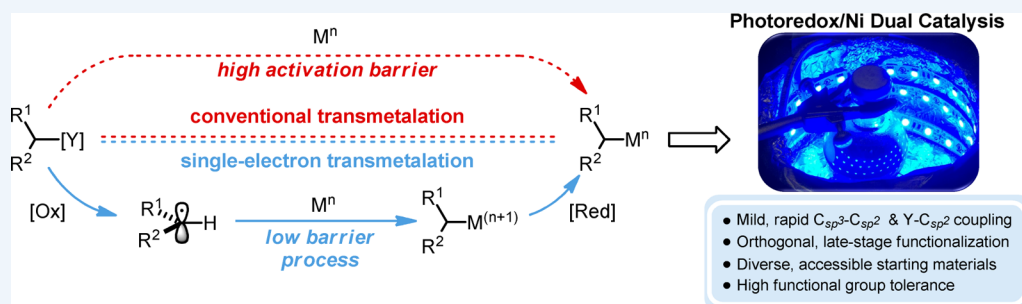


# Single-Electron Transmetalation via Photoredox/Nickel Dual Catalysis: Unlocking a New Paradigm for $sp^3-sp^2$ Cross-Coupling

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**CONSPECTUS:** The important role of transition metal-catalyzed cross-coupling in expanding the frontiers of accessible chemical territory is unquestionable. Despite empowering chemists with Herculean capabilities in complex molecule construction, contemporary protocols are not without their Achilles' heel:  $C_{sp^3}-C_{sp^2}/sp^3$  coupling. The underlying challenge in  $sp^3$  cross-couplings is 2-fold: (i) methods employing conventional, bench-stable precursors are universally reliant on extreme reaction conditions because of the high activation barrier of transmetalation; (ii) circumvention of this barrier invariably relies on use of more reactive precursors, thereby sacrificing functional group tolerance, operational simplicity, and broad applicability. Despite the ubiquity of this problem, the nature of the transmetalation step has remained unchanged from the seminal reports of Negishi, Suzuki, Kumada, and Stille, thus suggesting that the challenges in  $C_{sp^3}-C_{sp^2}/sp^3$  coupling result from inherent mechanistic constraints in the traditional cross-coupling paradigm. Rather than submitting to the limitations of this conventional approach, we envisioned that a process rooted in single-electron reactivity could furnish the same key metalated intermediate posited in two-electron transmetalation, while demonstrating entirely complementary reactivity patterns. Inspired by literature reports on the susceptibility of organoboron reagents toward photochemical, single-electron oxidative fragmentation, realization of a conceptually novel open shell transmetalation framework was achieved in the facile coupling of benzylic trifluoroborates with aryl halides via cooperative visible-light activated photoredox and Ni cross-coupling catalysis. Following this seminal study, we disclosed a suite of protocols for the cross-coupling of secondary alkyl,  $\alpha$ -alkoxy,  $\alpha$ -amino, and  $\alpha$ -trifluoromethylbenzyltrifluoroborates. Furthermore, the selective cross-coupling of  $C_{sp^3}$  organoboron moieties in the presence of  $C_{sp^2}$  organoboron motifs was also demonstrated, highlighting the nuances of this approach to transmetalation. Computational modeling of the reaction mechanism uncovered useful details about the intermediates and transition-state structures involved in the nickel catalytic cycle. Most notably, a unique dynamic kinetic resolution process, characterized by radical homolysis/recombination equilibrium of a  $Ni^{III}$  intermediate, was discovered. This process was ultimately found to be responsible for stereoselectivity in an enantioselective variant of these cross-couplings.

Prompted by the intrinsic limitations of organotrifluoroborates, we sought other radical feedstocks and quickly identified alkylbis(catecholato)silicates as viable radical precursors for Ni/photoredox dual catalysis. These hypervalent silicate species have several notable benefits, including more favorable redox potentials that allow extension to primary alkyl systems incorporating unprotected amines as well as compatibility with less expensive Ru-based photocatalysts. Additionally, these reagents exhibit an amenability to alkenyl halide cross-coupling while simultaneously expanding the aryl halide scope. In the process of exploring these reagents, we serendipitously discovered a method to effect thioetherification of aryl halides via a H atom transfer mechanism. This latter discovery emphasizes that this robust cross-coupling paradigm is "blind" to the origins of the radical, opening opportunities for a wealth of new discoveries. Taken together, our studies in the area of photoredox/nickel dual catalysis have validated single-electron transmetalation as a powerful platform for enabling conventionally challenging  $C_{sp^3}-C_{sp^2}$  cross-couplings. More broadly, these findings represent the power of rational design in catalysis and the strategic use of mechanistic knowledge and manipulation for the development of new synthetic methods.

## 1. INTRODUCTION

Central to the goals of new synthetic methods development should be the deliverance of protocols exhibiting characteristics

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complementary to those transformations representing the state-of-the-art. In doing so, the sum of readily accessible chemical space can be continuously expanded as newly reported methods compensate for inadequacies of the prior art. In this context, an understanding of reaction mechanism and its impact on the observable outcomes of organic transformations (yield, regioselectivity, stereoselectivity, functional group tolerance, etc.) is perhaps the most important enabling tool in the realization of such platforms. Indeed, frequently the shortcomings of a transformation can be traced directly to the biases inherent to and inseparable from its mechanistic underpinnings. These indicators of a mechanistic paradigm, nearing the bounds of its finite potential, signal the need for the development of methods relying on new and fundamentally distinct activation modes. From this alteration of the mechanistic fabric of a transformation naturally flows new types of reactivity, selectivity, and functional group compatibility, enabling the synthesis of previously inaccessible chemical architectures and driving the field of organic synthesis perpetually forward.

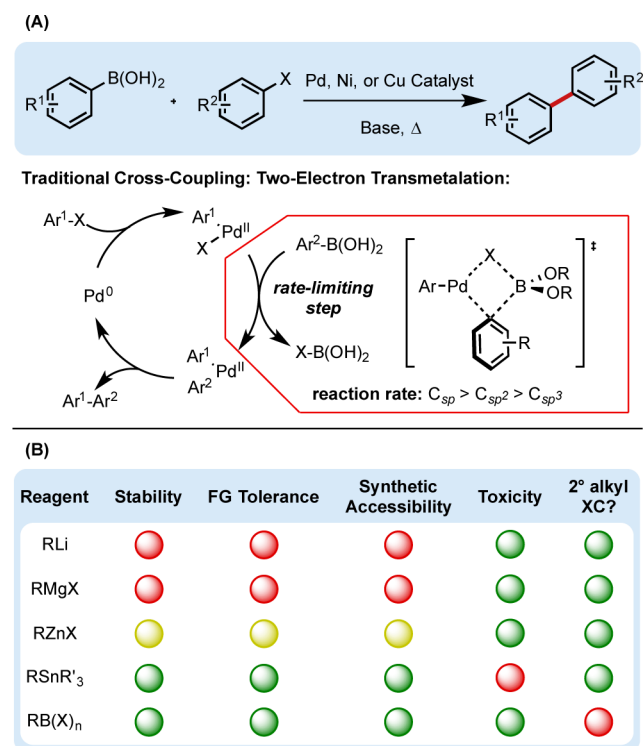
It is from this perspective that our laboratory became interested in the longstanding challenge of secondary alkylboron cross-coupling. Despite the near-omnipresence of cross-coupling methods, and the Suzuki–Miyaura reaction in particular, in the synthesis of complex molecules, the application of secondary alkylboron reagents in these transformations has remained limited.<sup>1</sup> The challenges associated with this union are made particularly evident in light of the relative successes realized with nearly all other commonly employed organometallic reagent classes (Li,<sup>2</sup> Mg,<sup>3</sup> Zn,<sup>4</sup> and Sn<sup>5</sup>) in secondary  $C_{sp^3}$ – $C_{sp^2}$  cross-couplings (Figure 1). Nevertheless, the corresponding organoboron variants remain highly desirable because of the innate

properties of boronic acids and related derivatives, most notably air and moisture stability, low toxicity, and relative ease of preparation, storage, and handling.<sup>6</sup>

