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C(sp^3)–C(sp^2) cross-coupling of alkylsilicates with borylated aryl bromides – an iterative platform to alkylated aryl- and heteroaryl boronates†

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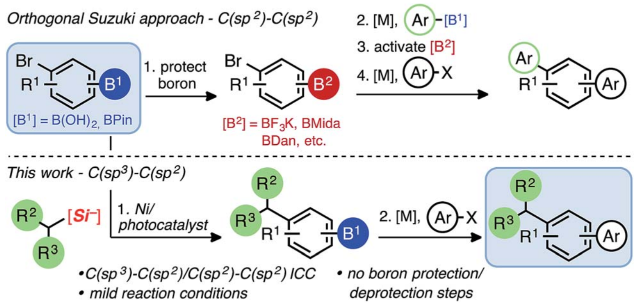
The attractive field of iterative cross-coupling has seen numerous advances, although almost exclusively in the union of sp^2-hybridized partners. Conspicuously absent from this useful synthetic manifold is the inclusion of sp^3-hybridized pronucleophiles that can undergo transmetalation under mild conditions. Described here is the use of primary and secondary ammonium alkylsilicates, which undergo facile C(sp^3)–C(sp^2) cross-coupling with borylated aryl bromide partners under photoredox/nickel dual catalysis conditions. This operationally simple procedure allows the production of alkylated small molecules possessing boronate ester (BPin, Bneopentyl, BMIDA) functional handles. Because of the extremely mild reaction conditions and the innocuous byproduct generated upon fragmentative oxidation of silicates, the corresponding borylated compounds were isolated in good to excellent yields. Aryl bromides bearing unprotected boronic acids are also generally tolerated for the first time and prove useful in multistep syntheses. Unlike many previously reported photoredox/Ni dual cross-couplings, the C(sp^3)–C(sp^2) bonds were forged using a transition metal-free photocatalyst, allowing a substantial increase in sustainability as well as a cost reduction. Because the developed Ni-catalyzed cross-coupling does not require discrete boron speciation control, as in many popular orthogonal Pd-based methods, this protocol represents a significant advance in atom- and step-economy.

Introduction

Iterative cross-coupling strategies in the presence of reactive handles for the rapid assembly of multifunctionalized small molecules have seen numerous advances in recent years,[1] capitalizing on decades of increasingly reliable C(sp^2)–C(sp^2) cross-coupling approaches. Arenes and heteroarenes constitute the core structural feature in many materials (pharmaceuticals or agrochemicals), and polysubstituted arenes allow multidirectional syntheses, greatly extending accessible chemical space. Although significant improvements have been realized, primarily in the context of iterative Suzuki–Miyaura cross-coupling reactions,[2] other traditional C–C cross-coupling methods have been associated with various constraints, such as high temperatures, long reaction times, and the need for strong bases and/or protecting groups.

N-Methyliminodiacetic boronates (BMIDA),[3] 1,8-diaminonaphthalenes (BDAN),[4] and trifluoroborates (BF_3K)[5] are the most popular modes of boron protection ([B^2], Scheme 1) in Pd-based iterative cross-coupling, unmasking the latent functional group through solvent swaps/hydrolysis sequences to unveil the reactive boronic acid or ester ([B^1]). Burke has been instrumental in employing MIDA boronate esters in an iterative and recently automated context.[6] However, boronic acids and pinacol boronates remain the most widely employed and versatile partners because of their high and predictable reactivity using transition metal catalysis, even though protection/functionalization from these commercially available species is often non-ideal in terms of atom- and step economy.[7]

In a separate vein, the general union of C(sp^3) pronucleophiles with C(sp^2) partners [aryl- or alkenyl(pseudo)halides] in



Scheme 1 Comparison between traditional orthogonal cross-coupling reactions and this work. ICC = iterative cross-coupling.

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the presence of reactive handles (*e.g.*, boronic acids or boronates) has been a longstanding challenge under traditional Pd-based catalysis and still represents a formidable transformation for which a direct solution remains elusive.[8] A powerful synthetic paradigm was recently unveiled by several groups, including our own, combining mild photoredox catalysis with transition metal cross-coupling, granting access to new C(sp^3)–C(sp^2) bond-forming reactions of alkyl radicals.[9] This process takes advantage of a facile single electron transmetalation step, circumventing the high-energy and difficult two-electron transmetalation required by traditional alkyl pronucleophiles (*e.g.*, alkylboron reagents).

