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CATALYTIC AROMATIC BORYLATION *VIA IN SITU*-GENERATED BORENIUM SPECIES

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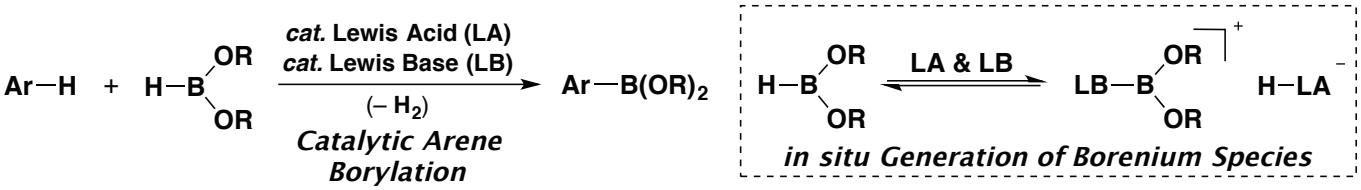
Abstract – We have developed a catalytic direct borylation of arenes *via in situ*-generated borenium species. The choice of appropriate Lewis base was crucial to achieve the catalytic system. Electron-rich arenes were borylated in a regioselective manner.

This paper is dedicated to Prof. Masakatsu Shibasaki on the occasion of his 70th birthday and for his outstanding achievement in asymmetric cooperative catalysis.

Carbon–boron bonds are rather stable among carbon–hetero element bonds, while they can efficiently convert to carbon–carbon, carbon–oxygen, carbon–nitrogen bonds, and so on, with an appropriate activation and/or catalyst. Thus, arylboronic esters among the organoboron compounds are quite versatile building blocks in organic chemistry.[1] In particular, they have been widely utilized in transition metal-catalyzed cross-coupling reaction (*i.e.*, Suzuki–Miyaura cross-coupling reaction). In addition, structures of arylboron compounds have recently emerged as a core of functional molecules, such as organic electronics and pharmaceuticals, due to the characteristic electronic and structural perturbation by boron atom with an empty 2p orbital instead of carbon atom. Several methods to prepare arylboronates are available. The conventional and mostly reliable reaction sequence is composed of the lithiation (by deprotonation or halogen-lithium exchange reaction) and an electrophilic trapping step with some boron reagents. Aryl halides are the convenient materials in the preparation of arylboronates by transition metal-catalyzed borylation[2] or borylation *via* anionic mechanisms.[3] The direct borylation of simple

unfunctionalized arenes is highly attractive; the development of Ir-catalyzed C–H borylation strategies offered great progress in arene borylation chemistry.[4] Given the requirement for the broader structures and efficient synthesis of arylboron compounds, the development of borylation reactions of simple arenes with diverse selectivity is more and more important.

Recently, increasing attention has been devoted to another type of direct arene borylation, namely electrophilic aromatic borylation reaction, based on the use of electrophilic boron species.[5] Ingleson and co-workers elegantly demonstrated that the borenium cation generated from stoichiometric amounts of *B*-chlorocatecholborane, $AlCl_3$, and triethylamine efficiently promoted the electrohphilic aromatic borylation reaction of electron-rich arenes.[6] It should be noted that high regioselectivity was achieved in the direct borylation reaction, through the electronic substituent effects, which is complementary to Ir-catalyzed system. Thus, the development of a catalytic variant of the direct arene borylation reaction should be significant as alternative chemo- and regio-selective preparation methods of arylboronates.[7] Herein, we report a catalytic direct arene borylation based on *in situ*-generation of borenium species (Scheme 1).



