C(sp³)–C(sp²) 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 sp²-hybridized partners. Conspicuously absent from this useful synthetic manifold is the inclusion of sp³-hybridized pronucleophiles that can undergo transmetalation under mild conditions. Described here is the use of primary and secondary ammonium alkylsilicates, which undergo facile C(sp³)–C(sp²) 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(sp³)–C(sp²) 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,† capitalizing on decades of increasingly reliable C(sp²)–C(sp²) 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,‡ 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),¹ 1,8-diaminonaphthalenes (BDAN),⁴ and trifluoroborates (BF₃K)⁵ are the most popular modes of boron protection ([B¹]), 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 ([B¹]). 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(sp³) pronucleophiles with C(sp²) partners [aryl- or alkenyl(pseudo)halides] in
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.9 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(sp3)–C(sp3) 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., alkyboron reagents).

Most recently, we reported the use of ammonium alkylsilicates that smoothly react with aryl bromides, generating new sp3–sp2 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 halides9e or sulfonates in high yields. In comparison to previous reports using potassium alkyltrifluoroborates9k,11,14 and carboxylic acid derivatives9e,12 in photoredox/nickel-mediated C(sp3)–C(sp2) cross-couplings, reactions involving ammonium alkylsilicate radical precursors do not require any additives or additional base, allowing exceptional functional group tolerance, especially for prolig functional groups. The relatively low oxidation potential of the ammonium silicates (E0 = +0.75 V vs. SCE for 1° alkylsilicates, on average)11 allows the use of the less expensive and readily available [Ru(bpy)3]2+-[PF6]3 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-BF3K nucleophiles with borylated bromoarenes.14 This departure from strictly C(sp2) 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 sp3-hybridized bromides and sp2-hybridized boronic acids, where orthogonality is based solely on boron speciation (Scheme 1),13 the applicability of mildly-generated sp3-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.

Table 1 Reaction optimization

| Entry | Variation from standard | % yield (HPLC) |
|-------|-------------------------|---------------|
| 1     | No variation            | 99            |
| 2     | No light                | 2             |
| 3     | No [Ru(bpy)3][PF6]3     | 0             |
| 4     | No [NiCl2(dme)]         | 0             |
| 5     | [Ir(dF(CF3)2ppy)2(bpy)][PF6] instead of [Ru] | 96 |
| 6     | 4CzIPN (4) instead of [Ru] | 98 |
| 7     | [Ni(COD)]2 instead of [NiCl2(dme)] | 90 |
| 8     | +3 equiv. HTMP           | 76            |
| 9     | 4CzIPN (4) with CFL     | 95            |
| 10    | 4CzIPN (4) with white LEDs | 94 |

Though successful in C(sp3)–C(sp3)/C(sp3)–C(sp2) cross-couplings, alkyl-BF3Ks possess several drawbacks, notably the release of BF3 upon oxidative fragmentation. This byproduct is corrosive and can inhibit reaction progression. Additionally, BF3 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(sp3)–C(sp3) dual catalytic cross-coupling of alkylsilicates with borylated aryl bromides, complementing the paucity of Pd- and Ni-based C(sp3)–C(sp3) 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][PF6]3 (2 mol%), alongside [NiCl2(dme)]/dbtbpy (5 mol% of each; dbtbpy = 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.16b After 16 h we observed full conversion (99%, entry 1, Table 1) to the desired C(sp3)–C(sp3) 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 4CzIPN17f 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
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(sp³)–C(sp³) 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% [NiCl₂(dme)] and
[dbbpy]). 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(sp³)–
C(sp³) cross-coupling is tolerant of relatively reactive pina-
colboronates 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 none-
theless useful reagents in cross-coupling chemistry. Having

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theless useful reagents in cross-coupling chemistry. Having

established the effectiveness of the 4CzIPN organic photoca-
catalyst (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 Pinacolboron-
ates 9 and 12 and the neopentyl boronate ester adducts
(14 and 15) were isolated in good yields following standard
column chromatography.

Interestingly, yields obtained for 9 and 12 while using
4CzIPN (Table 3) are in the same range as those obtained using
[Ru(bpy)₃]([PF₆]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 puri-
fication. Nevertheless, the prepared BMIDA boronate esters
can be useful intermediates in the automated, iterative assembly
of complex molecules.6 The 1,8-diaminonaphthalene (RBDan)
adds (18 and 19) uniformly provided trace desired product.

The attractiveness of a simplified assembly of alkylated are-
nes 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 BPin intermediates,
which are known to be particularly sensitive because of their reactivity,
have never been successfully alkylated under a transition metal-
mediated process. The bicycloheptysilicate (35) coupled

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Table 2: Examination of various primary and secondary ammonium alkylsilicates with borylated bromoarene 2

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Table 3: Examination of various boron protecting groups

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a Isolated yields. Ar = 4-phenyl pinacol boronate. [NiCl₂(dme)] was complexed with dbbpy prior to reaction setup, although pre-
complexation was shown to not always be necessary, see ESI. Reactions run on 0.5 mmol of bromide 2 for the allotted time. 4 1.00
gram (3.5 mmol) of 2, dbbpy (3 mol%), [NiCl₂(dme)] (3 mol%) and 4CzIPN (1.5 mol%).
Table 4 Combinatorial examination of silicate and borylated aryl bromide coupling partners

| R               | N                      | O                  | F                  |
|-----------------|------------------------|--------------------|--------------------|
| [NiCl₂(dme)]    | -                      | -                  |                    |
| 4CzIPN          | 40°C / C14C            | 90 min (70%, 2 steps); | |
| 3-bromoaacetophenone (1 equiv.) | dioxane/H₂O | 90°C / C14C | 72% | 2 steps; |
| 30% H₂O₂, 1 M NaOH, THF, rt, 1 h (80%, 2 steps). |

Scheme 2 Example of iterative C(sp³)-C(sp³)/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-bromoacacetophenone, [Pd(PPh₃)₄], Cs₂CO₃, dioxane/H₂O, 90°C (72%, 2 steps); (c) 30% H₂O₂, 1 M NaOH, THF, rt, 1 h (80%, 2 steps).

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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. Bicyclohexylsilicate 35 was subjected to a standard C(sp^3)−C(sp^3) cross-coupling with 4-bromophenyl-borononic 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^3) 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 allylsilicates were found to be exceptional alkyllating agents in the presence of various brominated ary1- 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 allylsilicides with (hetero)aryl bromides, various boronate ester functional groups were largely allowable while forking C(sp^3)−C(sp^3) 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(0), light, and a cost-effective organic photocatalyst in place of late transition metal-based photocatalysts constitutes an unparalleled method toward multifunctionalized, alkyllated arenes.

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