Most recently, we reported the use of ammonium alkylsilicates that smoothly react with aryl bromides, generating new sp^3–sp^2 C–C bonds.[10] Under this photoredox/Ni dual cross-coupling protocol, a variety of unactivated ammonium alkylsilicates were cross-coupled with various (hetero)aryl and alkenyl halides[10e] or sulfonates in high yields. In comparison to previous reports using potassium alkyltrifluoroborates[9b,11,14] and carboxylic acid derivatives[9e,12] in photoredox/nickel-mediated C(sp^3)–C(sp^2) cross-couplings, reactions involving ammonium alkylsilicate radical precursors do not require any additives or additional base, allowing exceptional functional group tolerance, especially for protic functional groups. The relatively low oxidation potential of the ammonium silicates (E^0 = +0.75 V *vs.* SCE for 1° alkylsilicates, on average)[13] allows the use of the less expensive and readily available [Ru(bpy)$_3$](PF$_6$)$_2$ photocatalyst. Collectively, the extremely mild reaction parameters used for alkylsilicates and the virtually barrierless nature of alkyl-to-nickel transfer should allow the general inclusion of diverse, reactive handles under this odd-electron manifold.

We recently unveiled the first general and mechanistically orthogonal union of alkyl-BF$_3$K nucleophiles with borylated bromoarenes.[14] This departure from strictly C(sp^2) coupling partners in an iterative fashion offers a potentially powerful tool to access structurally more elaborate molecules in short order. Unlike conventional, orthogonal Suzuki reactions between sp^2-hybridized bromides and sp^2-hybridized boronic acids, where orthogonality is based solely on boron speciation (Scheme 1),[15] the applicability of mildly-generated sp^3-carbon nucleophiles is a feature that not only complements Pd-based iterative cross-coupling protocols, but one that is mechanistically distinct from preexisting cross-coupling methods, suggesting broad impact.

Though successful in C(sp^3)–C(sp^2)/C(sp^2)–C(sp^2) cross-couplings, alkyl-BF$_3$Ks possess several drawbacks, notably the release of BF$_3$ upon oxidative fragmentation. This byproduct is corrosive and can inhibit reaction progression. Additionally, BF$_3$ can be problematic for the tolerance of some functional groups, and its generation requires the addition of exogenous base. In the presence of boronate esters, these inherent limitations prevented the straightforward isolation of the intermediate boron-containing compounds.[14] Therefore, we envisioned a mild C(sp^3)–C(sp^2) dual catalytic cross-coupling of alkylsilicates with borylated aryl bromides, complementing the paucity of Pd- and Ni-based C(sp^3)–C(sp^2) orthogonal Suzuki–Miyaura strategies. Successful execution would be a welcomed advance to the field by accelerating the modular synthesis of complex small molecules.[16]

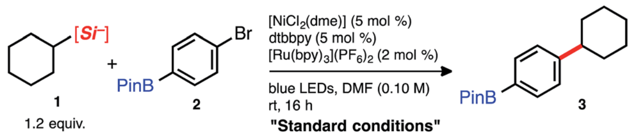
Results and discussion

We began by gauging the reactivity and tolerability of cyclohexylsilicate **1** with a borylated bromoarene, 4-bromophenyl pinacolboronate (**2**). The combination of photocatalyst [Ru(bpy)$_3$](PF$_6$)$_2$, (2 mol%), alongside [NiCl$_2$(dme)]/dtbbpy (5 mol% of each; dtbbpy = 4,4′-di-*tert*-butyl-2,2′-bipyridine) in the presence of blue LEDs was previously shown to be suitable for cross-coupling and was attempted first.[10a] After 16 h we observed full conversion (99%, entry 1, Table 1) to the desired C(sp^3)–C(sp^2) coupled pinacol ester **3** by HPLC analysis, without any byproducts (*e.g.*, protodeboronation or oxidation) traditionally associated with Pd-catalysis or more harsh coupling conditions.

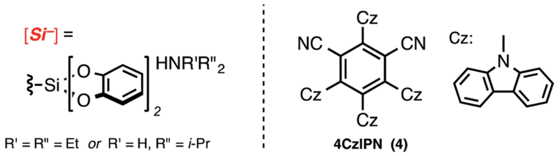
To verify that the proposed mechanistic events are transpiring as hypothesized, control experiments in the absence of blue LEDs, photocatalyst, and nickel (entries 2–4, Table 1, respectively) afforded none of the desired coupled product, only starting material (**2**). Fortunately, the organic photocatalyst 4CzIPN[17] **4** provided **3** in comparable yield to the ruthenium photocatalyst (entry 6, Table 1), as did the more strongly oxidizing iridium photocatalyst (entry 5, Table 1). Additionally, organic photocatalyst **4** was compatible with a standard 26 W compact fluorescent lightbulb (CFL) and white LEDs (95% and 94% yield, entries 9 and 10, respectively).

