b) A. Dey, S. Agasti, D. Maiti, *Org. Biomol. Chem.* **2016**, *14*, 5440 – 5453.

[4] a) G. Brasche, J. Garcia-Fortanet, S. L. Buchwald, *Org. Lett.* **2008**, *10*, 2207 – 2210; b) X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864 – 13867; c) Z. Wu, F. Luo, S. Chen, Z. Li, H. Xiang, X. Zhou, *Chem. Commun.* **2013**, *49*, 7653 – 7655; d) H. Xu, M. Shang, H.-X. Dai, J.-Q. Yu, *Org. Lett.* **2015**, *17*, 3830 – 3833.

[5] a) C. L. Ciana, R. J. Phipps, J. R. Brandt, F.-M. Meyer, M. J. Gaunt, *Angew. Chem. Int. Ed.* **2011**, *50*, 458 – 462; *Angew. Chem.* **2011**, *123*, 478 – 482; b) L. Marchetti, A. Kantak, R. Davis, B. Deboef, *Org. Lett.* **2015**, *17*, 358 – 361; c) B. Berzina, I. Sokolovs, E. Suna, *ACS Catal.* **2015**, *5*, 7008 – 7014; d) A. Pialat, J. Bergès, A. Sabourin, R. Vinck, B. Liégault, M. Taillefer, *Chem. Eur. J.* **2015**, *21*, 10014 – 10018; e) I. Sokolovs, E. Suna, *J. Org. Chem.* **2016**, *81*, 371 – 379; f) S.-K. Xiang, J.-M. Li, H. Huang, C. Feng, H.-L. Ni, X.-Z. Chen, B.-Q. Wang, K.-Q. Zhao, P. Hu, C. Redshaw, *Adv. Synth. Catal.* **2015**, *357*, 3435 – 3440.

[6] a) Z. Yu, B. Ma, M. Chen, H. Wu, L. Liu, J. Zhang, *J. Am. Chem. Soc.* **2014**, *136*, 6904 – 6907; b) Y. Liu, Z. Yu, J. Z. Zhang, L. Liu, F. Xia, J. Zhang, *Chem. Sci.* **2016**, *7*, 1988 – 1995.

[7] a) X. Guo, C.-J. Li, *Org. Lett.* **2011**, *13*, 4977 – 4979; b) A. van der Werf, N. Selander, *Org. Lett.* **2015**, *17*, 6210 – 6213.

[8] C. Cheng, J. F. Hartwig, *Science* **2014**, *343*, 853 – 857.

[9] Y. Saito, Y. Segawa, K. Itami, *J. Am. Chem. Soc.* **2015**, *137*, 5193 – 5198.

[10] a) S. Bag, T. Patra, A. Modak, A. Deb, S. Maity, U. Dutta, A. Dey, R. Kancherla, A. Maji, A. Hazra, M. Bera, D. Maiti, *J. Am. Chem. Soc.* **2015**, *137*, 11888 – 11891; b) T. Patra, S. Bag, R. Kancherla, A. Mondal, A. Dey, S. Pimparkar, S. Agasti, A. Modak, D. Maiti, *Angew. Chem. Int. Ed.* **2016**, *55*, 7751 – 7755; *Angew. Chem.* **2016**, *128*, 7882 – 7886.

[11] a) C. N. Iverson, M. R. Smith III, *J. Am. Chem. Soc.* **1999**, *121*, 7696 – 7697; b) J. Y. Cho, C. N. Iverson, M. R. Smith III, *J. Am. Chem. Soc.* **2000**, *122*, 12868 – 12869; c) J. Y. Cho, M. K. Tse, D. Holmes, R. E. Maleczka, Jr., M. R. Smith III, *Science* **2002**, *295*, 305 – 308; d) T. Ishiyama, J. Takagi, K. Ishida, N. Miyaura, N. R. Anastasi, J. F. Hartwig, *J. Am. Chem. Soc.* **2002**, *124*, 390 – 391; e) T. Ishiyama, J. Takagi, J. F. Hartwig, N. Miyaura, *Angew. Chem. Int. Ed.* **2002**, *41*, 3056 – 3058; *Angew. Chem.* **2002**, *114*, 3182 – 3184. For a general review, see: f) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890 – 931.