Although a few reports have documented the successful cross-coupling of secondary alkylboron reagents with aryl halides,<sup>7</sup> these methods invariably suffer from limitations that significantly reduce their utility as general platforms for  $C_{sp^3}$ – $C_{sp^2}$  bond formation (Figure 2). Most of these protocols rely on elevated reaction temperatures and the use of superstoichiometric aqueous base, introducing potential incompatibility with thermally or hydrolytically sensitive compounds. Alternatively, stoichiometric Ag additives introduce complications related to reagent cost and excessive waste generation. Functional group tolerance reported in these studies has been generally modest and limited mostly to simple aromatic and heteroaromatic systems, with unprotected protic functional groups (e.g., alcohols, amines, protic heterocycles, etc.) notable only in their absence. Furthermore, all previously reported methods for Pd-catalyzed cross-coupling of electronically unactivated and sterically nonbiased secondary alkylboron reagents suffer, in some capacity, from isomerization of unsymmetrical alkyl fragments. This undesired side reaction arises from the intermediacy of a  $\pi$ -bound Pd–olefin complex III generated via  $\beta$ -hydride elimination of the post-transmetalation, secondary alkylpalladium species (Figure 3A).<sup>8</sup> Subsequent hypopalladation produces regioisomeric alkylpalladium species I and IV, ultimately affording isomeric products II and V upon reductive elimination. Highlighting this ever-present limitation is the continued failure of 2-methylcycloalkylboron reagents in Pd-catalyzed cross-coupling (Figure 3B).<sup>7c–e</sup>

Upon consideration of this most prominent methodological gap, it became apparent that the limitations of secondary alkylboron cross-coupling could ultimately be attributed to the simple fact that compounds of this type are extraordinarily unreactive in transmetalation relative to analogous  $sp^2$  hybridized congeners. Furthermore, we recognized that this limitation was fundamentally symptomatic of a mechanistic flaw entrenched within the underlying two-electron activation mode. Transmetalation rates for organometallic nucleophiles follow a general trend of  $C_{sp^2} > C_{sp^3}$ ,<sup>9</sup> a hallmark of the anionic, two-electron character of the classical mechanistic paradigm. Nevertheless, even from the earliest days of cross-coupling, the nature of the transmetalation step has remained unchanged, so the “secondary alkyl problem” has persisted. Here, we posited that an ideal solution to this longstanding challenge would consist of a mechanistic sea-change, manifesting as an inversion of the reactivity hierarchy of a conventional transmetalation, thus rendering  $C_{sp^3}$  reagents most reactive. Operating within this new mechanistic regime would thereby permit the facile development of  $C_{sp^3}$ – $C_{sp^2}$  cross-coupling methods because of the now-advantageous biases fundamental to the new activation mode.

In considering the details of this proposal, it quickly became evident that a mechanistic framework wherein transmetalation occurs via the intermediacy of a radical would be inherently favorable for applications in  $C_{sp^3}$  cross-coupling, because the stability trends of carbon-centered radicals ( $C_{sp^3} > C_{sp^2} > C_{sp}$ ) perfectly complement the trends observed for transmetalation (Figure 4A). Conceptually, we envisioned that such a process might be initiated by single-electron oxidation and demetallative fragmentation of an appropriate organometallic reagent to generate a radical, which could then be captured by a transition metal catalyst to forge the desired  $M$ – $C_{sp^3}$  bond. Importantly, this transformation is formally oxidative at the transition metal center, inconsistent with the redox-neutral profile of a conventional



**Figure 1.** (A) Mechanism of conventional Suzuki–Miyaura cross-coupling. (B) Comparison of organometallic reagents in cross-coupling. XC = cross-coupling, FG = functional group (green = high/good, yellow = moderate, red = low/poor).

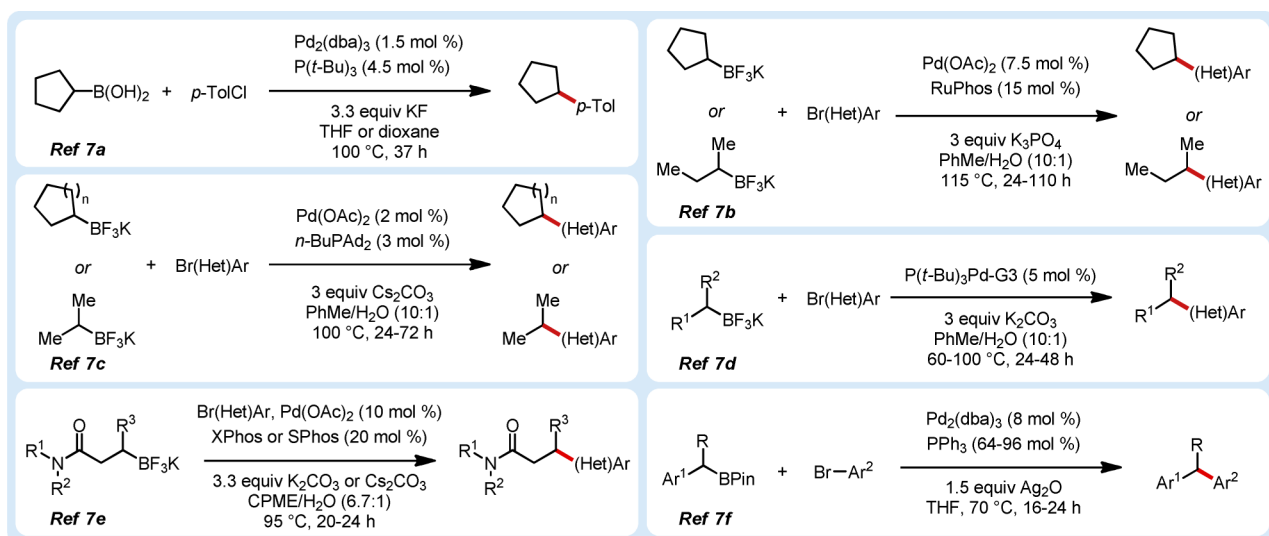


Figure 2. Notable examples of secondary alkyl Suzuki–Miyaura cross-coupling.

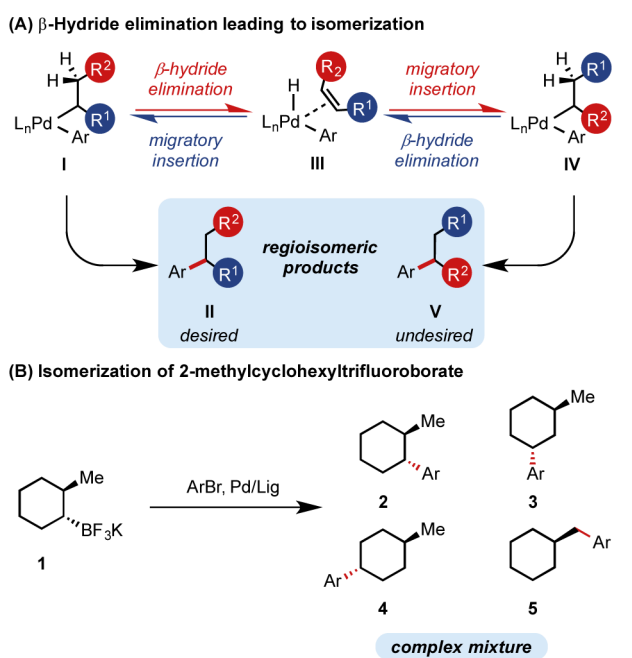


Figure 3. (A) Isomerization via  $\beta$ -hydride elimination/reinsertion. (B) Product mixture formed upon cross-coupling of 2-methylcyclohexyltrifluoroborate.

transmetalation. Accordingly, subsequent single-electron reduction of the transition metal center is required to return the catalyst to its original oxidation state. Comprehensively, this series of events, which we have coined “single-electron transmetalation”, is the formal equivalent of a transmetalation but avoids entirely the high-energy transition state associated with the conventional two-electron transmetalation.

