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Making Dimethylamino a Transformable Directing Group by Nickel-Catalyzed C–N Borylation

Hua Zhang,[a] Shinya Hagihara,[a] and Kenichiro Itami*[a, b]

Abstract: The dimethylamino (Me_2N) group is arguably the most versatile functional group capable of highly efficient and site-selective directed aromatic functionalizations at the *ortho*-, *meta*-, and *para*-positions depending on reaction conditions. While the repertoire of Me_2N-directed reactions is growing at a rapid pace, the lack of a general method to transform this group to other functionalities hampers its wider application in organic synthesis. Here we report nickel-catalyzed C–N borylations of aryl- and benzyl-dimethylamines that permit the conversion of a huge library of largely underutilized Me_2N-containing organic molecules into various functional molecules by taking advantage of the wealth of existing C–B functionalization methods.

The dimethylamino (Me_2N) group is arguably the most versatile functional group capable of highly efficient and site-selective directed aromatic functionalizations (Figure 1). Classically, the Me_2N group induces *ortho*/*para*-selective electrophilic aromatic substitution (S_EAr) reactions when directly attached to an aromatic ring.[1] Through the strong complex-induced proximity effect with organolithium reagents, the Me_2N group features prominently in directed *ortho*-metalation (DoM) reactions of aromatics.[2–6] In a similar fashion, a range of transition-metal-catalyzed C–H functionalization reactions (DoCH) are known to be directed by the Me_2N group.[7–16] More recently, a palladium-catalyzed *meta*-selective aromatic C–H functionalization (D*m*CH) employing the Me_2N group as a directing group has been reported by the Dong group.[17] While the repertoire of Me_2N-directed reactions is growing at a rapid pace, the lack of a general method to transform this group into other functionalities hampers its wider application in organic synthesis.[10,17,18] We imagined that, if the C–N borylation of aryl- and benzyl-dimethylamines could be devised, it would enable the conversion of a huge library of Me_2N-containing organic molecules into various functional molecules by taking advantage of the wealth of existing C–B functionalization methods.[19,20] We report herein a novel aromatic and benzylic C–N borylation method catalyzed by nickel–phosphine complexes (Figure 1).

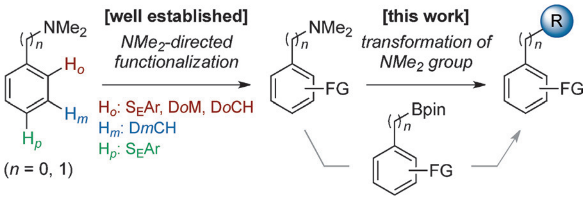

Figure 1. Transformations of the versatile dimethylamino group into various functional groups enabled by aromatic/benzylic C–N borylation.

Prior to our investigation, only a handful of C–N borylation reactions had been reported, in contrast to significant efforts devoted to the development of transition-metal-catalyzed C–N-bond-converting processes.[21–25] Wang developed the metal-free borylation of anilines by use of diazonium salts, with substrate classes limited to primary anilines.[26] The group of Chatani achieved the nickel-catalyzed C–N borylation of aromatic amides.[27] However, remarkably, the borylation of tertiary anilines and benzylic amines still remains unexplored. The recent success of aryl and benzylic ammonium salts in cross-coupling reactions encouraged us to explore the possibility of utilizing these in C–N borylation reactions.[28–39]

We began by investigating the borylation of phenyl ammonium salt **1a** (0.2 mmol), which can be prepared from *N*,*N*-dimethylaniline by simple N-methylation. Bis(pinacolato)diboron (B_2pin_2, 0.4 mmol) was employed as the boron source in the presence of nickel catalysts. After extensive screening, the best result was obtained when the reaction was conducted in the presence of $[Ni(cod)_2]$ (10 mol%; cod = 1,5-cyclooctadiene), tri-*n*-butylphosphine (P*n*Bu_3, 20 mol%), and NaO*t*Bu (2.0 equiv) in 1,4-dioxane at 70 °C for 24 h affording phenylboronic pinacol ester (**2a**) in 85% GC yield (Figure 2).

