

# Haloselective Cross-Coupling via Ni/Photoredox Dual Catalysis

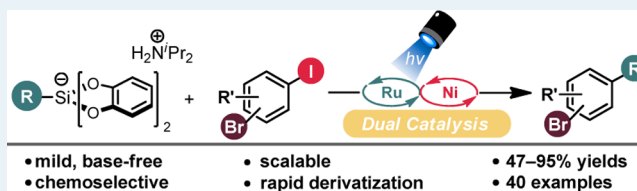
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**S** Supporting Information

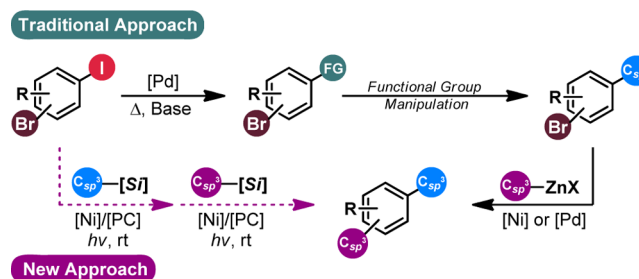
**ABSTRACT:** The chemoselective functionalization of polyfunctional aryl linchpins is crucial for rapid diversification. Although well-explored for  $C_{sp^2}$  and  $C_{sp}$  nucleophiles, the chemoselective introduction of  $C_{sp^3}$  groups remains notoriously difficult and is virtually undocumented using Ni catalysts. To fill this methodological gap, a “haloselective” cross-coupling process of arenes bearing two halogens, I and Br, using ammonium alkylbis(catecholato)silicates, has been developed. Utilizing Ni/photoredox dual catalysis,  $C_{sp^3}$ – $C_{sp^2}$  bonds can be forged selectively at the iodine-bearing carbon of bromo(iodo)arenes. The described high-yielding, base-free strategy accommodates various protic functional groups. Selective electrophile activation enables installation of a second  $C_{sp^3}$  center and can be done without the need for purification of the intermediate monoalkylated product.

**KEYWORDS:** nickel/photoredox dual catalysis, bromo(iodo)arenes, hypervalent silicon, cross-coupling, selective functionalization



Chemoselective processes facilitate rapid divergence in organic synthesis.<sup>1</sup> Innate chemical discrimination stemming from myriad factors is often the crux not only of elegant synthetic chemistry but of nature’s precise manipulation of the chemical world. Whereas nature relies on enzymes to effect chemoselective transformations, synthetic chemists increasingly rely on transition metal catalysts to enhance structural complexity selectively and efficiently.<sup>2</sup> Indeed, great strides have been made recently, particularly in chemoselective C–C cross-coupling.<sup>3</sup> In this context, approaches include selective oxidative addition via differences in C–X bond enthalpies, exploiting the disparate transmetalation rates of nucleophiles, and mechanistic discrimination.<sup>3</sup>

Although seemingly well-developed in the area of  $C_{sp^2}$ – $C_{sp^2}$  cross-coupling, the ability to forge  $C_{sp^3}$ – $C_{sp^2}$  bonds when using bromo(iodo)aryl compounds in a “haloselective” manner remains challenging. The recalcitrance of bench-stable  $C_{sp^3}$  nucleophiles (e.g., organoboron or organostannyl species) toward  $C_{sp^3}$ – $C_{sp^2}$  cross-coupling requires laborious, harsh methods to be employed.<sup>4</sup> As such, chemoselective cross-coupling is inherently intractable using these reagents. Alternatively, more reactive nucleophiles (e.g., organozinc species) have been used sporadically with success for chemoselective functionalization via Pd-mediated cross-coupling, although no cohesive study has been performed on this topic.<sup>5</sup> Moreover, analogous Ni-mediated processes are virtually undocumented in the literature. More often than not, a multistep approach is used to install the desired alkyl group wherein selectivity is achieved via  $C_{sp^2}$ – $C_{sp^2}$  or  $C_{sp^2}$ – $C_{sp}$  cross-coupling (i.e., using Pd-based catalysts) followed by a functional group interconversion (i.e., reduction to an alkane; see Figure 1).<sup>6</sup> Although reliable, these multistep processes are inherently less direct and efficient than the former approaches, particularly if installation of an additional  $C_{sp^3}$  center is desired.