Although this manifold was unprecedented at the commencement of our studies, circumstantial evidence seemed to uphold the feasibility of this approach. The oxidation of organometallic reagents to radicals had been well preceded in the oxidative Minisci-type arylations and alkylations of heteroarenes with organoboron reagents.<sup>10</sup> A variety of prior reports had established the feasibility of radical addition to transition metal catalysts, most notably the wealth of literature on Ni-catalyzed cross-coupling of

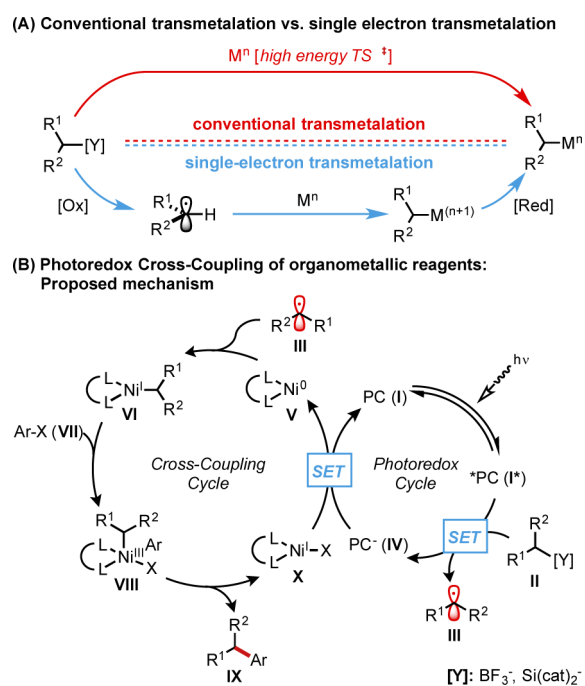


Figure 4. (A) Conceptual basis for single-electron transmetalation. (B) Proposed mechanism of photoredox/nickel dual catalytic cross-coupling. PC = photocatalyst.

alkyl electrophiles<sup>11</sup> and the work of Sanford, Glorius, and Toste in photoredox/transition metal dual catalysis.<sup>12</sup> Lastly, the single-electron reduction potentials of transition metal complexes typically employed in cross-coupling reactions (e.g., Pd and Ni) are often reported to occur at redox potentials accessible by common reagents.

Despite largely encouraging literature precedents, bringing single-electron transmetalation to fruition was complicated by the need for both a single-electron oxidation and single-electron reduction to occur simultaneously, selectively, and efficiently in a single reaction vessel. These criteria would render stoichiometric reagents ineffective because of unproductive reductant/oxidant quenching. Here, we turned to photoredox catalysis as the ideal enabling technology because of the capabilities of this process to

promote redox-neutral, odd-electron processes efficiently by selectively catalyzing oxidative and reductive single-electron transfers (SETs) in complex settings had been well established.<sup>13</sup>

## 2. SINGLE-ELECTRON TRANSMETALATION IN CROSS-COUPLING

### 2.1. Proof of Concept Studies: Benzyltrifluoroborates

Based on their established single-electron oxidation potentials,<sup>14</sup> potassium organotrifluoroborates were selected as promising carbon radical progenitors. Encouragingly, Akita and co-workers had previously employed the photocatalyst, **6**, for oxidation of tetracoordinate organoboron reagents, engaging the resultant alkyl radicals in heterocoupling with (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) and conjugate additions into electron-poor olefins.<sup>16</sup> Our investigations began with nickel as the transition metal cocatalyst because of its demonstrated competence in room-temperature oxidative addition and the favorable single-electron reduction potentials of Ni<sup>I</sup>X complexes.<sup>15</sup> Mechanistically, we envisioned that visible light excitation of Ir complex **I** (Figure 4B) would generate a long-lived and highly oxidizing triplet state I\*, which could engage organotrifluoroborate **II** in SET, triggering oxidative fragmentation to radical species **III** with concomitant release of BF<sub>3</sub>. This radical could then add to Ni<sup>0</sup> complex **V** to generate Ni<sup>I</sup>-alkyl species **VI**. Subsequent oxidative addition into aryl bromide **VII** would afford high-valent Ni<sup>III</sup> complex **VIII**, reductive elimination from which would forge the desired C<sub>sp<sup>3</sup></sub>-C<sub>sp<sup>2</sup></sub> linkage in **IX**. Finally, SET from the reduced form of the photocatalyst to Ni<sup>I</sup> species **X** would return Ni<sup>0</sup> and the resting state photocatalyst.

We selected the cross-coupling of benzylic trifluoroborates with (hetero)aryl bromides as a prototype in our efforts to establish proof of concept for this dual catalytic manifold. In an

unexpected turn of good fortune, product was observed in the first attempted cross-coupling, validating our rational design principles. Control experiments unequivocally supported the essential role of both catalysts and visible light irradiation. Further optimization of reaction conditions led to identification of amines as beneficial additives. Although we have been unable to identify the role these additives serve, we suspect that they are involved in neutralizing the BF<sub>3</sub> generated upon oxidation of the organotrifluoroborate. We have consistently observed similar effects in subsequent studies involving organotrifluoroborates (*vide infra*).

Examination of substrate scope and functional group compatibility revealed the tolerance of a variety of aryl bromides and benzylic trifluoroborates (Figure 5).<sup>16</sup> Most notably, the mildness of the reaction conditions contrast sharply with those previously reported for conventional cross-couplings of benzylic boron reagents, leading to improved tolerance of sensitive functional groups.<sup>17</sup> Particularly pleasing was the observed compatibility with protic functional groups that are often challenging in conventional Suzuki coupling reactions. A large variety of N-heterocyclic bromides, of broad interest for applications in the synthesis of small molecule therapeutics, were also employed. Even substrates bearing functional groups known to react with radicals, including 4-bromostyrene, could be employed without competitive side reactions or polymerization, a particularly encouraging sign regarding the generality of these methods.

Reaction conditions optimized for primary benzyltrifluoroborates were effective in the cross-coupling of a secondary  $\alpha$ -(benzyloxy)-alkyltrifluoroborate (eq 1). This experiment not only demonstrated compatibility with substrates bearing  $\beta$ -hydrogen atoms but also suggested a nearly unparalleled level of adaptability and predictability with regard to the scope of the organoboron reagent.