With suitable reaction conditions in hand for the photoredox/Ni dual-catalyzed cross-coupling of 4-bromophenyl

Table 1 Reaction optimization



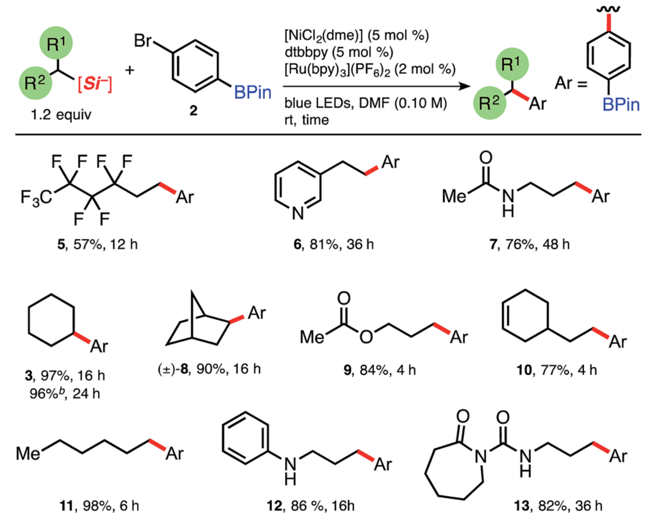
Entry	Variation from standard	% yield (HPLC)
1	No variation	99
2	No light	2
3	No [Ru(bpy)$_3$](PF$_6$)$_2$	0
4	No [NiCl$_2$(dme)]	0
5	[Ir{dF(CF$_3$)$_2$ppy}$_2$(bpy)]PF$_6$ instead of [Ru]	96
6	4CzIPN (**4**) instead of [Ru]	98
7	[Ni(COD)$_2$] instead of [NiCl$_2$(dme)]	90
8	+3 equiv. HTMP	76
9	4CzIPN (**4**) with CFL	95
10	4CzIPN (**4**) with white LEDs	94



pinacolboronate (**2**), we set out to determine the generality of the developed protocol using a library of ammonium alkylsilicates. A range of ammonium alkylsilicates were well tolerated, and various 2° and even 1° alkylsilicates were effectively cross-coupled in good to excellent yields without compromising the integrity of the boronate ester (Table 2). Brønsted and Lewis basic 3-pyridyl (**6**) and aniline (**12**) adducts can be generated and isolated from the corresponding silicates without issue. As the developed protocol requires no additives or base, protic amide **7** and urea **13** can be suitably cross-coupled with **2**. To our knowledge, these often problematic moieties have never been cross-coupled in the presence of pinacolboronates, notably expanding the alkyl partners and functional groups that can be integrated under this C(sp^3)–C(sp^2) cross-coupling manifold. To demonstrate the scalability of this photocatalyzed reaction, 1.0 g of 4-bromophenyl pinacolboronate **2** was coupled in a simple round bottom flask (see ESI†) and also afforded adduct **3** in excellent yield (96%, Table 2), moreover with reduced catalyst loading {1.5 mol% 4CzIPN, 3 mol% [$NiCl_2$(dme)] and [dtbbpy]}. It is also worth noting that the crude reaction profiles in nearly all cases are exceptionally clean following a simple basic workup and extraction.[18]