**Figure 1.** Current strategies versus the envisioned approach for selective electrophilic activation of bromo(iodo)aryl linchpins.

Thus, no general solution for  $C_{sp^3}$ – $C_{sp^2}$  coupling using bromo(iodo)arenes in a haloselective manner has been reported, despite the fact that such transformations would allow access to useful linchpins for polyfunctional arene construction.

The recent emergence of Ni/photoredox dual catalysis has resulted in a rapid, one-step approach to install alkyl groups and represents an alternative to the two classical  $C_{sp^3}$ – $C_{sp^2}$  cross-coupling extremes (i.e., reactive nucleophiles or harsh conditions).<sup>7,8</sup> In this dual catalytic manifold, a benchtop-stable  $C_{sp^3}$  pro-nucleophile is controllably activated by photocatalyst-mediated, single-electron transfer (SET) oxidation to generate the active nucleophile, an alkyl radical. Ultimately, this catalytic system endows chemists with a platform that enables facile, mild  $C_{sp^3}$ – $C_{sp^2}$  bond formation with the added benefit of broad tolerance toward sensitive moieties. Moreover, numerous feedstocks for pro-nucleophiles have been identified, such as

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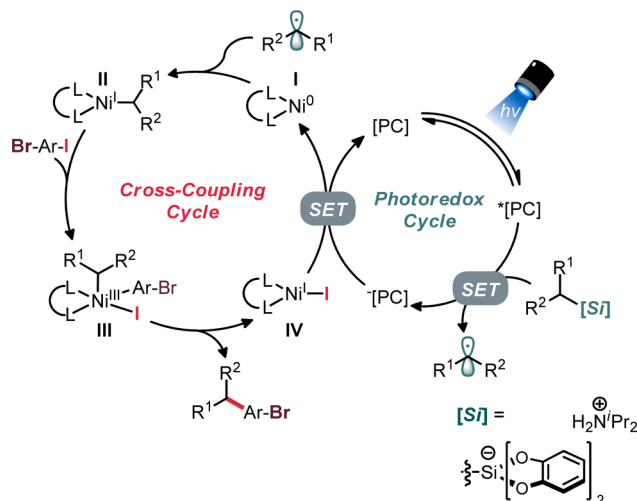
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organotrifluoroborates,<sup>9a,b</sup> carboxylic acids,<sup>9c,d</sup> alkylbis-(catecholato)silicates,<sup>9e-g</sup> 4-alkyl-1,4-dihydropyridines (DHPs),<sup>9h,i</sup> and even activated C–H bonds.<sup>9j-l</sup> Consequently, substantial structural diversity in the nucleophilic partner can be readily accessed. Because of the mild conditions and the generally less electron-rich ligands employed, Ni/photoredox dual catalysis presents a broadly applicable solution to the challenge of chemoselective cross-coupling in the bromo-(iodo)arene scaffold. Given the improved clinical success of drug molecules possessing higher fractions of C<sub>sp<sup>3</sup></sub> centers,<sup>10</sup> the realization of such a solution would enable the modular synthesis of polyfunctional arenes via the controlled functionalization of each synthetic handle and access to molecules with higher 3D complexity.

