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Ortho/Ipso Alkylborylation of Aryl Iodides

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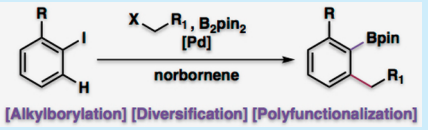
Supporting Information

ABSTRACT: This work describes a method for the difunctionalization of aryl iodides to generate polysubstituted arenes via Pd catalysis. The reaction hinges on the unique interplay between norbornene and the metal catalyst to impart a guided *ortho* C−H alkylation event followed by a programmatic *ipso* borylation to provide a diverse array of substituted arene products. The utility of this transformation is demonstrated through the functionalization of the boronic ester to a variety of valuable functionalities.



When challenged with the task of molecular diversification, the hero(in)es of drug discovery aim to have the most malleable synthetic route available to allow for expedient access to broad molecular space.[1] In turn, the synthetic efficiency with which pharmaceutical leads can be explored has a direct effect on the success of a given drug discovery program.[2] The invention of new chemical transformations that provide *both* the multifunctionalization of simple precursors[3] *and* handles for broad diversification[4] remain attractive for the rapid generation of translational molecular complexity and diversity.

Biologically active molecules and derivatives with multifunctionalized aromatic rings (e.g., **1**−**3**, Figure 1A) can be arduous to prepare depending on the substituents and their relative positioning.[5] More specifically, relevant bioactive molecules such as **1**[6] and **2**[7] have proven difficult to prepare due to the proximity of substituents and/or the inability of desired groups (e.g., CF_3, Cl) to controllably allow for innate and regioselective polyfunctionalization. Important therapeutics like naloxone (**3**)[8] exacerbate this problem by having further aryl substitution in addition to an increased molecular complexity.[9]

In an effort to address these issues, it was hypothesized that the installation of a boronic ester could serve as a functional handle to allow for diversification. When this borylation is combined with a guided alkylation at the *ortho* position (see **4**), the aforementioned substitution patterns found in **1**−**3** and/or derivatives thereof could be more effectively accessed.[10] Finally, it was envisioned that these highly substituted boronic esters would arise from simple aryl halide precursors such as **5** that could be either commercially available or easily prepared.

Guided C−H functionalization[11] via Pd/norbornene (NBE) dual catalysis has been an instrumental tool in the polyfunctionalization of aromatic rings.[12] With regard to arene alkylation, Catellani demonstrated one of the first examples in 1999, where aryl iodides (**6**) were converted to alkylated cinnamates (**7**) using alkyl iodides, acrylates, Pd, and NBE.[13] Later, as the scope of electrophiles and nucleophiles were expanded,[12] Ritter demonstrated that an *ortho*/*ipso* aminoborylation was easily achieved under a similar catalytic

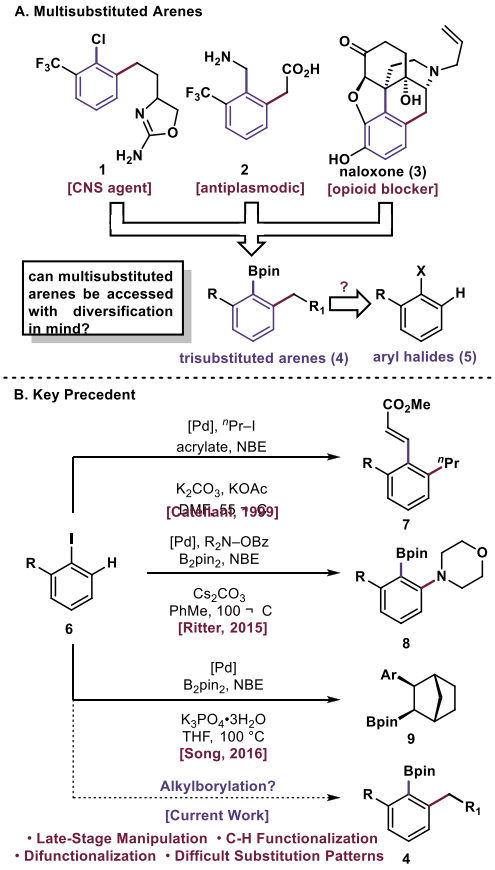


Figure 1. (A) Inspiration of the alkylborylation. (B) Prior work that provided a platform for the method.

manifold producing anilines (see **8**). This elegant transformation demonstrated the ability for the Catellani reaction to be molded for modularity and would allow for molecular diversification following arene difunctionalization.[14] In addition, Dong very recently showed an example of borylation in

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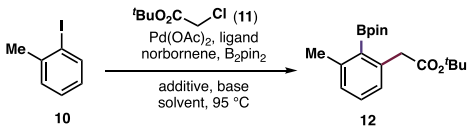
Catellani-type arene difunctionalization reactions.[15] It was evident from this prior work that the desired alkylborylation reaction might be possible, but not without considering potential setbacks. One major consideration was described in 2016, where Song and co-workers demonstrated that the aryl borylation of NBE was facile to form **9**, while avoiding *ortho*/*ipso* Catellani-type arene difunctionalization.[16] To the authors' knowledge, the catalytic *ortho*/*ipso* alkylborylation to produce products like arene **4** remained unknown[17] and could provide access to high-value borylated products.