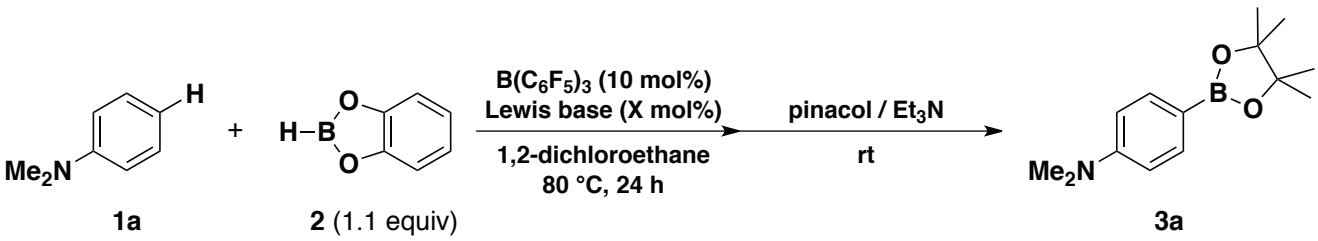
Scheme 1. Catalytic arene borylation *via* electrophilic *in situ*-generated borenium species

We hypothesized that *in situ*-generation of borenium species should be realized by the B–H bond activation of dialkoxyborane reagents ($H–B(OR)_2$) using an appropriate combination of Lewis acid (LA) and Lewis base (LB), as shown in Scheme 1. In this scenario, LA should be "hydride-philic" to release the hydride adduct ($H–LA^-$). The choice of LB is principally important due to the following reasons; 1) LB should coordinate to the boron atom to afford and stabilize the borenium species ($[LB–B(OR)_2]^+$).[8] 2) The generated borenium species should be sufficiently electrophilic at the boron center to react with arenes. 3) To achieve the catalytic use of LB in the generation of borenium species, LB should be released from the boron center after the electrophilic reaction with arenes.

Thus, we commenced our studies by screening suitable LB in the reaction of *N*,*N*-dimethylaniline (**1a**, 1.0 equiv.) with catecholborane (**2**, 1.1 equiv.) in the presence of $B(C_6F_5)_3$ (10 mol%) as "hydride-philic" LA in 1,2-dichloroethane at 80 °C (Table 1). Strongly-coordinating, oxygen-based LBs, such as THF, DMF, DMSO, and $O=PPh_3$ did not promote borylation reaction at all (entries 1-4). Instead, the use of diphenyl ether (**4a**) and bis(4-fluorophenyl) ether (**4b**) promoted the desired borylation reaction, and the borylated

product **3a** was generated in 53 and 69% NMR yield after transesterification to pinacol ester (entries 5 and 6). A nitrogen-based LB, triphenylamine (**4c**) also promoted the reaction moderately (entry 8). In contrast to THF, a structurally-related sulfur-based LB, tetrahydrothiophene (THT, **4d**), was a good promoter in this reaction (76% yield, entry 9), while lower yields were observed with tetrahydrothiopyran (**4e**) and diphenyl sulfide (**4f**) (entries 10 and 11). The background reaction slightly proceeded in the absence of additional LB, and probably the model substrate **1a** would partially work as LB in entry 12. Next, the reduced loading of LB was examined, aiming to establish a catalytic direct arene borylation reaction. The catalytic use (10 mol%) of **4b** decreased the chemical yield, compared with the results of stoichiometric amount of the same LB (entry 13 vs 6). Different tendency was observed with **4d**; the use of catalytic amount of **4d** kept high reaction efficiency and afforded the borylated product in a comparable chemical yield (74%, entry 14). Among the LBs screened (entries 15-18), **4d** afforded the optimal reaction outcome.