The effect of alteration to the standard conditions (effect of reaction parameters) is listed in Figure 2. In the absence of $[Ni(cod)_2]$, essentially no borylation occurred. The use of nickel(II) salts as catalyst precursors resulted in somewhat lower yields. Product **2a** was obtained in lower yield without P*n*Bu_3. The use of other monodentate phosphine ligands (PCy_3, $PCyp_3$, PPh_3) and diphosphine ligands (1,3-bis(diphenylphosphino)propane; dppp) resulted in much lower yields. N-Heterocyclic car-

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[a] *Dr. H. Zhang, Prof. Dr. S. Hagihara, Prof. Dr. K. Itami*
Institute of Transformative Bio-Molecules (WPI-ITbM) and
Graduate School of Science, Nagoya University
Chikusa, Nagoya 464-8602 (Japan)
E-mail: itami@chem.nagoya-u.ac.jp

[b] *Prof. Dr. K. Itami*
JST-ERATO, Itami Molecular Nanocarbon Project
Nagoya University, Chikusa, Nagoya 464-8602 (Japan)

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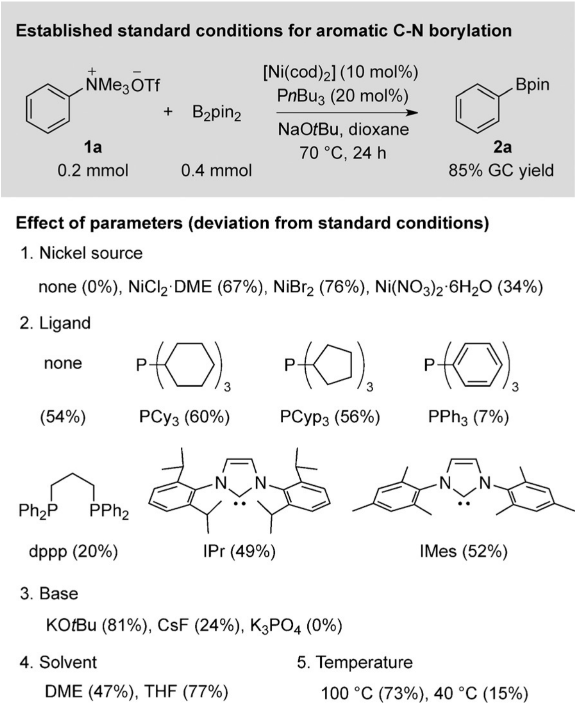
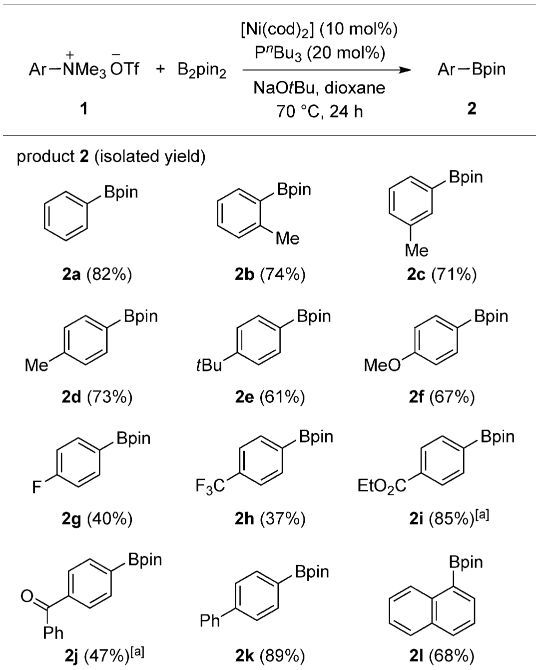
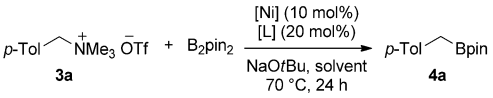


Figure 2. Nickel-catalyzed C–N borylation of phenyl ammonium salt **1a** and effect parameters.