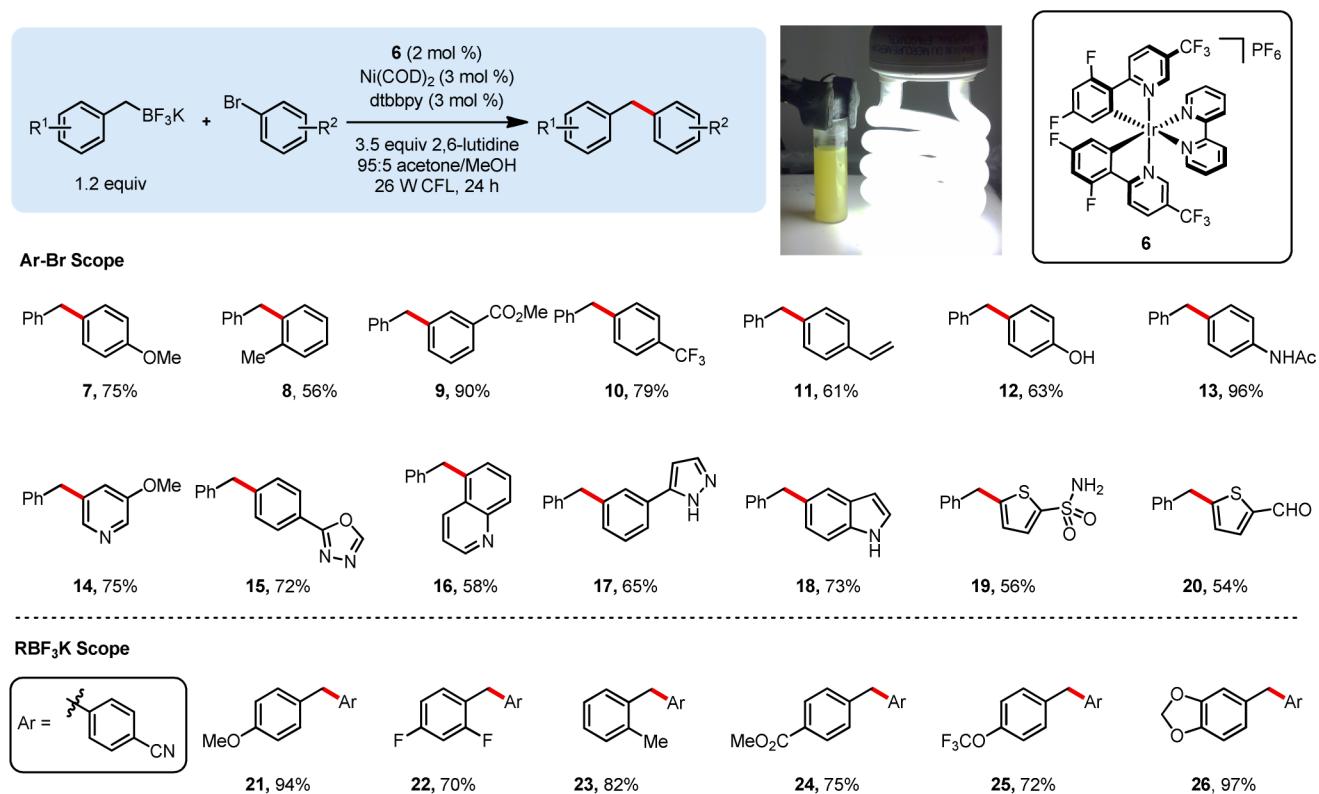
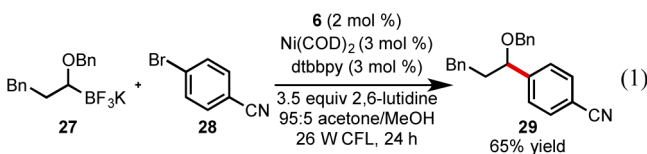
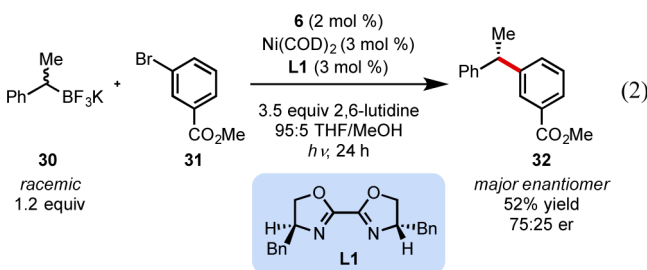


Figure 5. Cross-coupling of benzyltrifluoroborates with (hetero)aryl bromides.

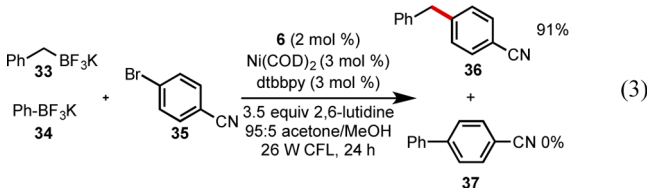
Whereas the reactivity of new substrates in Suzuki reactions is often frustratingly difficult to predict, partially because of subtle and ill-defined stereoelectronic influences exerted upon the precarious transmetalation transition state, this preliminary experiment suggested that redox potentials may hold substantial predictive power in the success or failure of substrates in this new class of cross-couplings.



This seminal report also documented proof of concept regarding stereoconvergent C–C bond formation in the synthesis of enantioenriched **32**, albeit in modest ee (eq 2). It is important to note that stereoconvergent cross-coupling of secondary alkylboron reagents has never been demonstrated in conventional cross-coupling reactions because of the stereospecific nature of the two-electron transmetalation.<sup>5</sup> As such, this process circumvents a mechanistic limitation of the classical cross-coupling paradigm, offering, for the first time, opportunities for the synthesis of enantioenriched products from racemic organoboron compounds.



To demonstrate the advantages of the single-electron transmetalation paradigm in  $C_{sp^3}$  cross-coupling, we performed a competition experiment wherein one aryl bromide substrate was exposed to both a benzyltrifluoroborate and an aryltrifluoroborate. Under conventional Suzuki coupling conditions, only **37** is observed, adhering to two-electron transmetalation rate trends. However, utilizing photoredox/nickel dual catalysis, only **36**, arising from selective activation of the  $sp^3$  hybridized reagent, was obtained (eq 3). This experiment illustrates the dramatic inversion of reactivity afforded by simple alteration of the underlying activation mode and establishes single-electron transmetalation as a manifold that is *broadly preferable* to conventional processes for applications with  $sp^3$ -hybridized organometallics, because the inherent biases of the mechanism now explicitly favor use of these reagents.

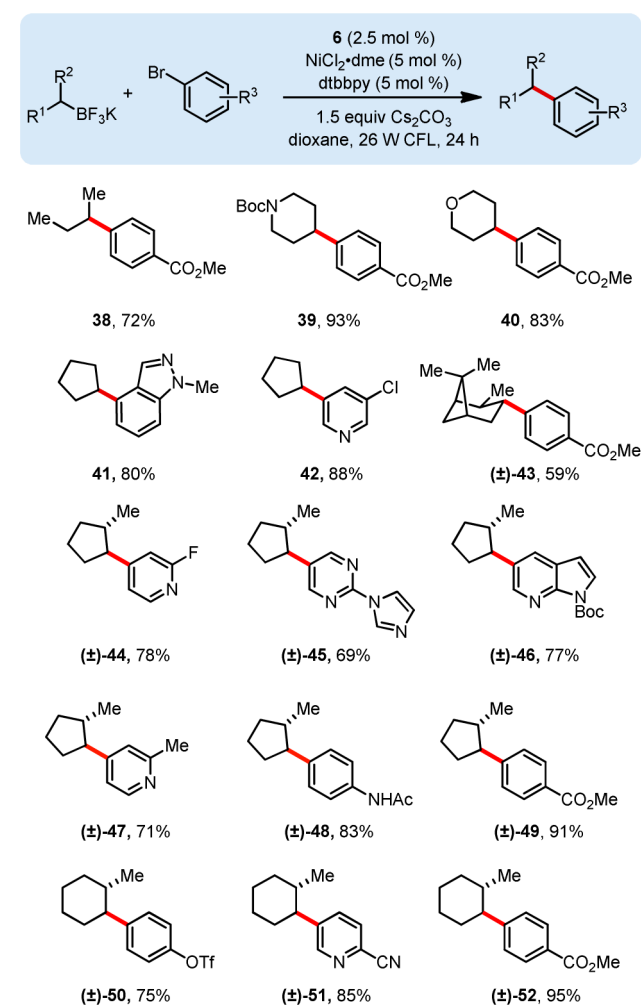


## 2.2. Extension to Unactivated Secondary Alkyltrifluoroborates

Although the cross-coupling of benzylic nucleophiles represented an ideal first step for the envisioned single-electron transmetalation

paradigm, we realized that greater generality would be required to achieve parity with other cross-coupling manifolds. Moving forward, we envisioned that the mild nature of the current transformations could have profound implications for unactivated secondary alkyl cross-coupling. Indeed, the wealth of literature where  $\beta$ -hydride elimination is not observed in Ni catalyzed  $C_{sp^3}$ – $C_{sp^2}$  and  $C_{sp^3}$ – $C_{sp^3}$  coupling reactions<sup>11</sup> and our own successes with  $\alpha$ -(benzyloxy)-alkyltrifluoroborates suggested that fruitful coupling would be possible.