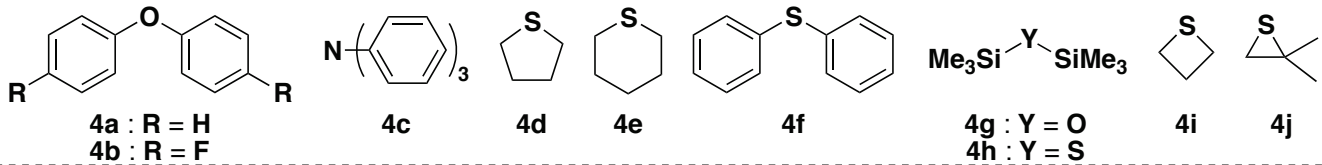
Table 1. Screening of Lewis base in stoichiometric/catalytic arene borylation



1a **2** (1.1 equiv) **3a**

Entry	Lewis base	X (mol%)	Yield (%)[a]	Entry	Lewis base	X (mol%)	Yield (%)[a]
1	THF	100	0	10	**4e**	100	24
2	DMF	100	0	11	**4f**	100	60
3	DMSO	100	0	12	–	–	24
4	$O{=}PPh_3$	100	0	13	**4b**	10	53
5	**4a**	100	53	14	**4d**	10	74
6	**4b**	100	69	15	**4g**	10	68
7	NEt_3	100	0	16	**4h**	10	63
8	**4c**	100	45	17	**4i**	10	64
9	**4d**	100	76	18	**4j**	10	66

[a] NMR Yields



4a : **R** = **H** **4b** : **R** = **F** **4c** **4d** **4e** **4f** **4g** : **Y** = **O** **4h** : **Y** = **S** **4i** **4j**

Several preliminary mechanistic insights should be considered. Firstly, when $B(C_6F_5)_3$ (0.02 mmol), **4d** (0.1 mmol), and catecholborane (**2**, 0.2 mmol) were dissolved in CD_2Cl_2 at room temperature, the peak corresponding to $[H–B(C_6F_5)_3]^-$ [9] was observed in ^{19}F and ^{11}B NMR spectra.[10] The formation of present hydride adduct (*i.e.*, $H–LA^-$) indicates the generation of borenium species under these conditions. Second, DFT calculations revealed that the activation energies of borylation step between the borenium species and **1a** were reasonably low using either **4d** or THF as LB (Figure 1). When **4d**-based borenium species was used, the corresponding borylated intermediate (**IM2**$_{THT}$) was more stable than the corresponding reactants (**IM1**$_{THT}$), and **4d** was smoothly liberated from the generated intermediate (Figure 1a). These results supported the idea that the use of **4d** as LB would realize the arene borylation *via in situ*-generated borenium species in a catalytic manner, which is consistent with the experimental results. In the case of THF-based system, the resultant intermediate (**IM2**$_{THF}$) was unstable, compared with **IM1**$_{THF}$, with the strong coordination of THF to the boron center (Figure 1b). Thus, the choice of appropriate Lewis base, among a variety of elements and structures, should be crucial to achieve a high catalytic efficiency in the direct aromatic borylation *via in situ*-generated borenium species.