Scheme 1. Ni-catalyzed C–N borylation of aryl ammonium salts **1**. Reaction conditions: **1** (0.2 mmol), B_2pin_2 (0.4 mmol), $[Ni(cod)_2]$ (10 mol %), P*n*Bu_3 (20 mol %), NaO*t*Bu (2.0 equiv), 1,4-dioxane (1.5 mL), 70 °C, 24 h. Isolated yield. [a] CsF (2.0 equiv), THF (1.5 mL).

Table 1. Optimization of Ni-catalyzed C–N borylation of benzylic ammonium salt **3a**.[a]



Entry	[Ni]	[L]	Solvent	Yield [%][b]
1	$[Ni(cod)_2]$	P*n*Bu_3	dioxane	70
2	$[Ni(cod)_2]$	P*n*Bu_3	THF	50
3	$[Ni(cod)_2]$	P*n*Bu_3	DME	72
4	$[Ni(cod)_2]$	PCy_3	DME	33
5	$[Ni(cod)_2]$	IPr HCl	DME	55
6	$NiBr_2$	P*n*Bu_3	DME	66
7	$NiCl_2$	P*n*Bu_3	DME	81
8	$Ni(NO_3)_2{\cdot}6\,H_2O$	P*n*Bu_3	DME	82

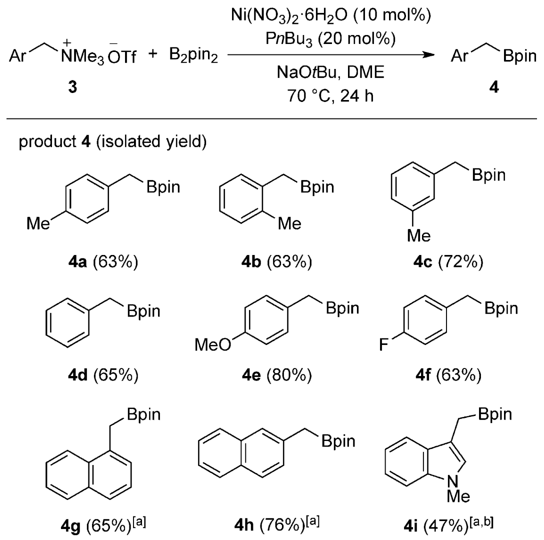
[a] Reaction conditions: **3a** (0.2 mmol), B_2pin_2 (0.4 mmol), Ni catalyst (10 mol %), ligand (20 mol %), NaO*t*Bu (2.0 equiv), solvent (1.5 mL), 70 °C, 24 h. [b] Determined by GC analysis using *n*-dodecane as an internal standard.

bene ligands (IPr and IMes) were also less efficient. The use of *tert*-butoxide-derived bases seems to be critical, with CsF and K_3PO_4 giving little or no borylated product in 1,4-dioxane. When DME or THF were used as the solvent, decreased yields were observed. Either increasing or lowering the temperature led to a decreased yield.

With the optimized reaction conditions in hand, a variety of aryl ammonium salts **1** were subjected to C–N borylation (Scheme 1). Aryl ammonium salts substituted with a methyl group in any position afforded the corresponding borylated products (**2b**, **2c**, and **2d**) in good yields. The position of the substituent seems to have no influence on the yield. Substrates bearing electron-donating substituents worked well under the standard conditions, whereas compared to electron-donating substituents, electron-withdrawing substituents like F and CF_3 furnished the corresponding products in lower yields. Ester and ketone groups could be tolerated under modified conditions using CsF as the base and THF as the solvent (**2i** and **2j**).

After establishing the conditions for the C–N borylation of aryl ammonium salts, we investigated the C–N borylation of benzylic amine derivatives that are another class of substrates used in a range of Me_2N-directed reactions. Reaction conditions were optimized using benzylic ammonium salt **3a** as the substrate (Table 1). Under conditions identical to those of aromatic C–N borylation, **3a** was successfully converted to the corresponding benzylic boronate **4a** in 70 % yield (Table 1, entry 1). While the use of THF as a solvent resulted in lower yield (entry 2), DME turned out to be a somewhat superior solvent (entry 3). As for the ligand, P*n*Bu_3 again proved to be a superior ligand in C–N borylation (entries 3–5). Nickel(II) salts such as $NiBr_2$ and $NiCl_2$ could also be used as catalyst precursors (entries 6 and 7), but even more pleasingly, we found that $Ni(NO_3)_2{\cdot}6\,H_2O$, which is much more stable and cheaper than $[Ni(cod)_2]$ ($Ni(NO_3)_2{\cdot}6\,H_2O$, \$167.5 for 1 kg; $[Ni(cod)_2]$, \$65.6 for 2 g from Sigma-Aldrich), functioned as a pre-catalyst providing **4a** in 82 % yield (entry 8).