Initially, based on the work of Catellani, Lautens, and others,[18] typical Pd/NBE-based conditions were employed to difunctionalize 10 using PPh_3 as a ligand with K_2CO_3 in MeCN (Table 1, entry 1). Perhaps not surprisingly, the major

Table 1. Reaction Optimization



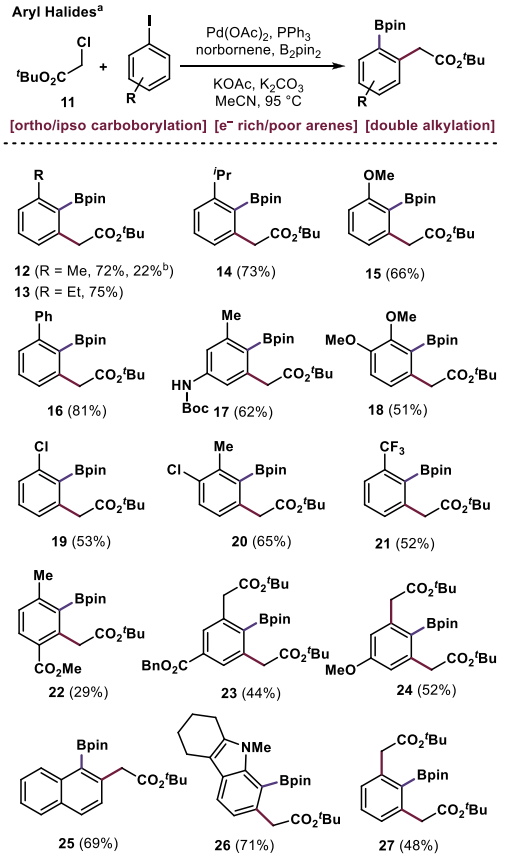
Entry[a]	Solvent	Base	Additive	Ligand	Yield (%)
1	MeCN	K_2CO_3	–	PPh_3	10[b]
2	DMF	K_2CO_3	KOAc	PPh_3	23
3	Dioxane	K_2CO_3	KOAc	PPh_3	11
4	MeCN	K_2CO_3	KOAc	PPh_3	44
5	MeCN	K_2CO_3	KOAc	RuPhos	15
6	MeCN	K_2CO_3	KOAc	DavePhos	34
7	MeCN	Cs_2CO_3	KOAc	PPh_3	28
8	MeCN	K_3PO_4	KOAc	PPh_3	39
9	MeCN	K_2CO_3	NaOAc	PPh_3	45
10	MeCN	K_2CO_3	KOAc	PPh_3	72[c]
11	MeCN	–	KOAc	PPh_3	21

[a]Conditions: **10** (0.16 mmol), B_2pin_2 (2 equiv), **11** (4 equiv), $Pd(OAc)_2$ (7 mol %), ligand (14 mol %), base (3 equiv), additive (6 equiv) at 0.09 mol/L. [b]80% of **9** was observed (Ar = *o*-tolyl). [c]Concentration was 0.03 mol/L.

product was the difunctionalization of NBE (**9**, Ar = *o*-tolyl), isolated in 80% yield, with only 10% yield of the desired aryl boronic ester (**12**). Encouraged by the reaction's feasibility, adding KOAc as an additive in the reaction allowed for an increased yield of the desired product to 44% (Scheme1, entry 4). Decreasing the concentration of the reaction mixture allowed for an increase to 72% isolated yield of the desired product (Scheme 1, entry 10). Modification of the solvent (entries 2–3), ligand (entries 5–6), or base/additive salt (entries 7–9) did not significantly improve the yield of **12**.