To investigate the tenability of this strategy, ammonium alkylbis(catecholato)silicates were utilized as “plug and play” radical progenitors.<sup>9e,f</sup> This choice was made for a number of reasons: (1) the ability to perform dual catalytic cross-coupling free of any additives (thus maximizing functional group tolerance and minimizing complications arising from additives), (2) the amenability to generating stabilized and destabilized radicals (thus allowing assessment of broad applicability), and (3) the known ease with which these hypercoordinate silicon species can be used in cross-coupling with an array of electrophiles (thus assessing electrophile fidelity). Additionally, the low redox potential ( $E^0 \sim 0.40\text{--}0.75$  V vs SCE) of ammonium alkylbis(catecholato)silicates and their tunable solubility properties (based on counterion structure) allow flexibility in the identity of the photocatalyst and solvent, respectively.<sup>9e,f</sup> Ultimately, haloselective cross-coupling was envisioned to occur via the mechanism shown in Scheme 1.<sup>11</sup> Speculatively, selective oxidative addition by the Ni<sup>I</sup> species II would provide discrimination between the iodine and bromine.<sup>12–14</sup>

### Scheme 1. Envisioned Catalytic Cycle for Selective Cross-Coupling of Dihaloarenes Using Ni/Photoredox Dual Catalysis



Using the previously optimized conditions for Ni/photoredox dual catalytic cross-coupling of alkylsilicates,<sup>9e</sup> a baseline for innate selectivity and conversion was observed to be 88:12 (3a:4a) at 95% conversion (Table 1, entry 1). Without any optimization, selective functionalization was possible with no detectable overalkylation. However, improvement of the

Table 1. Optimization of Haloselective Cross-Coupling<sup>a</sup>

entry	ligand	Ni (mol %)	ratio <sup>b</sup>	conversion <sup>b,c</sup>
1	dtbbpy	5	88:12	95%
2	dtbbpy	10	85:15	96%
3	dtbbpy	2.5	90:10	94%
4	diOMebpy	5	88:12	95%
5	diCF <sub>3</sub> bpy	5	n/a	0%
6	bpy	5	97:3	77%
7	neocup	5	92:8	17%
8	bphen	5	83:17	91%
9	phen	5	92:8	80%
10 <sup>d</sup>	phen	2.5	96:4	97% (82%)
11 <sup>d</sup>	bpy	2.5	98:2	95% (79%)

**Bipyridyl Ligands**

bpy: R<sup>1</sup> = R<sup>2</sup> = H  
diOMebpy: R<sup>1</sup> = OMe; R<sup>2</sup> = H  
diCF<sub>3</sub>bpy: R<sup>1</sup> = H; R<sup>2</sup> = CF<sub>3</sub>  
dtbbpy: R<sup>1</sup> = <sup>t</sup>Bu; R<sup>2</sup> = H