Bolstered by this knowledge, we explored the cross-coupling of unactivated secondary alkyltrifluoroborates. Although single-electron oxidation of this class of organoboron reagents by the photocatalyst excited state was mildly endergonic,<sup>16</sup> we expected that the breadth of the measured oxidation wave and the irreversibility of fragmentation might work in our favor to enable effective cross-coupling. Indeed, despite this potential hurdle, rapid identification of reaction conditions was made possible using high-throughput experimentation techniques.<sup>18</sup> Extension of these conditions to unsymmetrical secondary alkyltrifluoroborates confirmed the complete regioisomeric fidelity of the reaction (Figure 6). Moreover, sterically hindered 2-methylcycloalkyltrifluoroborates coupled without rearrangement for the first time. Furthermore, this report documented the first cross-coupling of challenging, fully saturated heterocyclic alkyltrifluoroborates



**Figure 6.** Cross-coupling of secondary alkyltrifluoroborates with (hetero)aryl bromides.

derived from piperidine and tetrahydropyran. Ultimately, and despite its relative infancy, the capabilities of this method largely equaled or surpassed those of conventional Suzuki coupling.

### 2.3. Cross-Coupling of Unique Synthons

With the goal of furthering the capabilities of this Ni/photoredox cross-coupling paradigm, we sought to engage other reagent subclasses that had previously been limited, recalcitrant, or entirely unreactive with conventional protocols. These included  $\alpha$ -aminomethyl-,<sup>19</sup>  $\alpha$ -alkoxymethyl-,<sup>20</sup> and  $\alpha$ -trifluoromethyltrifluoroborates<sup>21</sup> (Figure 7).

Taken together, this suite of methods is attractive for rapidly accessing architectures of high complexity through dissonant disconnections. The  $\alpha$ -aminomethyl coupling, for example, affords access to highly valuable unnatural amino acid derivatives. The  $\alpha$ -alkoxymethyl coupling provides a retrosynthetically unique approach to benzylic ethers or protected benzylic alcohol derivatives. Finally, the  $\alpha$ -trifluoromethylbenzyl coupling accesses novel 1,1-diaryltrifluoroethanes, compounds that are rare in the literature and that may exhibit unique physical or pharmacokinetic properties. As an added note, a large portion of the products generated by all three methods are wholly undocumented chemical entities, showcasing the power of the single-electron paradigm to expand three-dimensional chemical space through the installation of  $C_{sp^3}$ -hybridized centers.

### 2.4. Orthogonal Reactivity by Mechanistic Differentiation

From the outset of our studies, we were particularly intrigued by the implications that an odd-electron activation mode might have for the selective activation of differentially hybridized organoboron reagents. These suspicions were validated by the aforementioned competition experiment in our seminal report, thus setting the

stage for further exploration into the mechanistic differentiation of  $sp^2$ - and  $sp^3$ -hybridized boron reagents. In contrast to previously reported iterative organoboron couplings, which rely on unique structural motifs or differential protection to achieve selectivity,<sup>22</sup> single-electron transmetalation allows innate differentiation between two organoboron reagents based on their mode of activation (Figure 8). Here, an  $sp^2$  hybridized organoboron center, which prefers to react via two-electron transmetalation, is rendered inert in the odd-electron activation mode, without requirement for artificial attenuation of reactivity, as a result of its prohibitively high single-electron oxidation potential.

By exploitation of this electronic bias, cross-coupling of a variety of alkyltrifluoroborates could be accomplished using bromoarenes bearing a  $C_{sp^3}$ -B moiety.<sup>23</sup> This latter C-B bond could then be oxidized, furnishing elaborated phenols. To demonstrate that these sensitive boron functional groups remained intact under the reaction conditions, the Ar-Bpin was functionalized in an iterative fashion through either subsequent Pd-catalyzed cross-coupling or Rh-catalyzed conjugate addition, without intermediate purification.

### 2.5. Stereoconvergence and Mechanistic Considerations

To understand the intimate mechanistic details of this novel cross-coupling process, we turned to computational modeling.<sup>24</sup> In collaboration with the Kozlowski group, the cross-coupling of a benzylic radical with bromobenzene was examined to gain insight into the general potential energy surface (Figure 9). Here, two pathways were considered: (1) radical addition to  $Ni^0$  followed by oxidative addition and (2) oxidative addition by  $Ni^0$  followed by radical capture. The process of radical addition to  $Ni^0$  was

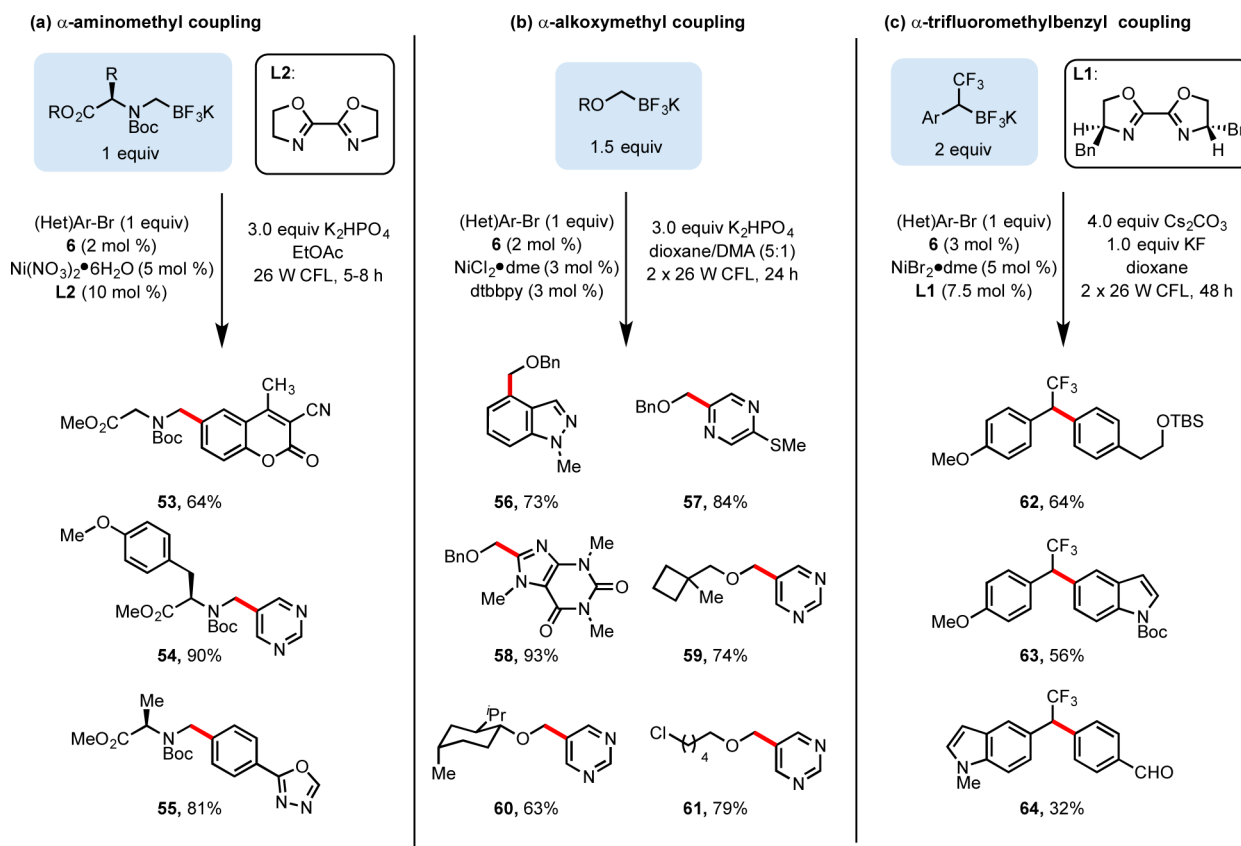
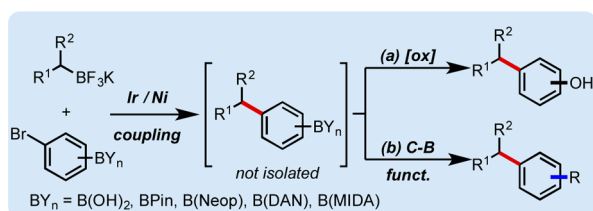
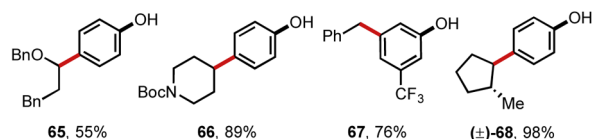
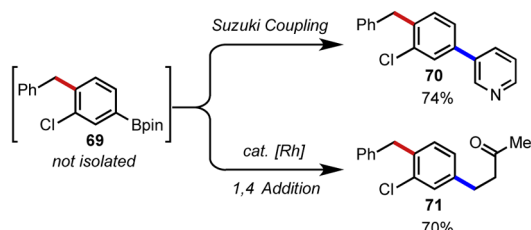