With optimized conditions in hand, the alkylborylation reaction was evaluated on various aromatic iodides (Scheme 1). Using *tert*-butyl chloroacetate **11** as the alkyl electrophile, it was discovered that substrates bearing alkyl substitution were compatible under the reaction conditions (**12**–**14**) in addition to aryl (**16**) and electron-donating substituents (**15**, **17**–**18**). Replacement of the iodide with an aryl bromide resulted in a decreased yield in the case of **12** (22%). Chlorides and other electron-withdrawing groups were tolerated in the reaction at the *ortho* (**19**, **21**), *meta* (**20**, **22**), or *para* position (**23**) of the arene coupling partners. The latter example is one example of utilizing this alkylborylation reaction to also afford (bis)-alkylated products that result in a trifunctionalization of the parent iodide. Futhermore, electron-rich (**24**) and electron-neutral substrates (**27**) function under this mode of double C–H activation. Lastly, bicyclic iodides such as 1-iodonaphthalene and a tetrahydrocarbazole coupled well to afford products **25** and **26**, respectively.

Scheme 1. Arene Scope of the *Ortho*/*Ipso* Alkylborylation



[a]Conditions: arene (0.16 mmol), B_2pin_2 (2 equiv), **11** (4 equiv), $Pd(OAc)_2$ (7 mol %), PPh_3 (14 mol %), K_2CO_3 (3 equiv), KOAc (6 equiv) at 0.03 mol/L. [b]2-Bromotoluene was the substrate.

Various alkyl electrophiles were also evaluated under the optimized reaction conditions (Scheme 2). With iodotoluene (**10**) as a model arene substrate, various chloroacetate esters (see **29**–**32**) underwent coupling to give the alkylborylated arenes with synthetically useful yields ranging from 57 to 70%. Additionally, chloroacetamides were coupled successfully giving tertiary amide **37** in 61% yield and secondary amide **38** in slightly reduced yield. Notably, the coupling of methyl iodide was successful to give the dimethylarene **36** and the coupling of benzyl chloride delivered **33** in a moderate 54% yield. When other alkyl halides (see **34** and **35**) were evaluated under these reaction conditions, KOAc had to be excluded from the reaction because of a competitive displacement of the iodide via substitution. As a result, the competitive NBE difunctionalization was difficult to avoid in these cases, as the KOAc was important for the promotion of C–H functionalization over norbornene difunctionalization (*vide supra*). Circumventing this issue proved challenging and is a limitation of the current method. It should be noted that, at present, all efforts to replace KOAc with other acetate, pivaloate, or benzoate salts have not significantly attenuated this observed substitution reaction on unactivated halide coupling partners. This fact oddly does not encompass the case of methylation, however, where the desired product (**36**) was isolated in 60% yield.

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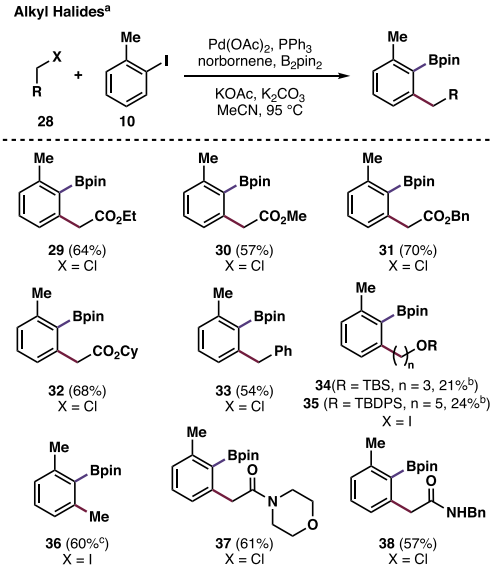
Scheme 2. Alkyl Scope of the *Ortho*/*Ipso* Alkylborylation