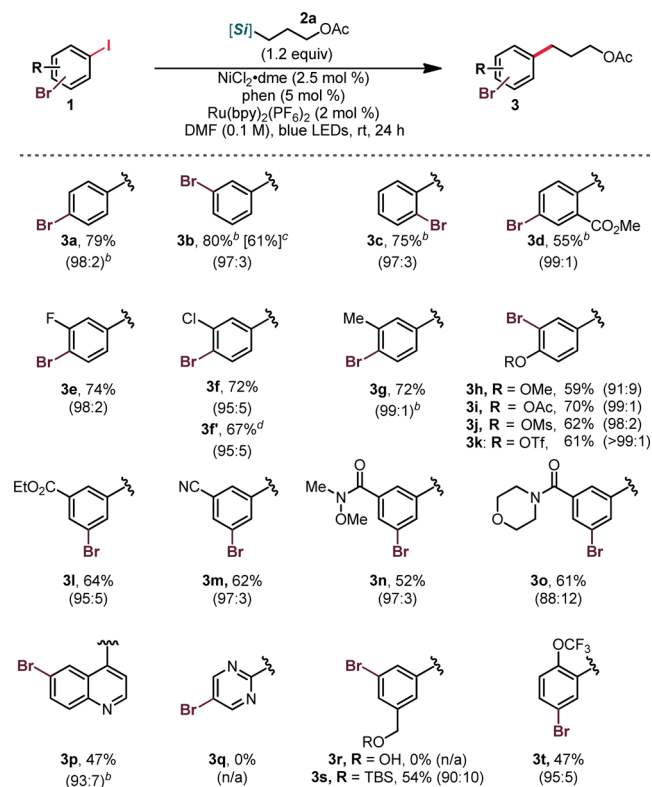
**Phenanthryl Ligands**

phen: R<sup>3</sup> = R<sup>4</sup> = H  
neocup: R<sup>3</sup> = H; R<sup>4</sup> = Me  
bphen: R<sup>3</sup> = Ph; R<sup>4</sup> = H

<sup>a</sup>Unless otherwise noted, reactions were run using 0.1 mmol of 1a for 16 h at 27 °C and using a 1:1 Ni/ligand ratio. <sup>b</sup>Conversions and ratios of 3a to 4a were determined by GC/MS and confirmed by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>c</sup>Values in parentheses indicate the isolated yields on a 0.5 mmol scale of 1a. <sup>d</sup>A 1:2 Ni/ligand ratio and 2.5 mol % of Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> were used.

selectivity was still needed. Given that selectivity might hinge on kinetic control of oxidative addition, ligand choice and Ni catalyst loading were examined. When using dtbbpy, Ni loading seemed to have a minimal effect, although lower loadings appeared to be preferable (entries 1–3). Next, a number of bipyridyl and phenanthryl ligands were examined. These two ligand classes have been shown to be privileged in the context of Ni/photoredox dual catalysis but are virtually undocumented in facilitating this type of selective alkyl–aryl coupling. Although substituted bipyridyl ligands failed to improve the ratio (entries 4 and 5), bipyridine itself gave excellent selectivity (entry 6). Selectivity did come at the cost of lowered conversion. Similarly, phenanthroline performed well (entry 9), whereas alteration of the substitution pattern of the phenanthryl core had deleterious effects on conversion (entry 7) or selectivity (entry 8). Using a lower Ni loading, a 2:1 ligand to metal ratio, and slightly increasing the loading of the photocatalyst resulted in excellent conversion and selectivity (entries 10 and 11). Ultimately, both protocols were scaled up and gave good yields of the desired cross-coupled product. Conceivably, these ligand systems are not as efficient at oxidative addition as dtbbpy from either Ni<sup>I</sup> (or Ni<sup>0</sup>) and thus provide further chemoselective enhancement from innate I/Br selectivity.<sup>15</sup>

With suitable conditions and two viable ligands identified, we next investigated the scope of the process (Table 2). First, the range of bromo(iodo)arenes that could be used was assessed using a representative 1° alkylsilicate, 2a. The reaction proved

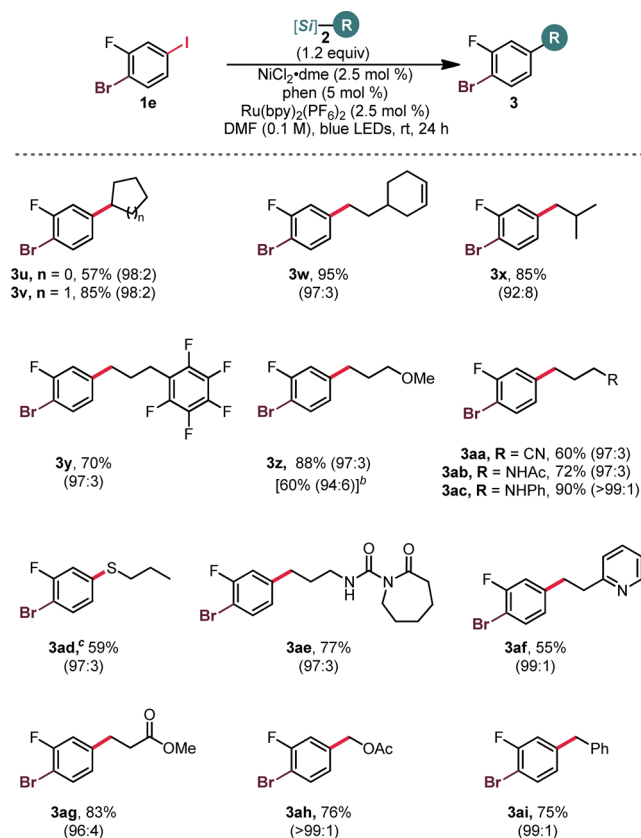
Table 2. Selective Cross-Coupling Using Alkylsilicate 2a<sup>4</sup>