Figure 7. Extension of photoredox/cross-coupling to various alkyltrifluoroborate classes.



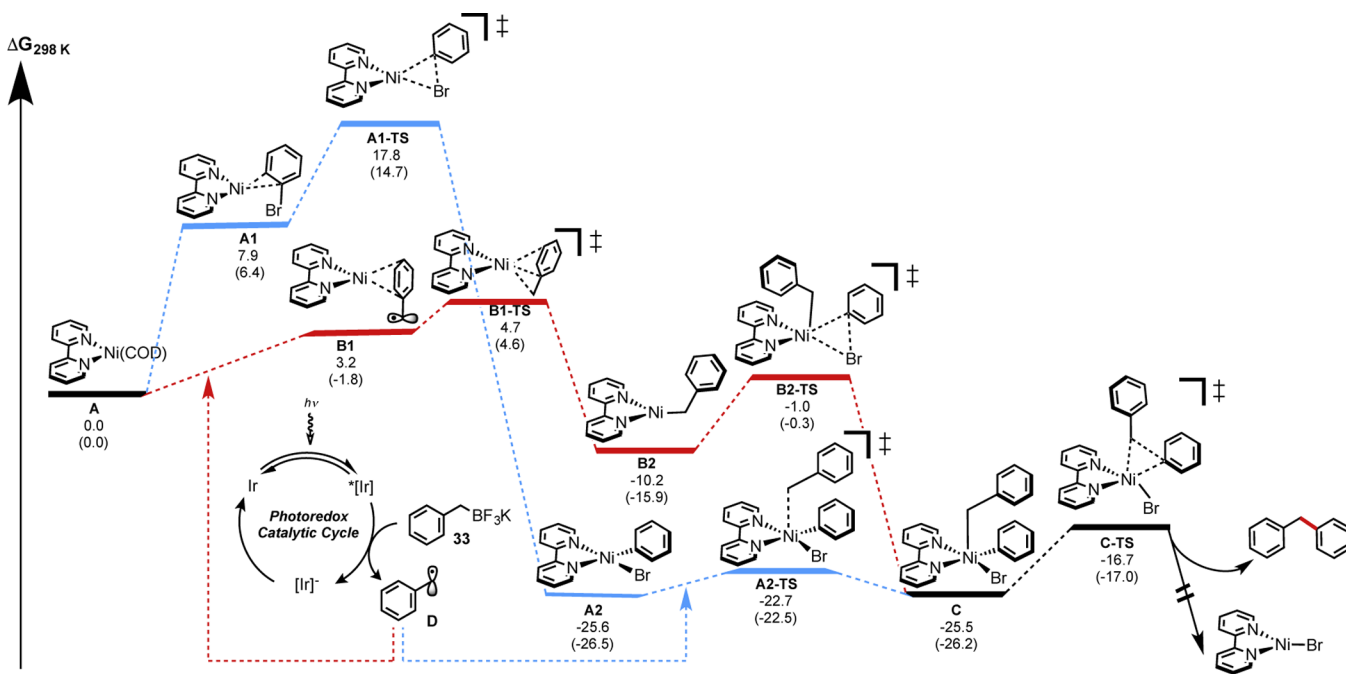
(a) Photoredox Cross-Coupling/Oxidation Sequence

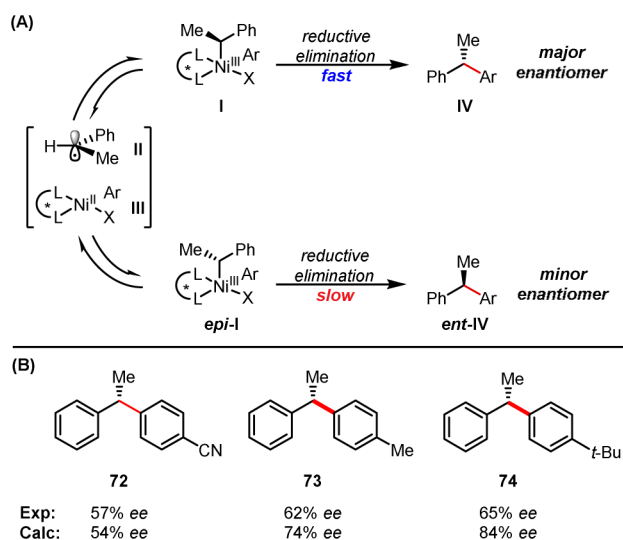
(b) Photoredox Cross-Coupling/ $C_{sp^2}$ -B Functionalization Sequence**Figure 8.** Mechanistic differentiation for selective organoboron cross-coupling.

found to be significantly more facile than competing oxidative addition, leading us to favor the pathway proceeding through a  $Ni^I$ -alkyl species over the related  $Ni^0$  pathway that had previously been proposed by our group as well as the groups of MacMillan and Doyle.<sup>25</sup> We believe it is likely that the  $Ni^I$  pathway predominates despite the low concentration of both radical and  $Ni^0$  under catalytically relevant conditions because of the large difference in activation energy.<sup>26</sup> However, these pathways are

exceedingly difficult to discern from one another experimentally, and it appears possible that both may operate simultaneously. Regardless, both mechanisms converge upon common  $Ni^{III}$  intermediate **C**, which affords product upon reductive elimination. Surprisingly, the barrier to reductive elimination is  $\sim 6.0$  kcal/mol higher than the microscopic reverse of radical addition to  $Ni^{II}$  complex **A2**, and the **A2**/radical pair and **C** were calculated to be of almost identical energy. Thus, **C** is predicted to exist in equilibrium with **A2** via spontaneous homolysis of the carbon–nickel bond, generating benzyl radical **D**. This result has profound implications when extrapolated to systems wherein chiral ligands are employed with a prochiral radical. In this scenario, where a fast, reversible process precedes a slower, irreversible step, the origin of stereoselectivity must be the reductive elimination, as dictated by the Curtin–Hammett principle. Accordingly, we propose a model described as a dynamic kinetic resolution, wherein enantioselectivity arises from rapid equilibration of diastereomeric  $Ni^{III}$  complexes **I** and *epi-I*, where interconversion of the two complexes occurs through Ni–C bond homolysis and subsequent recombination of the alkyl subunit from the *opposite* enantioface. (Figure 10A). Because irreversible  $C_{sp^3}$ – $C_{sp^2}$  bond formation proceeds faster for one of these diastereomeric  $Ni^{III}$  complexes, enantioenrichment of the cross-coupled products is observed.