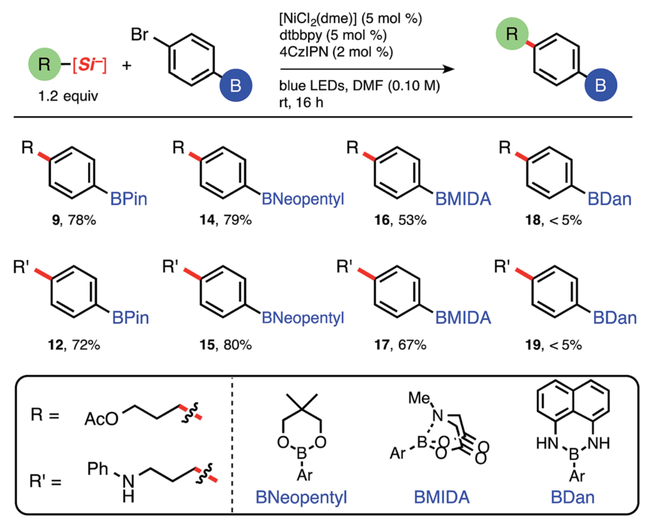
Satisfied with the functional group tolerance of primary and secondary ammonium alkylsilicates, we next explored other common boronate esters (Table 3). Although this mild C(sp^3)–C(sp^2) cross-coupling is tolerant of relatively reactive pinacolboronate esters and does not necessitate the use of more robust boron protecting groups as required in other iterative methods using Pd,[15] diverse masked boronate esters are nonetheless useful reagents in cross-coupling chemistry. Having established the effectiveness of the 4CzIPN organic photocatalyst (**4**), we decided to use the latter because it is free of costly transition metals (*i.e.*, Ir or Ru), and therefore inherently more sustainable and cost efficient (Table 3).[19] Pinacolboronates **9** and **12** and the neopentyl boronate ester adducts (**14** and **15**) were isolated in good yields following standard column chromatography.

Table 2 Examination of various primary and secondary ammonium alkylsilicates with borylated bromoarene **2**[a]



[a] Isolated yields. Ar = 4-phenyl pinacol boronate. [$NiCl_2$(dme)] was complexed with dtbbpy prior to reaction setup, although precomplexation was shown to not always be necessary, see ESI. Reactions run on 0.5 mmol of bromide **2** for the allotted time. [b] 1.00 gram (3.5 mmol) of **2**, dtbbpy (3 mol%), [$NiCl_2$(dme)] (3 mol%) and 4CzIPN (1.5 mol%).

Table 3 Examination of various boron protecting groups[a]

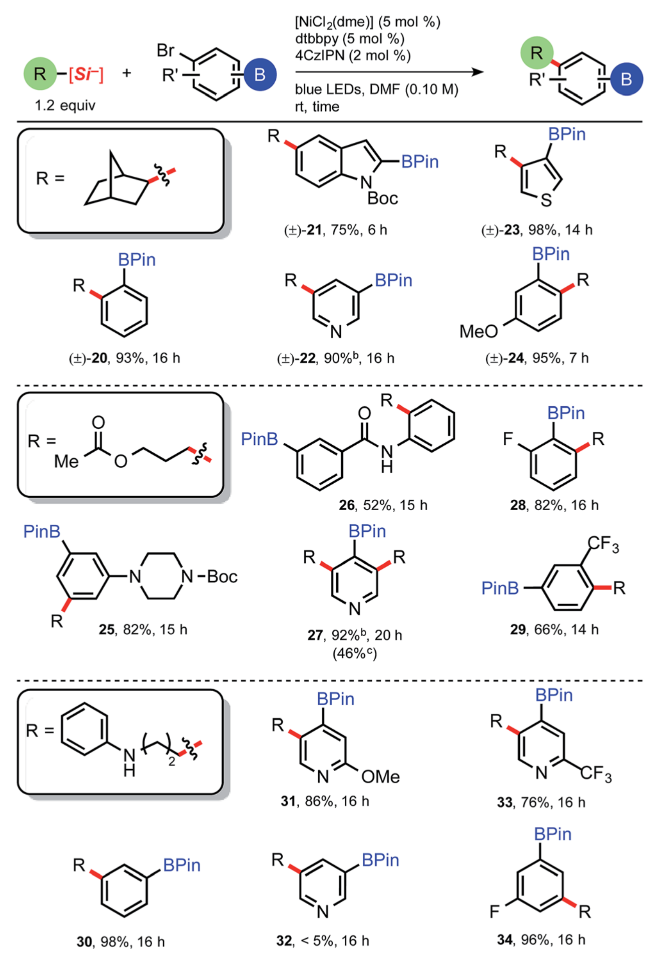


[a] Isolated yields. [$NiCl_2$(dme)] was complexed with dtbbpy ligand prior to reaction setup, see ESI. Reactions run on 0.5 mmol of aryl bromide.