<sup>a</sup>Unless otherwise noted, reactions were performed using **1** (1.0 equiv, 0.5 mmol), **2a** (1.2 equiv), NiCl<sub>2</sub>·dme (2.5 mol %), Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (2 mol %), and phen (5 mol %) in DMF (0.1 M) at rt for 24 h, irradiating with blue LEDs; ratios of **3**:**4** are indicated in parentheses, and these values were obtained before purification. All yields are isolated yields after purification. <sup>b</sup>Performed using bpy as a ligand. <sup>c</sup>Value in brackets denotes the yield on a 5 mmol scale using phen as the ligand. <sup>d</sup>Product obtained as its 1° alcohol rather than acetate by modification of the workup.

quite general, accommodating a number of functional groups and giving excellent chemoselectivity in nearly all cases (Table 2). Although in general phen was primarily used, bpy could be used interchangeably with little to no effect on yield or selectivity. Unsubstituted bromo(iodo)arenes underwent haloselective cross-coupling in good yield regardless of the substitution pattern of the two halides (**3a–c**). In addition, scale up of this process proved facile and did not compromise selectivity. Both electron-donating and electron-withdrawing groups were well-tolerated. Aryl substitution did appear to impact the efficiency and/or selectivity of the described cross-coupling process, with both steric and electronic changes having subtle yet noticeable effects on either product ratio or yield. Indeed, the substrates derived from 2-bromo-4-iodophenol (**3h–3k**), as well as **3t**, best illustrate these sorts of effects. Of note are the polyfunctional arenes **3f**, **3j**, and **3k**, which, in addition to the bromide handle, possess a third site for additional functionalization. We serendipitously discovered that when attempting to isolate **3f**, a minor change in the order of the workup (base wash prior to acid wash) led to the facile hydrolysis of the acetoxy group. Thus, the free alcohol, **3f'**, could also be obtained under near identical reaction conditions. Heteroaromatics generally proved challenging or low yielding in the described cross-coupling process (possibly because of competitive ligation, poor catalyst efficiency, or catalyst

deactivation), although some success was observed with a quinoline-based system (**3p**). Finally, although a benzylic alcohol failed under the optimized conditions, TBS-protection restored reactivity (**3s**) and enabled successful cross-coupling, albeit with somewhat diminished chemoselectivity.

The diversity in radical structure was next assessed (Table 3). Gratifyingly, a variety of alkylsilicates were successfully

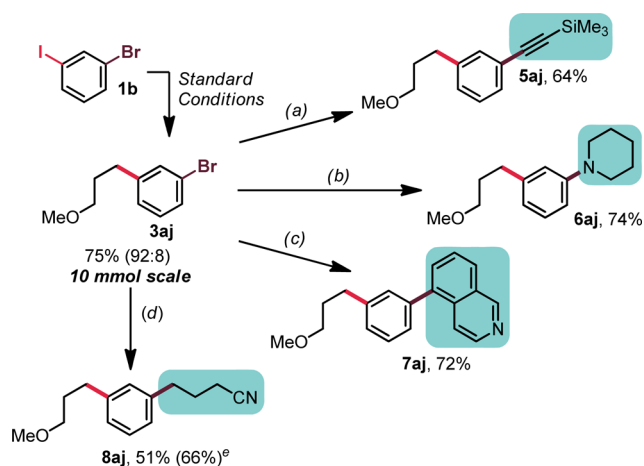
Table 3. Selective Cross-Coupling of **1e** with Various Alkylsilicates<sup>4a</sup>