[12] a) J. F. Hartwig, *Chem. Soc. Rev.* **2011**, *40*, 1992 – 2002; b) H. Tajuddin, P. Harrisson, B. Bitterlich, J. C. Collings, N. Sim, A. S. Batsanov, M. S. Cheung, S. Kawamorita, A. C. Maxwell, L. Shukla, J. Morris, Z. Lin, T. B. Marder, P. G. Steel, *Chem. Sci.* **2012**, *3*, 3505 – 3515.

[13] a) S. Kawamorita, H. Ohmiya, K. Hara, A. Fukuoka, M. Sawamura, *J. Am. Chem. Soc.* **2009**, *131*, 5058 – 5059; b) T. Ishiyama, H. Isou, T. Kikuchi, N. Miyaura, *Chem. Commun.* **2010**, *46*, 159 – 161; c) H. Itoh, T. Kikuchi, T. Ishiyama, N. Miyaura, *Chem. Lett.* **2011**, *40*, 1007 – 1008; d) S. Kawamorita, T. Miyazaki, H. Ohmiya, T. Iwai, M. Sawamura, *J. Am. Chem. Soc.*

2011, *133*, 19310 – 19313; e) P. C. Roosen, V. A. Kallepalli, B. Chattopadhyay, D. A. Singleton, R. E. Maleczka, Jr., M. R. Smith III, *J. Am. Chem. Soc.* **2012**, *134*, 11350 – 11353; f) Y. Kuninobu, T. Iwanaga, T. Omura, K. Takai, *Angew. Chem. Int. Ed.* **2013**, *52*, 4431 – 4434; *Angew. Chem.* **2013**, *125*, 4527 – 4530; g) B. Ghaffari, S. M. Preshlock, D. L. Plattner, R. J. Staples, P. E. Maligres, S. W. Krska, R. E. Maleczka, Jr., M. R. Smith III, *J. Am. Chem. Soc.* **2014**, *136*, 14345 – 14348; h) I. Sasaki, T. Amou, H. Ito, T. Ishiyama, *Org. Biomol. Chem.* **2014**, *12*, 2041c2044; i) L. V. A. Hale, K. A. McGarry, M. A. Ringgold, T. B. Clark, *Organometallics* **2015**, *34*, 51 – 55; j) H.-L. Li, Y. Kuninobu, M. Kanai, *Angew. Chem. Int. Ed.* **2017**, *56*, 1495 – 1499; *Angew. Chem.* **2017**, *129*, 1517 – 1521. For a recent review, see: k) A. Ros, R. Fernández, J. M. Lassaletta, *Chem. Soc. Rev.* **2014**, *43*, 3229 – 3243.

[14] a) Y. Kuninobu, H. Ida, M. Nishi, M. Kanai, *Nat. Chem.* **2015**, *7*, 712 – 717; b) R. Bisht, B. Chattopadhyay, *J. Am. Chem. Soc.* **2016**, *138*, 84 – 87; c) H. J. Davis, M. T. Mihai, R. J. Phipps, *J. Am. Chem. Soc.* **2016**, *138*, 12759 – 12762.

[15] a) V. Bagutski, A. Del Grosso, J. A. Carrillo, I. A. Cade, M. D. Helm, J. R. Lawson, P. J. Singleton, S. A. Solomon, T. Marcelli, M. J. Ingleson, *J. Am. Chem. Soc.* **2013**, *135*, 474 – 487; b) A. Del Grosso, J. A. Carrillo, M. J. Ingleson, *Chem. Commun.* **2015**, *51*, 2878 – 2881.