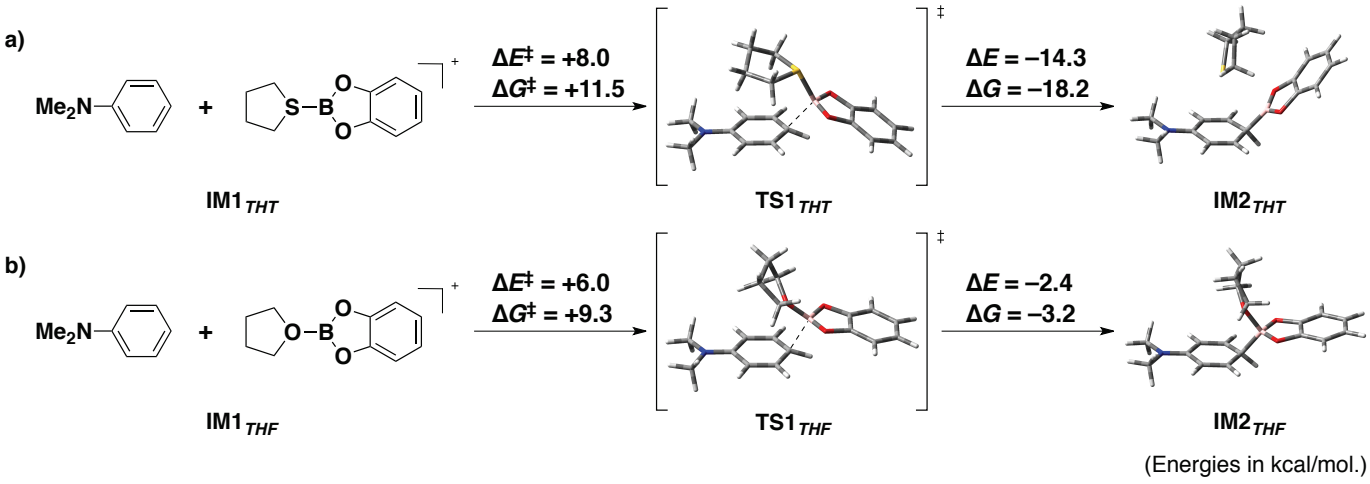
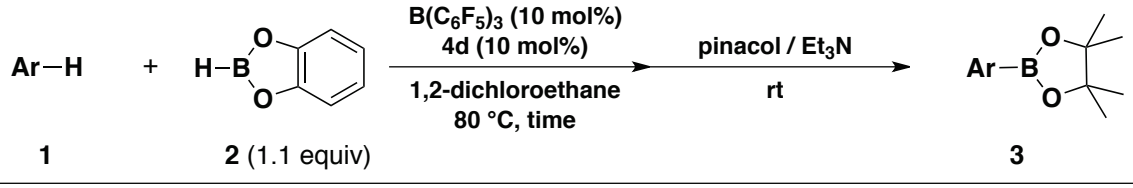


Figure 1. Calculated activation energies of the borylation step at B3LYP/6-31++G** level of theory

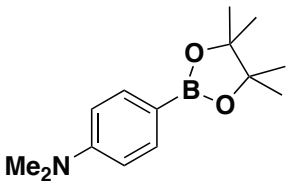
After the optimization of reaction conditions, the substrate scope of catalytic arene borylation was investigated, as summarized in Table 2. Using 10 mol% of $B(C_6F_5)_3$ and **4d** in the presence of **2** (1.1 equiv.) in 1,2-dichloroethane at 80 °C, a variety of electron-rich aromatic compounds were directly converted to the corresponding arylboronates.[11,12] The borylation reaction of **1a** proceeded smoothly in a regioselctive manner, and the desired product **3a** was isolated in 82% yield after 12 h. The 3-Cl or 3-Br derivatives (**3b** and **3c**) were also obtained in good yields. *N*-Phenylpyrrolidine and *N*-phenylpiperidine were also borylated under the identical conditions to afford **3d** and **3e** in 92 and 53% yields, respectively. Reaction of *N*-methyltetrahydroquinoline gave the 6-borylated product **3f** as a sole product in 79% yield.

Rather unstable borylated dihydrophenazine derivative **3g** was isolated in 53% yield with concomitant formation of trace amount of the diborylated product. These borylation conditions were applicable not only for benzene ring, but also for heteroarenes, such as pyrrole, thiophene, and indole derivatives; **3h**, **3i**, and **3h** were obtained in reasonable yields.

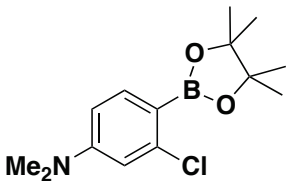
Table 2. Scope of catalytic arene borylation *via* electrophilic *in situ*-generated borenium species



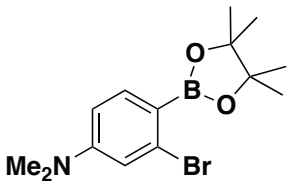
1 **2** (1.1 equiv) **3**



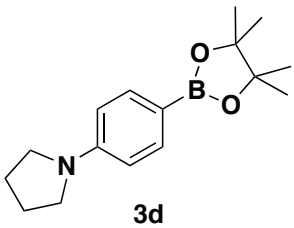
3a
82% (12 h)