We next sought to validate this model experimentally through the correlation of calculated and experimentally determined ee values for various substrates. Computational results suggested that bulky *para*-substituents on the aryl bromide educe unfavorable steric interactions with the ligand architecture in the reductive elimination transition state leading to the minor enantiomer, thus providing higher enantioselectivity. Indeed, a positive correlation of size to stereoselectivity was observed experimentally for three test substrates bearing cyano, methyl, and *tert*-butyl substituents (Figure 10B). Importantly, the stereochemical consequences of these modifications would be difficult to predict in the absence of this mechanistic insight.

**Figure 9.** Computed potential energy surface for competing pathways in Ni/photoredox dual catalytic cross-coupling.  $\Delta G$  values in kcal mol<sup>-1</sup>. Calculations performed at SMD-water-(U)M06/6-311+G(d,p)//UB3LYP/6-31G(d) and SMD-water-(U)M06/6-311+G(d,p)//UB3LYP/LANL2DZ (Reproduced from ref 24. Copyright 2015 American Chemical Society.).



**Figure 10.** Stereoconvergence in single-electron transmetalation: (A) Ni<sup>III</sup> dynamic kinetic resolution; (B) experimental validation of the stereochemical model.

## 2.6. C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>2</sup> Cross-Coupling Using Alkylsilicates

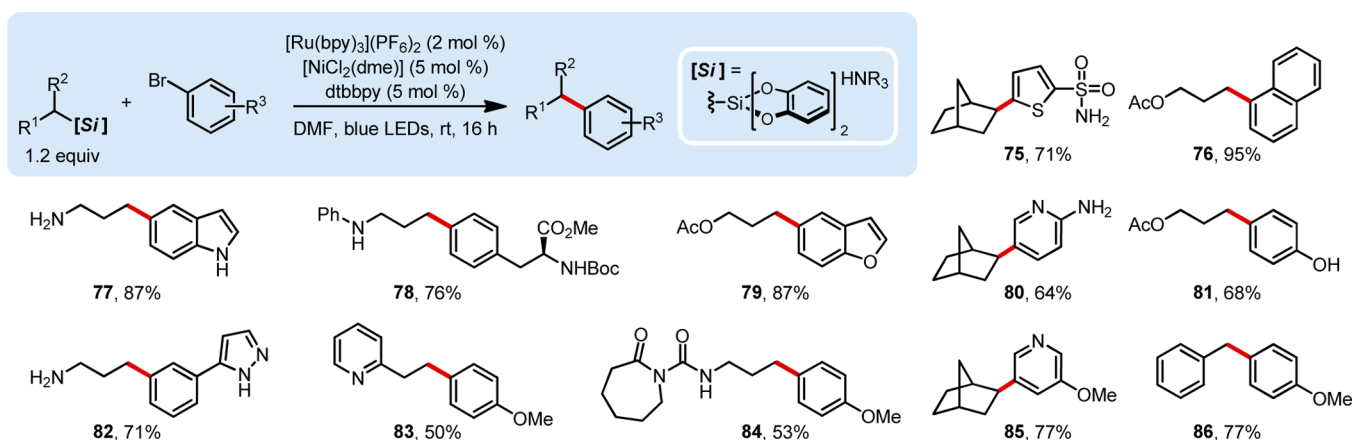
Although alkyltrifluoroborate salts are exceptional radical precursors, they possess several drawbacks (e.g., limited solubility profile, release of BF<sub>3</sub> upon photooxidation, necessitating exogenous base, high oxidation potential, requiring use of expensive Ir-based photocatalysts, etc.) that prompted us to explore alternate coupling partners. Based on reports by Nishigaichi,<sup>27</sup> we posited that not only could hypervalent alkylbis(catecholato)silicates serve as viable alkyl radical forebears but the innocuous orthosilicate produced by Si–C bond fragmentation would obviate the need for basic additives. First prepared by Frye<sup>28</sup> in 1964, alkylsilicates have, until recently, remained more curiosities than reagents for organic synthesis. Apart from the elegant reports by DeShong<sup>29</sup> and Hosomi and their co-workers,<sup>30</sup> examples of alkylsilicates as partners in C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>2</sup> cross-coupling were rare and, to the best of our knowledge, their use in C<sub>sp</sub><sup>3</sup>–C<sub>sp</sub><sup>2</sup> bond construction was virtually unknown. Despite this lack of precedent, initial evaluation of these hypervalent species seemed promising. Alkylammonium alkylbis(catecholato)silicates are nonhygroscopic, benchtop stable, free-flowing powders that can be easily prepared from inexpensive trimethoxyalkylsilanes and whose solubility properties can be tuned based on the identity of the ammonium counterion. More importantly, cyclic voltammetry

studies revealed that even primary alkylsilicates fell well within the oxidative capabilities of state-of-the-art photoredox catalysts such as **6** and [Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> (*E*<sup>0</sup> ≈ +0.37 to +0.75 V vs SCE).<sup>31</sup>

We quickly determined that both **6** and [Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> were suitable photocatalysts in the cross-coupling of alkylbis(catecholato)silicates.<sup>32</sup> Consistent with the fact that the intermediate radical is generally independent of its source material, the transition metal cross-coupling cycle was found to be largely unaffected when using alkylsilicates in place of organotrifluoroborates. As such, both Ni<sup>II</sup> and Ni<sup>0</sup> sources, in conjunction with 2,2'-bipyridyl ligands, were effective in promoting the desired cross-coupling. A combination of practical and economic factors led us to select [Ru(bpy)<sub>3</sub>](PF<sub>6</sub>)<sub>2</sub> and [NiCl<sub>2</sub>(dme)] as the ideal catalytic system, with best results obtained in anhydrous DMF. When assessing the scope of the optimized cross-coupling, an emphasis was placed on challenging cross-couplings. Hence, we focused on substrates recalcitrant toward oxidative addition (e.g., 4-bromoanisole), systems bearing protic functional groups (e.g., alcohols, amides, etc.), and alkylsilicates bearing unprotected amines. Various electronically disparate arenes were well-tolerated, giving good to excellent yields of the cross-coupled products. Similarly, numerous heteroaromatic species were amenable to cross-coupling under these reaction conditions. Moreover, unactivated primary and secondary alkylsilicates could be employed under identical conditions.<sup>33</sup> Figure 11 provides representative examples synthesized via this protocol. During the course of this investigation, the groups of Fensterbank and Goddard reported the use of related potassium organobis(catecholato)silicates as alkyl radical precursors.<sup>34</sup>

## 2.7. Alkenylation of Alkylsilicates

Based on the successful integration of carboxylic acids bearing an  $\alpha$ -heteroatom with alkenyl halides for photoredox/Ni dual catalysis described by MacMillan,<sup>35</sup> we envisioned that alkylsilicates could be utilized in a similar manner. If successful, this would also overcome the somewhat restrictive scope of MacMillan's approach as well as our inability to employ alkyltrifluoroborates in this type of transformation, while simultaneously expanding the capabilities of alkylsilicates.<sup>36</sup> Conditions developed for cross-coupling alkylsilicates with aryl bromides were seamlessly transitioned to the cross-coupling of alkenyl halides (Cl, Br, and I), with complete retention of double bond geometry in all cases. Although amine-containing alkylsilicates performed poorly in this cross-coupling, a range of other silicates (including those bearing protic functional groups, such as amides) could be employed (Figure 12).