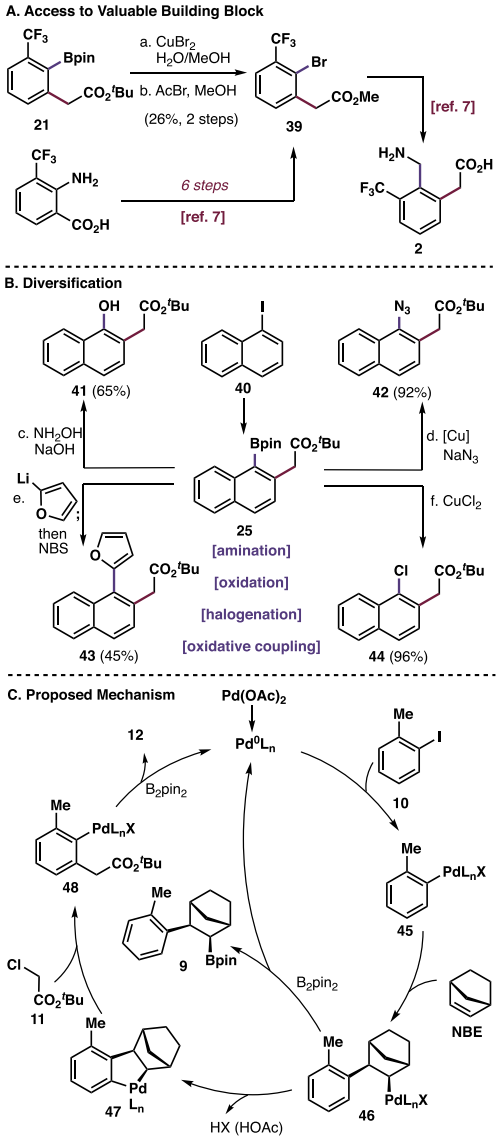


[a]Conditions: 10 (0.16 mmol), B_2pin_2 (2 equiv), 28 (4 equiv), $Pd(OAc)_2$ (7 mol %), PPh_3 (14 mol %), K_2CO_3 (3 equiv), KOAc (6 equiv) at 0.03 mol/L. [b]KOAc not added. [c]7 equiv of MeI were used.

As a main goal of this synthetic study was to provide an avenue for diversification of the alkylborylation products, various postmethodological modifications were pursued (Scheme 3). First, boronic ester **21** was converted to an aryl bromide mediated by Cu and then transesterified under acidic conditions to give methyl ester **39** (Scheme 3A). This methyl ester is very expensive, only available from limited suppliers.[19] Additionally, this intermediate was important in the investigation of derivatives such as **2** (Figure 1) aimed at treating infection with *Toxoplasma gondii*.[7] Our new route to this intermediate (three steps from a commercial aryl iodide) compares favorably to the known synthetic route which previously required twice the number of synthetic steps.[7] Additionally, boronic ester **25**was elaborated to several different derivatives that have no prior route for preparation. For example, under oxidative conditions, boronic ester **25** was converted to naphthol **41**.[20] Copper mediated azidation and chlorination of **25** were also accomplished in 92% and 96% yield to give **42** and **44**, respectively.[14] Lastly, oxidative coupling of 2-lithiofuran was also accomplished to deliver **43** in 45% yield (Scheme 3B).[21]

The proposed mechanism of the alkylborylation is depicted in Scheme 3C. After reduction of the Pd salt to Pd^0, oxidative addition of the aryl iodide occurs to give arylpalladium intermediate **45**. Migratory insertion of this species across NBE gives alkylpalladium **46** which, in the presence of KOAc, seems to predominantly and competitively promote the formation of palladacycle **47**. It is hypothesized that the acetate additive helps promote this C−H palladation event,[22] while the absence of the acetate anion largely results in the formation of **9** via transmetalation and reductive elimination of the catalyst. Furthermore, dilution of the reaction (*vide supra*) favors the formation of the alkylborylated arenes over norbornene difunctionalization by putatively slowing the rate of transmetalation from **46** relative to the intramolecular arene C−H palladation en route to **47**. Following oxidative incorporation of the alkyl chloride **11** and subsequent reductive alkylation, NBE is extruded to afford arylpalladium intermediate **48**,

Scheme 3. Diversification and Proposed Mechanism



[a]Conditions: (a) $CuBr_2$, $MeOH/H_2O$ 1:1, 80 °C; (b) AcBr, MeOH, 0 °C−rt, 12 h, 26%; (c) NH_2OH, NaOH, EtOH, 12 h, 65%; (d) NaN_3, $Cu(OAc)_2$, MeOH, 50 °C, 95%; (e) furan, BuLi, THF, 0 °C−rt, 3 h; then **26**, THF, −78 °C; then NBS, THF, −78 °C−rt, 12 h, 45%; (f) $CuCl_2$, 1:1 $MeOH/H_2O$, 4 h, 80 °C, 96%.

which then undergoes borylation with B_2pin_2 to afford **12** and regenerate the catalyst. It is worth noting that while acetate salts have been known to improve Catellani-type reactions in the past,[22] this work provides further insight into the beneficial role it has in mitigating undesired side reactions like in the formation of **9**.

In conclusion, we have developed an *ortho*/*ipso* alkylborylation reaction that provides access to multisubstituted arenes in moderate to good yield. In addition to the arenes explored, a selection of activated alkyl halides have also provided alkylated derivatives that are poised for further elaboration in addition to the boronic esters, which have demonstrated synthetic utility for the synthesis of valuable arene building blocks. It is anticipated that these will be of value for drug discovery and can be valuable starting points for complex molecule synthesis (e.g., **3**). Finally, the "acetate effect" that is crucial to the

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success of this transformation remains of particular intrigue for future study. While pertinent to shepherding the desired reactivity described above, its distinct role in promoting these catalytic transformations will also be a focus for future reaction development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03674.

Experimental details and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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