A variety of benzylic ammonium salts **3** were subjected to C–N borylation under the influence of $Ni(NO_3)_2{\cdot}6\,H_2O$/P*n*Bu_3 (Scheme 2). Benzylic ammonium salts substituted with



Scheme 2. Ni-catalyzed C–N borylation of benzylic ammonium salts **3**. Reaction conditions: **3** (0.2 mmol), B_2pin_2 (0.4 mmol), $Ni(NO_3)_2·6H_2O$ (10 mol %), $PnBu_3$ (20 mol %), NaO*t*Bu (2.0 equiv), DME (1.5 mL), 70 °C, 24 h. Isolated yield. [a] NaO*t*Bu (1.5 equiv), THF (1.5 mL). [b] 50 °C.

a methyl group at the *ortho*- or *meta*-position afforded the corresponding borylated products (**4b** and **4c**) in good yields. The borylation of benzylic ammonium salts bearing methoxy and fluoro groups produced the desired boronic esters **4e** and **4f** in 80 and 63 % yield, respectively. 1-Naphthylmethyl and 2-naphthylmethyl boronic esters (**4g** and **4h**) were obtained in good yields under modified conditions using THF as the solvent. Notably, indole substrate **3i** could also be borylated to form the corresponding product **4i** in 47 % yield at 50 °C.

On the basis of the above results and previous studies, we propose a mechanism for this borylation process. The oxidative addition of aryl or benzylic ammonium salt (**1** or **3**) to the Ni^0–$PnBu_3$ species with the elimination of NMe_3 is likely the first step. When nickel(II) salts are applied as precatalysts, the active Ni^0 species should be generated by the action of $PnBu_3$ and/or B_2pin_2. The thus-formed organonickel(II) triflate then undergoes σ-bond metathesis with B_2pin_2 to afford (boryl)organonickel(II) species. It is likely that the *tert*-butoxide base facilitates this σ-bond metathesis step.[40–42] Finally, the reductive elimination of the C–B bond produces the borylated product (**2** or **4**), regenerating the active Ni^0 species.