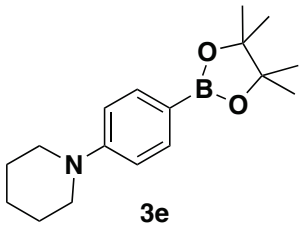
3b
82% (24 h)



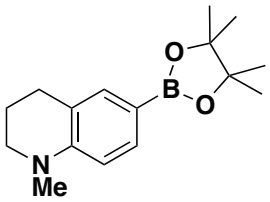
3c
59% (24 h)



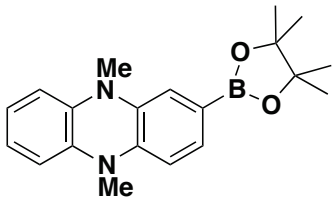
3d
92% (24 h)



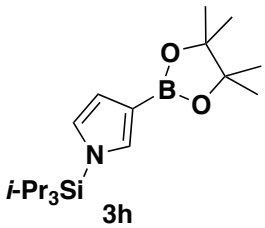
3e
53% (24 h)



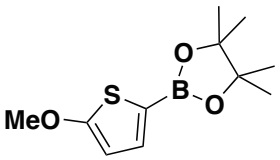
3f
79% (24 h)



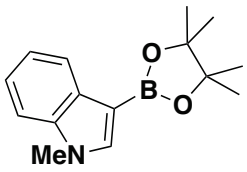
3g
53% (48 h)



3h
53% (42 h)



3i
27% (72 h)



3j
67%[a] (40 h)

[a] NMR Yield. The reduced product (*N*-methylindoline) and regioisomer (5-borylated) were generated (3% and 13% yield, respectively).

In conclusion, we have developed the direct catalytic arene borylation reaction *via in situ*-generated borenium species. The choice of appropriate Lewis base was crucial to achieve "catalytic" borylation reaction. Generation of borenium species *in situ* under reaction conditions was suggested by NMR studies. Mechanistic details are still not clear and should be identified; for example, what does really act as "Brønsted base" to deprotonate the borylated intermediate (*i.e.*, $\mathbf{IM2}_{THT}$)? Further mechanistic investigations and improvement of reactivity and substrate scope based on mechanistic insights are the subjects of ongoing study.

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10. Judged from the ^{19}F NMR spectrum, 23% of $B(C_6F_5)_3$ was converted to $[H–B(C_6F_5)_3]^-$ under these conditions. DFT calculation at B3LYP/6-31++G** suggested that the formation of borenium species from $B(C_6F_5)_3$, **2**, and **4d** should be exothermic (ΔE = 14.9 kcal/mol). For details, see Supporting Information.

11. General Procedure for Catalytic Arene Borylation:

    In a 20 mL Schlenk tube under Ar, $B(C_6F_5)_3$ (51.2 mg, 0.10 mmol) was dissolved in distilled 1,2-dichloroethane (2 mL), followed by the addition of catecholborane (**2**, 117 μL, 1.1 mmol) and tetrahydrothiophene (9 μL, 0.10 mmol). Then, to the mixture was added the arene substrate (1.0 mmol), and the resulting mixture was heated to 80 °C (oil bath temp.) and stirred for the appropriate reaction time. After cooling to room temperature, excess Et_3N (2 mL, *ca.* 15 mmol) and then, pinacol (355 mg, 3 mmol) were added to the reaction mixture and stirred. The reaction mixture was quenched by aqueous NH_4Cl, extracted with EtOAc, washed with brine, and dried over Na_2SO_4. Purification by silica gel column chromatography (eluent: CH_2Cl_2/hexane) was performed to afford the borylated products.