<sup>a</sup>Unless otherwise noted, reactions were performed using **1e** (1.0 equiv, 0.5 mmol), **2** (1.2 equiv), NiCl<sub>2</sub>·dme (2.5 mol %), Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (2 mol %), and phen (5 mol %) in DMF (0.1 M) at rt for 24 h, irradiating with blue LEDs; ratios of **3**:**4** are indicated in parentheses, and these values were obtained before purification. All yields are isolated yields after purification. <sup>b</sup>Value in brackets denotes the yield when using the organic dye 4CzIPN (5 mol %) as the photocatalyst. <sup>c</sup>Product obtained as the thioether rather than thiol from (3-mercaptopropyl)silicate.

employed without compromising yield or chemoselectivity. Relatively simple 1° and 2° alkylsilicates performed well in the haloselective cross-coupling process. In addition, the organic dye 4CzIPN could be used in place of the Ru-based photocatalyst at a minimal cost of selectivity and yield (see **3z**). Nucleophilic partners that would be typically unattainable as their corresponding organometallics did not pose a problem in this process (**3aa–ae**, **3ag**, **3ah**). The reaction is highly tolerant of protic functional groups, a unique aspect of this process that cannot be mimicked with current protocols in haloselective C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>2</sup> cross-coupling (e.g., **3ab–ad**, **3ae**). Notably, the thiosilicate, used in the synthesis of **3ad**, undergoes hydrogen atom transfer (HAT) upon radical generation to furnish a thiyl radical that subsequently couples,

as disclosed in our previous report.<sup>16</sup> Thus, **3ad** was obtained as the corresponding thioether. Not only was this successful, but it also demonstrated that *S*-centered radicals are also amenable to selective coupling. Finally, stabilized radicals performed quite well in the haloselective cross-coupling (**3ah–ai**), despite the known reversibility of radical metalation.<sup>11</sup>

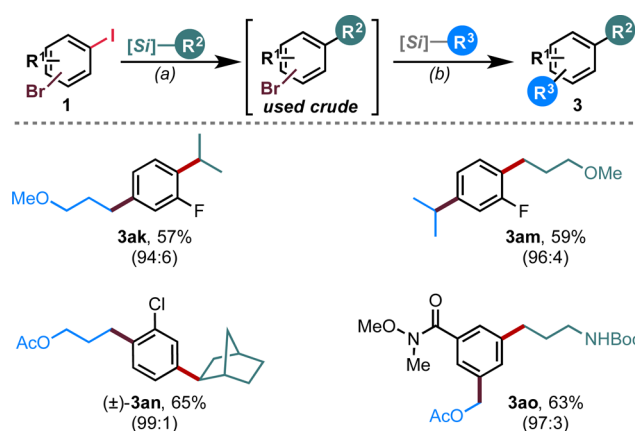
To showcase the utility of the described haloselective process further, a series of subsequent functionalization reactions were executed using **3aj** (Figure 2). In addition to demonstrating the