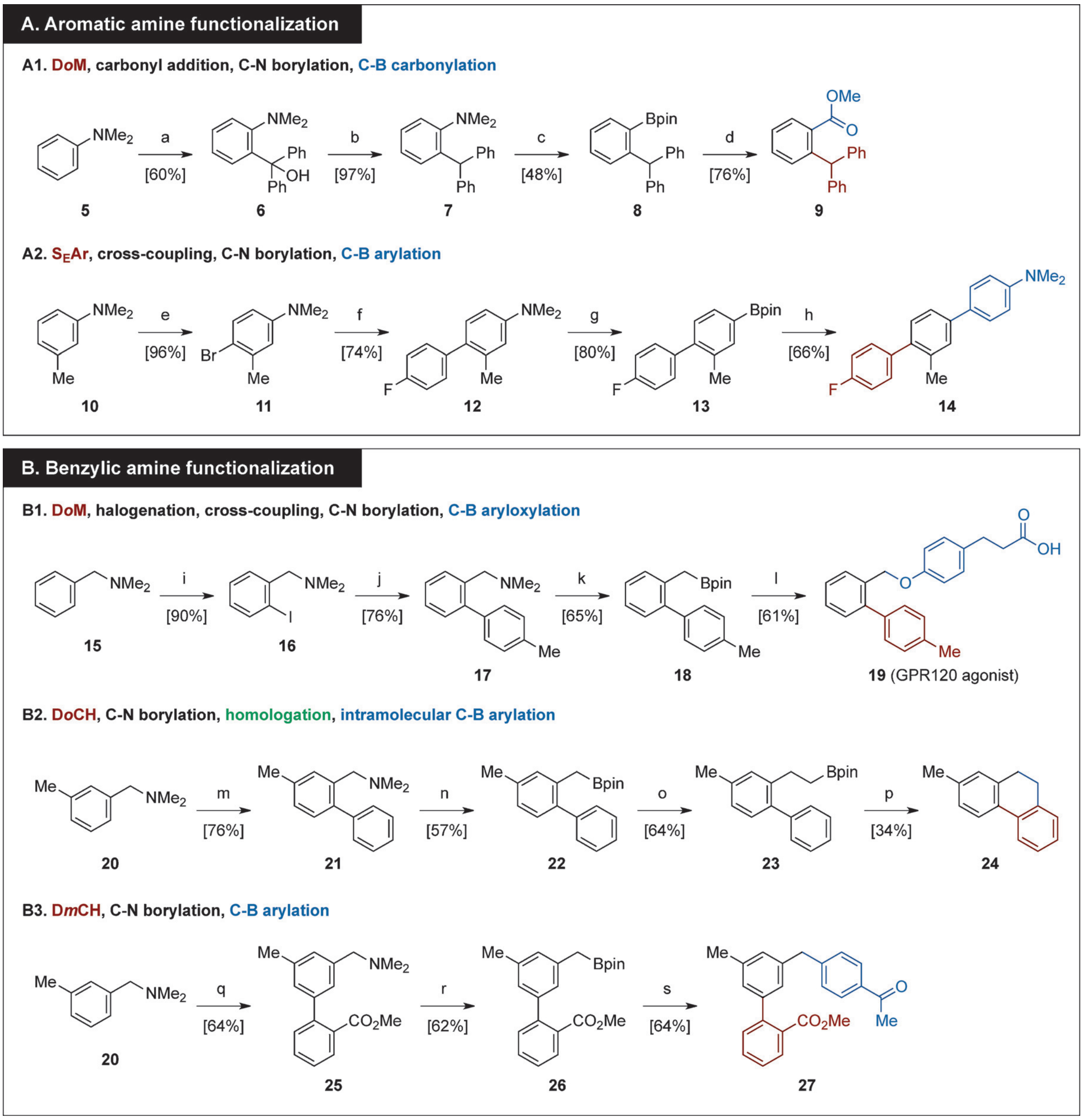
Finally the synthetic versatility of the nickel-catalyzed C–N borylation is demonstrated. As shown in Scheme 3, when coupled with a range of Me_2N-directed aromatic functionalization reactions and C–B transformations, the C–N borylation permits the synthesis of a range of substituted aromatics in a regiocontrolled and diversity oriented fashion. Depicted in Scheme 3A are the examples of aromatic amine functionalization. *N*,*N*-dimethylaniline (**5**) could be *ortho*-lithiated by the *n*BuLi–tetramethylethylenediamine (TMEDA) system and the thus-generated aryllithium underwent carbonyl addition to benzophenone to produce **6**. Further synthetic manipulation is possible. For example, with the aid of the neighboring Me_2N group, formal dehydroxylation of the tertiary alcohol can be conducted under the Pozharskii's conditions[43] followed by reductive N-methylation to produce **7** in 97 % yield. The NMe_2 group in **7** could be transformed to a Bpin group by N-methylation with methyl triflate followed by the C–N borylation under our conditions to furnish **8** in 48 % overall yield. The boronate **8** could then be subjected to palladium-catalyzed carbonylation to give *ortho*-substituted methyl benzoate **9** in 76 % yield.

The C–N borylation can also be coupled with a Me_2N-directed S_EAr reaction. For example, the Me_2N group can direct the *para*-selective bromination of **10** with NBS in the presence of a catalytic amount of NH_4OAc (96 % yield). The obtained bromide **11** undergoes smooth Suzuki–Miyaura coupling producing the corresponding biphenyl derivative **12**. The sequence of N-methylation followed by nickel-catalyzed C–N borylation furnished **13**, which was further subjected to a second Suzuki–Miyaura coupling with aryl bromide to produce Me_2N-containing terphenyl **14** in good overall yield.[44] Since the Me_2N group can be installed into organic molecules by various ways as exemplified in this case, the utility of the Me_2N-converting C–N borylation is enormous.