[16] a) Y. Nakao, K. S. Kanyiva, T. Hiyama, *J. Am. Chem. Soc.* **2008**, *130*, 2448 – 2449; b) Y. Nakao, Y. Yamada, N. Kashihara, T. Hiyama, *J. Am. Chem. Soc.* **2010**, *132*, 13666 – 13668; c) C.-C. Tsai, W.-C. Shih, C.-H. Fang, C.-Y. Li, T.-G. Ong, G. P. A. Yap, *J. Am. Chem. Soc.* **2010**, *132*, 11887 – 11889; d) S. Okumura, S. Tang, T. Saito, K. Semba, S. Sakaki, Y. Nakao, *J. Am. Chem. Soc.* **2016**, *138*, 14699 – 14704.

[17] T. M. Boller, J. M. Murphy, M. Hapke, T. Ishiyama, N. Miyaura, J. F. Hartwig, *J. Am. Chem. Soc.* **2005**, *127*, 14263 – 14278.

[18] For related discussions from DFT calculations, see: a) A. G. Green, P. Liu, C. A. Merlic, K. N. Houk, *J. Am. Chem. Soc.* **2014**, *136*, 4575 – 4583; b) J. Jover, F. Maseras, *Organometallics* **2016**, *35*, 3221 – 3226.

[19] a) K. B. Starowieyski, S. Pasynkiewicz, M. Skowrońska-Ptasińska, *J. Organomet. Chem.* **1975**, *90*, C43 – C44. For applications of MAD in organic synthesis, see: b) S. Saito, H. Yamamoto, *Chem. Commun.* **1997**, 1585 – 1592.

[20] a) J. Takagi, K. Sato, J. F. Hartwig, T. Ishiyama, N. Miyaura, *Tetrahedron Lett.* **2002**, *43*, 5649 – 5651; b) I. A. I. Mkhalid, D. N. Coventry, D. Albesa-Jove, A. S. Batsanov, J. A. K. Howard, R. N. Perutz, T. B. Marder, *Angew. Chem. Int. Ed.* **2006**, *45*, 489 – 491; *Angew. Chem.* **2006**, *118*, 503 – 505; c) S. A. Sadler, H. Tajuddin, I. A. I. Mkhalid, A. S. Batsanov, D. Albesa-Jove, M. S. Cheung, A. C. Maxwell, L. Shukla, B. Roberts, D. C. Blakemore, Z. Lin, T. B. Marder, P. G. Steel, *Org. Biomol. Chem.* **2014**, *12*, 7318 – 7327.

[21] G. Doledec, D. Commereuc, *J. Mol. Catal. A* **2000**, *161*, 125 – 140.

[22] M. A. Larsen, J. F. Hartwig, *J. Am. Chem. Soc.* **2014**, *136*, 4287 – 4299.

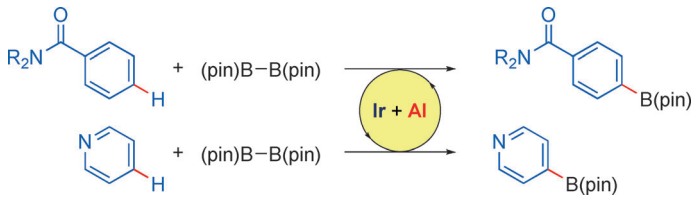
Manuscript received: February 4, 2017
Final Article published: ■■ ■■, ■■■■

Communications

C–H Borylation Reactions

L. Yang, K. Semba,
Y. Nakao* _____ ■■■■–■■■■

para-Selective C–H Borylation of (Hetero)Arenes by Cooperative Iridium/Aluminum Catalysis



Collect. Select. Reflect: *para*-Selective C–H borylation of benzamide and pyridine adducts is controlled by a combination of iridium and bulky aluminum-based Lewis acid catalysts. Variously substituted (hetero)arylboronates were prepared, which are versatile synthetic intermediates for complex multi-substituted aromatic compounds.