12. Compound Data of the Obtained Borylated Products:

    3a: CAS No. [171364-78-6] <Representative reference: *Angew. Chem. Int. Ed.*, 2011, **50**, 2102>
    According to the general procedure using *N*,*N*-dimethylaniline **1a**, **3a** was obtained in 82% yield as a white solid. ^1H NMR data were in accordance with those reported in the above reference.

    ^1H NMR (300.53 MHz, $CDCl_3$) δ 1.32 (s, 12H), 2.99 (s, 6H), 6.69 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H).

    3b: According to the general procedure using 3-chloro-*N*,*N*-dimethylaniline **1b**, **3b** was obtained in 82% yield as a white solid.

    mp 63-64 °C; ATR-FTIR (neat) *n* 659, 829, 861, 961, 1112, 1140, 1312, 1343, 1598, 2815, 2929, 2977 cm^{-1}; ^1H NMR (395.88 MHz, $CDCl_3$) δ 1.34 (s, 12H), 2.97 (s, 6H), 6.53 (dd, J = 8.8, 2.4 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H); $^{13}C\{^1H\}$ NMR (99.55 MHz, $CDCl_3$) δ 24.9, 40.1, 83.5, 109.6, 112.7, 138.1, 141.5, 153.0 (The carbon directly attached to the boron atom was not detected, probably due to quadropolar relaxation.); MS (ESI (+)) *m/z* calcd for $C_{14}H_{22}BClNO_2^+$ $[M+H]^+$ 282.1427, found 282.1427.

    3c: CAS No. [1278579-36-4] <Representative reference: *Angew. Chem. Int. Ed.*, 2011, **50**, 2102>
    According to the general procedure using 3-bromo-*N*,*N*-dimethylaniline **1c**, **3c** was obtained in 59% yield as a white solid. ^1H NMR data were in accordance with those reported in the above references.

    ^1H NMR (395.88 MHz, $CDCl_3$) δ 1.34 (s, 12H), 2.96 (s, 6H), 6.57 (dd, J = 8.8, 2.4 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H).

3d: CAS No. [852227-90-8] <Representative reference: *ChemCatChem*., 2016, **8**, 1319; U.S. Patent US 2013102595 A1>

According to the general procedure using *N*-phenylpyrrolidine **1d**, **3d** was obtained in 92% yield as a white solid. ^{1}H NMR data were in accordance with those reported in the above references.

^{1}H NMR (395.88 MHz, $CDCl_3$) δ 1.32 (s, 12H), 1.99-2.01 (m, 4H), 3.28-3.33 (m, 4H), 6.53 (d, *J* = 8.7 Hz, 2H), 7.67 (d, *J* = 8.7 Hz, 2H).

3e: CAS No. [852227-96-4] <Representative reference: *Org*. *Biomol*. *Chem*., 2014, **12**, 1603>

According to the general procedure using *N*-phenylpiperidine **1e**, **3e** was obtained in 53% yield as a white solid. ^{1}H NMR data were in accordance with those reported in the above reference.

^{1}H NMR (300.53 MHz, $CDCl_3$) δ 1.32 (s, 12H), 1.59-1.72 (m, 6H), 3.25 (t, *J* = 8.4 Hz, 4H), 6.89 (d, *J* = 8.7 Hz, 2H), 7.68 (d, *J* = 8.7 Hz, 2H).

3f: CAS No. [1374109-66-6] (No analytical data were reported.)