Shown in Scheme 3B are select examples of benzylic amine functionalization enabled by C–N borylation. As in the case of *N*,*N*-dimethylaniline (**5**), Me_2N-directed *ortho*-lithiation took place with benzyldimethylamine (**15**). The thus-formed aryllithium species could be trapped with I_2 to set the stage for the subsequent Suzuki–Miyaura coupling, yielding biphenyl derivative **17** in good overall yield. N-Methylation of **17** followed by C–N borylation catalyzed by the $Ni(NO_3)_2·6H_2O/PnBu_3$ system afforded the corresponding boronate **18** in 65 % yield over two steps. Boronate **18** was then successfully converted to GPR120 agonist **19** by a copper-catalyzed oxidative aryloxylation reaction and subsequent hydrolysis. GPR120, a receptor of unsaturated long-chain fatty acids, is an emerging new target for treatment of type 2 diabetes and metabolic diseases.[45–48]

Rather than the two-step, Me_2N-directed *ortho*-arylation protocol shown above, benzylic amine derivative **20** could be employed in a one-step Pd-catalyzed *ortho* C–H arylation with iodobenzene to afford substituted benzylamine **21**. Subsequent C–N borylation provided benzylic boronate **22** in 57 % yield. Benzylic boronates also have a number of interesting reactivities. For example, the homologation of **22** took place by treatment with CH_2ClBr/*n*BuLi to give **23** in 64 % yield.[49] After hydrolysis, the resulting alkylboronic acid underwent oxidative cyclization in the presence of a palladium catalyst. The resulting 9,10-dihydrophenanthrene **24** is an extremely useful structure in the synthesis of π-conjugated materials.[50] Benzylic amine **20** could also undergo palladium-catalyzed *meta* C–H arylation under Dong's conditions to afford **25**. The subsequent C–N borylation followed by Suzuki–Miyaura coupling then furnished densely substituted diarylmethane derivative **27** in good overall yield.

In summary, we have developed a novel and efficient C–N borylation of aryl and benzylic ammonium salts promoted by nickel-based catalysts. This simple yet powerful method merges an array of Me_2N-directed aromatic functionalization reactions (*ortho*/*para* electrophilic aromatic substitution, *ortho*