Interestingly, yields obtained for **9** and **12** while using 4CzIPN (Table 3) are in the same range as those obtained using [$Ru(bpy)_3$](PF_6)$_2$ (Table 2), proving the efficiency of the organic photocatalyst under this reaction manifold. The reactions employing BMIDA aryl bromide proceeded to nearly full, clean conversion, although yields of **16** and **17** were moderate (**16** isolated *via* crystallization) because of difficulties in purification. Nevertheless, the prepared BMIDA boronate esters can be useful intermediates in the automated, iterative assembly of complex molecules.[6] The 1,8-diaminonaphthalene (BDan) adducts (**18** and **19**) uniformly provided trace desired product.

The attractiveness of a simplified assembly of alkylated arenes bearing reactive, borylated handles may perhaps be most relevant in pharmaceutical discovery chemistry. Although successive, bidirectional reactions at both boron and the halogen are attractive processes, we were initially interested in isolating the alkylated BPin intermediates, as we surmised these may serve as more useful synthetic intermediates toward discretionary tandem reactions.[15d] From this viewpoint, we set out to demonstrate the breadth of structural diversity by examining three distinct ammonium alkylsilicates (Table 4) with various bromo-substituted aryl- and heteroaryl pinacol boronates. To our knowledge, heteroaromatic BPins, which are known to be particularly sensitive because of their reactivity, have never been successfully alkylated under a transition metal-mediated process. The bicycloheptylsilicate (**35**) coupled

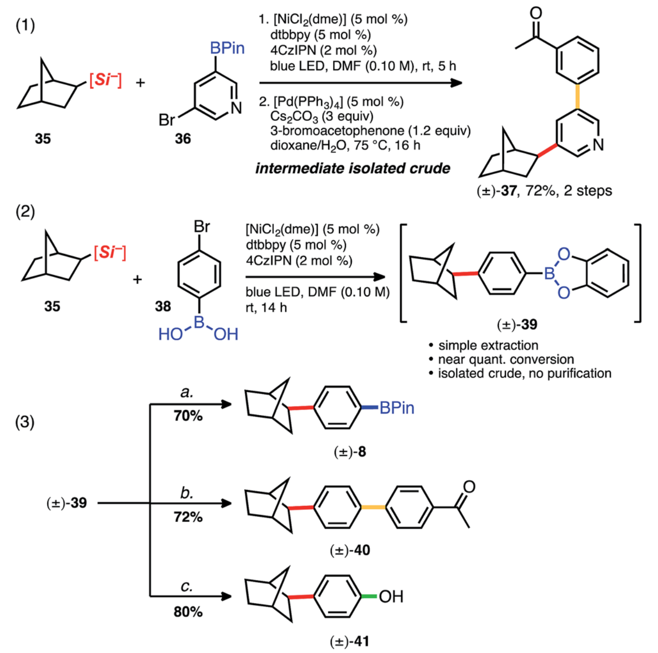
Table 4 Combinatorial examination of silicate and borylated aryl bromide coupling partners[a]



[a] Isolated yields. $[NiCl_2(dme)]$ was complexed with dtbbpy ligand prior to reaction setup, see ESI. Reactions run on 0.5 mmol of aryl bromide for the allotted time. [b] Yield without purification on silica. [c] Yield after purification on silica.

smoothly with hindered benzene-derived bromo BPins to afford **20** and **24** (Table 4), as well as several heteroarenes (**21–23**) for the first time. Boronate esters adjacent to heteroatoms as in **21** are notoriously challenging to couple under Pd-catalysis (owing to competitive protodeboronation),[20] but prove to be robust under these Ni-catalyzed conditions. 3-Bromopyridyl BPin (precursor to **22**) was an intriguing case, as the crude reaction mixture contained only **22** and residual catechol, yet **22** largely decomposed upon purification attempts (90% crude yield, see ESI†). We conjectured **22** could be carried on crude though subsequent transformations (*vide infra*).