According to the general procedure using *N*-methyl-1,2,3,4-tetrahydroquinoline **1f**, **3f** was obtained in 79% yield as a white solid.

mp 85-86 °C; ATR-FTIR (neat) *n* 673, 824, 851, 964, 1109, 1139, 1312, 1349, 1604, 2836, 2927, 2976 cm^{-1}; ^{1}H NMR (300.53 MHz, $CDCl_3$) δ 1.31 (s, 12H), 1.91-1.99 (m, 2H), 2.75 (t, *J* = 6.3 Hz, 2H), 2.91 (s, 3H), 3.26 (t, *J* = 5.7 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 1H), 7.40 (s, 1H), 7.53 (d, *J* = 8.4 Hz, 1H); ^{13}C{^{1}H} NMR (75.58 MHz, $CDCl_3$) δ 22.3, 24.9, 27.7, 38.9, 51.3, 83.2, 109.9, 121.7, 134.6, 135.4, 149.1 (The carbon directly attached to the boron atom was not detected, probably due to quadropolar relaxation.); MS (ESI (+)) *m/z* calcd for $C_{16}H_{25}BNO_2^+$ $[M+H]^+$ 274.1973, found 274.1975.

3g: According to the general procedure using 5,10-dihydro-5,10-dimethylphenazine **1g**, **3g** was obtained in 53% yield as an yellow-green solid.

mp 61-62 °C; ATR-FTIR (neat) *n* 680, 735, 1108, 1141, 1259, 1331, 1354, 1418, 1607, 2812, 2880, 2975 cm^{-1}; ^{1}H NMR (395.88 MHz, C_6D_6) δ 1.19 (s, 12H), 2.40 (s, 3H), 2.49 (s, 3H), 6.05-6.11 (m, 2H), 6.18 (d, *J* = 7.6 Hz, 1H), 6.67-6.68 (m, 2H), 7.13-7.14 (m, 1H), 7.75 (dd, *J* = 7.6, 1.6 Hz, 1H); ^{13}C{^{1}H} NMR (99.55 MHz, C_6D_6) δ 25.1, 31.6, 31.6, 83.5, 110.8, 111.1, 111.2, 117.0, 117.1, 121.3, 122.0, 130.3, 138.3, 138.6, 139.3, 142.3; MS (ESI (+)) *m/z* calcd for $C_{20}H_{26}BN_2O_2^+$ $[M+H]^+$ 337.2082, found 337.2074.

3h: CAS No. [953040-54-5] <Representative reference: *Angew*. *Chem*. *Int*. *Ed*., 2011, **50**, 2102>

According to the general procedure using 1-(triisopropyl)pyrrole **1h**, **3h** was obtained in 53% yield as a colorless oil. ^{1}H NMR data were in accordance with those reported in the above reference.

^{1}H NMR (395.88 MHz, $CDCl_3$) δ 1.09 (d, *J* = 8.0 Hz, 18H), 1.32 (s, 12H), 1.46 (sept, *J* = 8.0 Hz, 3H), 6.62 (dd, *J* = 1.2, 2.4 Hz, 1H), 6.81 (dd, *J* = 1.6, 2.4 Hz, 1H), 7.23 (dd, *J* = 1.2, 1.6 Hz, 1H).

3i: CAS No. [596819-12-4] <Representative reference: *J. Am. Chem. Soc.*, 2015, **137**, 12211>
According to the general procedure using 2-methoxythiophene **1i**, **3i** was obtained in 27% yield as a colorless oil. ^{1}H NMR data were in accordance with those reported in the above reference.
^{1}H NMR (395.88 MHz, $CDCl_3$) δ 1.32 (s, 12H), 3.92 (s, 3H), 6.30 (d, J = 4.0 Hz, 1H), 7.33 (d, J = 4.0 Hz, 1H).
3j: CAS No. [837392-62-8] <Representative reference: *Angew. Chem. Int. Ed.*, 2011, **50**, 2102>
According to the general procedure using *N*-methylindole **1j**, **3j** was obtained in 67% NMR yield using 1,3,5-trimethoxybenzene as an internal standard. ^{1}H NMR data were in accordance with those reported in the above reference.
^{1}H NMR (300.53 MHz, $CDCl_3$) δ 1.36 (s, 12H), 3.79 (s, 3H), 7.14-7.24 (m, 2H), 7.31-7.34 (m, 1H), 7.52 (s, 1H), 8.03 (d, J = 6.9 Hz, 1H).