Scheme 3. Synthetic versatility of C–N borylation. Reaction conditions: a) *n*BuLi, TMEDA, benzophenone, ether, HOAc; b) conc. HCl, reflux; NH_4OH; $(HCHO)_n$, $NaBH_4$, CF_3CH_2OH, reflux; c) TfOMe (3 equiv), CH_2Cl_2, 70 °C, 72 h; [Ni(cod)$_2$] (10 mol %), P*n*Bu$_3$ (20 mol %), B$_2$pin$_2$ (2 equiv), NaO*t*Bu (2 equiv), dioxane, 70 °C, 24 h; d) Pd(OAc)$_2$ (10 mol %), PPh$_3$ (20 mol %), *p*-benzoquinone (1 equiv), CO, MeOH, RT, 12 h; e) NH_4OAc (10 mol %), NBS (1 equiv), MeCN, RT, 12 h; f) (4-fluorophenyl)boronic acid (1.25 equiv), [Pd(PPh$_3$)$_4$] (2 mol %), K_3PO_4 (2 equiv), MeOH/H_2O, 95 °C, 16 h; g) TfOMe (1.1 equiv), CH_2Cl_2, 12 h; [Ni(cod)$_2$] (10 mol %), P*n*Bu$_3$ (20 mol %), B$_2$pin$_2$ (2 equiv), NaO*t*Bu (2 equiv), dioxane, 70 °C, 24 h; h) 4-bromo-*N*,*N*-dimethylaniline, [Pd(PPh$_3$)$_4$] (5 mol %), Na_2CO_3 (10 equiv), toluene/EtOH/H_2O, 100 °C, 24 h; i) *n*BuLi, I_2, Et$_2$O, RT; j) *p*-tolylboronic acid (2 equiv), [Ph(PPh$_3$)$_4$] (2 mol %), Na_2CO_3 (2 equiv), toluene/EtOH/H_2O, 100 °C, 12 h; k) TfOMe (1.3 equiv), Et$_2$O, 12 h; Ni(NO$_3$)$_2$·6 H_2O (10 mol %), P*n*Bu$_3$ (20 mol %), B$_2$pin$_2$ (2 equiv), NaO*t*Bu (2 equiv), THF, 70 °C, 24 h; l) methyl 3-(4-hydroxyphenyl)propanoate (2 equiv), Cu(OAc)$_2$ (10 mol %), *t*BuOO*t*Bu (2 equiv), toluene, 100 °C, 24 h; LiOH (3 equiv), THF/H_2O, RT; m) [Pd(PPh$_3$)$_4$] (5 mol %), AgOAc (1.5 equiv), PhI (10 equiv, Cu(OAc)$_2$·H_2O (50 mol %), AcOH, CF_3CH_2OH, 95 °C, 60 h; n) TfOMe (1.3 equiv), Et$_2$O, 12 h; Ni(NO$_3$)$_2$·6 H_2O (10 mol %), P*n*Bu$_3$ (20 mol %), B$_2$pin$_2$ (2 equiv), NaO*t*Bu (2 equiv), THF, 70 °C, 24 h; o) $BrCH_2Cl$ (2 equiv), *n*BuLi (2 equiv), THF, −78 °C to RT; p) $NaIO_4$ (3 equiv), HCl, THF/H_2O, RT; Pd(OAc)$_2$ (20 mol %), Ag_2CO_3 (1 equiv), *p*-benzoquinone (0.5 equiv), *t*BuOH, 100 °C, 16 h; q) Pd(OAc)$_2$ (10 mol %), AsPh$_3$ (25 mol %), norbornene, AgOAc, methyl 2-iodobenzoate, CsOAc, LiOAc·H_2O, Cu(OAc)$_2$·H_2O, HOAc, PhCl, 100 °C, 24 h; r) TfOMe (1.3 equiv), Et$_2$O, 12 h; Ni(NO$_3$)$_2$·6 H_2O (10 mol %), P*n*Bu$_3$ (20 mol %), B$_2$pin$_2$ (2 equiv), NaO*t*Bu (2 equiv), THF, 70 °C, 24 h; s) [Pd(PPh$_3$)$_4$] (8 mol %), PPh$_3$, Ag$_2$O, K_2CO_3, 1-(4-iodophenyl)ethanone, DME, 85 °C, 20 h.

metalation, *ortho* arylation, *meta* arylation, etc.) with a variety of C–B bond transformations (oxidation, homologation, cross-coupling, carbonylation, oxidative cyclization, etc.). Although both of these organic transformations have been developed independently, the development described herein permits the strategic merging of these two versatile transformations through the use of the Me$_2$N group as a transformable directing group. We believe that the present new reaction will have an effect on the way chemists plan and execute the synthesis of highly substituted aromatic compounds.

Experimental Section

General procedure for aromatic C–N borylation

A 20 mL glass vessel equipped with J. Young O-ring tap containing a magnetic stirring bar was dried with a heat-gun under reduced pressure and filled with nitrogen after cooling to room temperature. After adding aryl ammonium salt **1** (0.2 mmol) and bis(pinacolato)diboron (101.6 mg, 0.4 mmol), the vessel was introduced inside an argon-atmosphere glovebox. In the glovebox, [Ni(cod)$_2$] (5.5 mg, 0.02 mmol) and sodium *tert*-butoxide (38.4 mg, 0.4 mmol) were added to the vessel, which was sealed with an O-ring tap and then taken out of the glovebox. Then, $\mathrm{P}n\mathrm{Bu}_3$ (8.1 mg, 0.04 mmol) and 1,4-dioxane (1.5 mL) were added to the vessel under a nitrogen atmosphere. The vessel was heated at 70 °C for 24 h in an oil bath with stirring. After cooling the reaction mixture to room temperature, the mixture was concentrated and directly purified by preparative thin-layer chromatography (PTLC; hexane/ethyl acetate as the eluent) to afford the borylation product **2**.

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Keywords: catalysis · C–N borylation · dimethylamino group · directing group · nickel

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