The 3-acetoxypropylsilicate was found to be a suitable substrate when paired with various borylated aryl- and heteroaryl bromides. The more structurally complex bromo piperazinylarene and 2-bromophenylbenzamide BPins afforded **25** and **26**, respectively, in acceptable yields (82% and 52%; Table 4). The dialkylated pyridine **27** suffered from higher than normal instability on silica, yet in this case could be isolated pure in a modest 46% yield. Protic and even mildly Brønsted acidic substrates are traditionally incompatible under basic Suzuki cross-coupling conditions, and in this context, the aniline-derived silicate (3^{rd} box, Table 4) together with various borylated aryl bromides was next examined. Collectively, alkylation of various bromoarenes proceeded in generally high yields, including the electron-rich 2-methoxypyridyl BPin **31** and the electron-poor 2-trifluoromethylpyridyl BPin **33**. 5-Bromopyridyl-3-pinacol boronate **32** was not compatible with this particular silicate. Observing clean crude reaction profiles from the $C(sp^3)$–$C(sp^2)$ cross-coupling, we surmised purification limitations (*i.e.*, for compounds **22** and **27**, Table 4) could be overcome by directly reacting the crude cross-coupled BPin in a following transformation. Alkylated pyridyl BPin **22** expressed uncharacteristic instability on silica gel and thus provided an opportunity to investigate this notion. Silicate **35** and bromopyridyl BPin **36** were subjected to the standard reaction conditions using 4CzIPN (**4**), and following a basic aqueous workup and isolation, the alkylated crude material (**22**) was next subjected to standard Suzuki conditions with 3-bromoacetophenone (Scheme 2, eqn (1)). The reaction proceeded smoothly (even in the presence of trace residual catechol and 4CzIPN), and difunctionalized pyridine **37** was isolated in 72% yield over 2 steps. In direct comparison to other orthogonal cross-coupling reactions, it is evident that this iterative $C(sp^3)$–$C(sp^2)$, $C(sp^2)$–$C(sp^2)$ coupling does not require boron speciation control,[1b,15a] activation, deprotection, or neighboring group control[3] of any kind, streamlining accessibility to multifunctionalized molecules.



Scheme 2 Example of iterative $C(sp^3)$–$C(sp^2)$/Suzuki cross-coupling and the compatibility of bromoarylboronic acids. Isolated yields. (a) Pinacol (2 equiv.), THF, 40 °C, 90 min (70%, 2 steps); (b) 3-bromoacetophenone, $[Pd(PPh_3)_4]$, Cs_2CO_3, dioxane/H_2O, 90 °C (72%, 2 steps); (c) 30% H_2O_2, 1 M NaOH, THF, rt, 1 h (80%, 2 steps).

We next questioned whether these mild and base-free reaction conditions were tolerant of bromoarylboronic acids. Arylboronic acids arguably represent the most accessible and convenient modular building blocks in cross-coupling chemistry, yet notoriously require protection in multistep syntheses because of their high reactivity under various modes of catalysis. Bicycloheptylsilicate **35** was subjected to a standard C(sp^3)–C(sp^2) cross-coupling with 4-bromophenyl-boronic acid **38** using **4** as the photocatalyst (Scheme 2, eqn (2)). Full conversion was accomplished after 14 h, but esterification of the boronic acid had occurred, generating the catechol boronate ester (**39**, Scheme 2).

Even though catecholboronate esters are among the most sensitive of all the boronate functional groups, **39** nonetheless proved synthetically useful if promptly reacted. Thus, catechol **39** was subsequently transformed in several different ways. Alkylation and subsequent protection with pinacol afforded BPin **8** in good yield (70%, 2 steps; Scheme 2, eqn (3)). Subjection of **39** to Suzuki–Miyaura conditions afforded arylated **40** in 72% yield over two steps, and straightforward oxidation of **39** also proceeded smoothly, generating phenol **41** in 80% yield over 2 steps. To our knowledge, these tandem 2-step syntheses beginning from unadulterated arylboronic acids are the first examples of C(sp^3)–C(sp^2) cross-coupling with such general tolerance of these abundant building blocks. Collectively, reactions using bromoboronic acids are comparable in yield and setup to those employing more robust bromoaryl BPins.

Conclusions

In summary, secondary and primary ammonium alkylsilicates were found to be exceptional alkylating agents in the presence of various brominated aryl- and heteroaryl boronate esters, and for the first time, ubiquitous boronic acids prove to be generally tolerable substrates to more elaborate compounds. Indeed, because of the extremely mild reaction conditions and single-electron regime used for the cross-coupling of ammonium alkylbis(catecholato)silicates with (hetero)aryl bromides, various boronate ester functional groups were largely allowable while forging C(sp^3)–C(sp^2) bonds. Moreover, unlike most of the methods reported so far, the versatile, alkylated (hetero)aryl boronates can be isolated in high yields or carried through in crude form. Under this photoredox/Ni dual-catalysis manifold, the implementation of readily available Ni(II), light, and a cost-effective organic photocatalyst in place of late transition metal-based photocatalysts constitutes an unparalleled method toward multifunctionalized, alkylated arenes.

Acknowledgements

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