**Figure 2.** Diversification of **3aj**. Conditions: (a) **3aj** (0.5 mmol, 1 equiv), TMS-acetylene (3 equiv), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mol %), CuI (5 mol %), Et<sub>3</sub>N (0.2 M), 80 °C, 48 h; (b) **3aj** (1 mmol, 1 equiv), piperidine (1.5 equiv), XPhos G2 (2 mol %), Cs<sub>2</sub>CO<sub>3</sub> (2.5 equiv), toluene/*t*-BuOH (5:1, 0.4 M), 80 °C, 18 h; (c) **3aj** (0.5 mmol, 1 equiv), organotrifluoroborate (1.5 equiv), Pd(PPh<sub>3</sub>)<sub>2</sub>Cl<sub>2</sub> (5 mol %), Cs<sub>2</sub>CO<sub>3</sub> (3 equiv), THF/H<sub>2</sub>O (2:1, 0.25 M), 80 °C, 18 h; (d) **3aj** (1 mmol, 1 equiv), alkylic silicate (1.2 equiv), [Ni(dtbbpy)(H<sub>2</sub>O)<sub>4</sub>]Cl<sub>2</sub> (5 mol %), and Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (2 mol %), DMF (0.1 M), blue LEDs, rt, 24 h. (e) The yield in parentheses indicates the yield of sequential coupling, starting from **1b** on 0.5 mmol scale without isolation of **3aj**.

value of the haloselective process, the requisite amount of **3aj** for these studies presented the opportunity to push the limits of the scalability of this cross-coupling reaction. The reaction proved to be quite scalable and can be performed on 10 mmol scale (and likely greater) with minimal effect on yield and chemoselectivity. Subsequent installation of C<sub>sp</sub><sup>2</sup> or C<sub>sp</sub><sup>3</sup> centers via Suzuki or Sonogashira coupling processes, respectively, proceeded very smoothly, affording good yields of the corresponding cross-coupled products. Buchwald–Hartwig-type amination similarly was successful, affording the piperidinyll adduct **6aj** in 74% yield. Finally, installation of a second C<sub>sp</sub><sup>3</sup> center via a second Ni/photoredox cross-coupling of an alkylic silicate was successful, giving **8aj** in 51% yield. This process was later repeated starting from **1b** without intermediate isolation, providing an improved 66% yield of the desired product.

Recognizing the power of this method for selective electrophile activation and to build on our successful sequential process with **8aj**, a series of tandem C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>2</sup> cross-coupling reactions were successfully attempted (Figure 3). Using the now-established conditions for the haloselective process, the first alkyl group was installed at the iodo position in three distinct bromo(iodo)arenes. After a simple aqueous workup, the crude product was subjected to the standard conditions for Ni/photoredox dual catalytic cross-coupling, thus installing a



**Figure 3.** Tandem C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>2</sup> cross-coupling. Numbers in parentheses are ratios of 3:4 after the first coupling. Conditions: (a) **1** (1.0 equiv, 0.5 mmol), alkylic silicate (1.2 equiv), NiCl<sub>2</sub>·dme (2.5 mol %), Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (2 mol %), and phen (5 mol %) DMF (0.1 M), blue LEDs, rt, 24 h; (b) alkylic silicate (1.2 equiv), [Ni(dtbbpy)(H<sub>2</sub>O)<sub>4</sub>]Cl<sub>2</sub> (5 mol %), and Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (2 mol %), DMF (0.1 M), blue LEDs, rt, 24 h.

second alkyl group at the bromo position.<sup>9e,f</sup> This demonstrates the ability of this process to install alkyl groups regioselectively (compare **3ak** to **3am**) and further validates the selective electrophile-activation paradigm. In addition, the overall yields were quite good, equating to greater than 75% per chemical step for all four examples.

In summary, a mild, user-friendly method for the selective electrophilic activation of bromo(iodo)arenes using ammonium alkylic bis(catecholato)silicates is presented. The described “haloselective” reaction tolerates an array of functional groups, including those bearing acidic protons, and is highly scalable. The monofunctionalized products can be readily paired with existing cross-coupling technology, affording a means to fuse classical two-electron cross-coupling with single-electron transformations. Sequential Ni/photoredox cross-coupling of these polyfunctional arenes enables two unique C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>2</sup> bonds to be forged selectively. The conditions outlined here can likely be extended to other radical progenitors, further emphasizing the utility of the described process for rapid diversification.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b01773.

Experimental procedures and characterization data for all compounds (DOCX)

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### Notes

The authors declare no competing financial interest.

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