**Figure 11.** Cross-coupling of (hetero)aryl bromides with alkylsilicates.



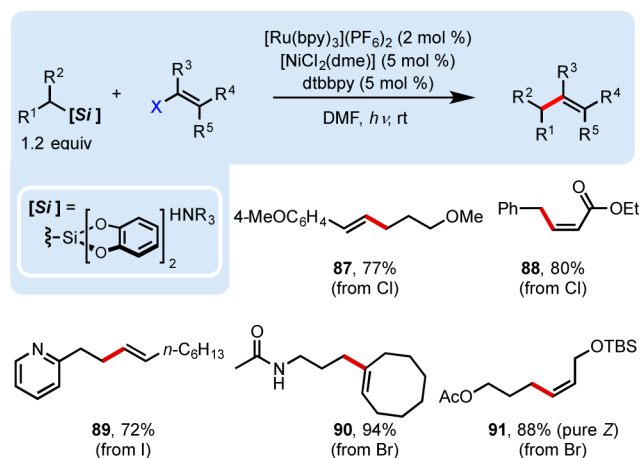


Figure 12. Cross-coupling of alkenyl halides with alkylsilicates.

## 2.8. Diversifying the Azaborine Scaffold

Moving forward, we sought to explore the capabilities of photoredox cross-coupling in the context of novel (hetero)aryl halide fragments. Here, we pursued a marriage of our interest in dual catalysis with our ongoing program in the synthesis of azaborines, compounds characterized by a structurally and electronically unique B–N bond embedded within an unsaturated ring. This B–N unit can serve as an isosteric surrogate for C=C bonds in aromatic systems, which has garnered interest from medicinal chemists for exploration as new pharmacophores.<sup>37</sup> A variety of 2,1-borazaronaphthalenes were smoothly engaged as cross-coupling partners with alkylsilicates.<sup>38</sup> Use of this approach facilitated expansion of the library of naphthalene isosteres to include systems that would be wholly inaccessible using conventional approaches (Figure 13).

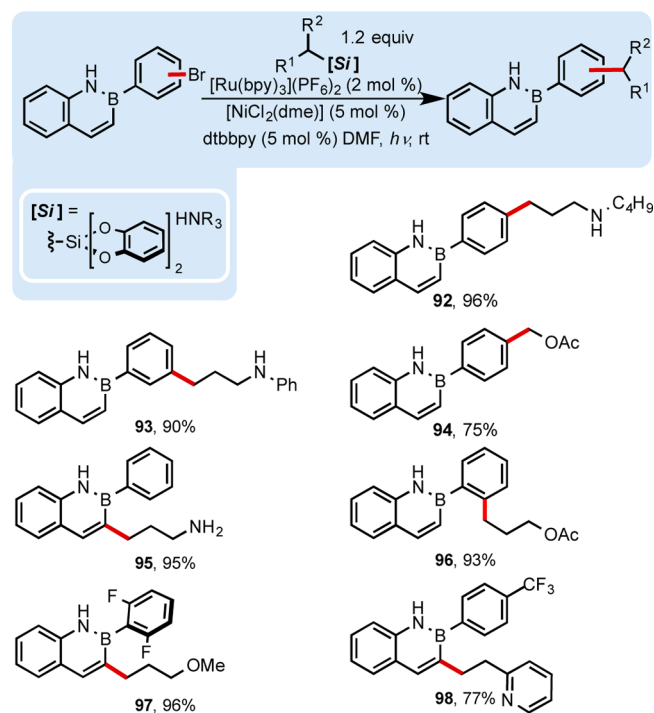


Figure 13. Cross-coupling of brominated 2,1-borazaronaphthalenes with alkylsilicates.

## 2.9. Thioetherification of (Hetero)aryl Bromides

During our investigation of the amenability of various alkylsilicates in dual catalysis, we encountered an unusual phenomenon when

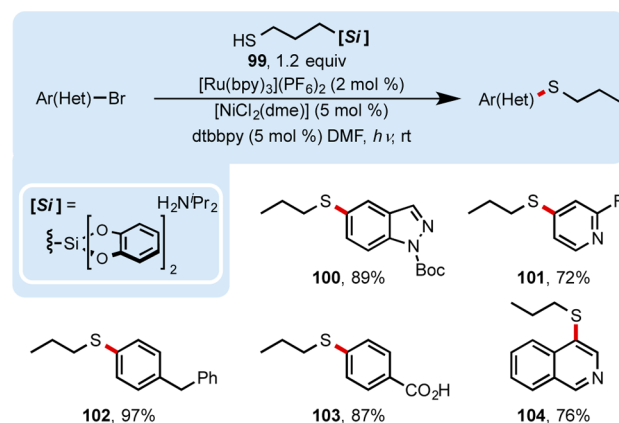


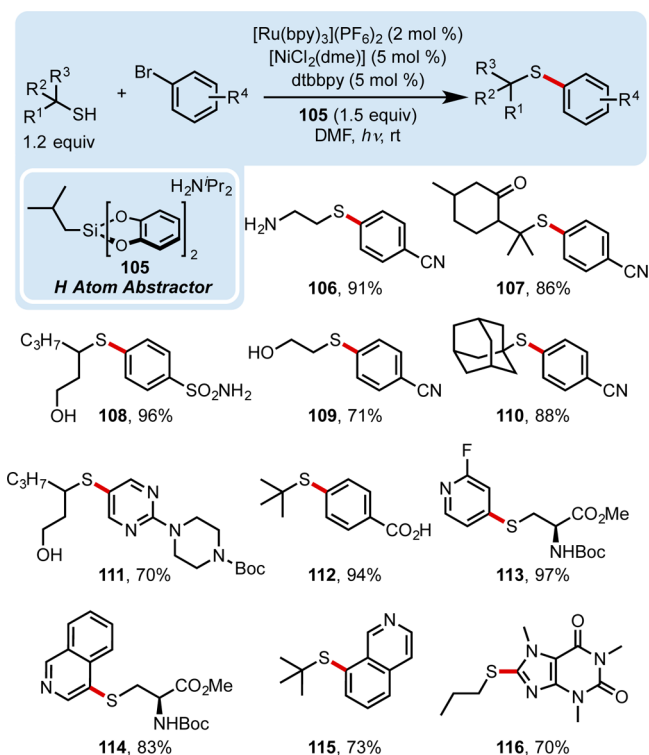
Figure 14. Cross-coupling of (hetero)aryl halides with 99.

attempting to perform the alkylation displayed in Figure 14.<sup>39</sup> Rather than obtaining the expected  $C_{sp^3}$ – $C_{sp^2}$  cross-coupling, we serendipitously discovered a thioetherification process. This unexpected but synthetically attractive finding was likely a consequence of a rapid hydrogen-atom transfer (HAT) from the thiol moiety (thus generating a thiyl radical) to the photochemically generated alkyl radical. The significant difference in bond dissociation energy (BDE) between C–H and S–H bonds [primary C–H BDE (ethane) = 101 kcal mol<sup>−1</sup> versus S–H BDE (methanethiol) = 88 kcal mol<sup>−1</sup>] renders this process irreversible.<sup>40</sup> The thiyl radical is then funneled into the Ni catalytic cycle and can subsequently participate in cross-coupling. Thus, we explored the scope of this process in the context of various (hetero)aryl bromides. The process was compatible with electron-poor to electron-neutral arenes as well as a diverse array of heteroaromatic species with yields ranging from 62% to 97%.

Given the irreversible and rapid nature of HAT when using 99, we envisioned that intermolecular HAT from a thiol using an alkylbis(catecholato)silicate as a H atom abstractor might be a plausible means of diversifying the scope further. Such a strategy was indeed possible, and a number of alkylsilicates served as effective H atom abstractors. Ultimately, we elected to use 105 (Figure 15) for practical reasons: isobutyltrimethoxysilane is inexpensive (\$0.06 per gram), and the volatile alkane byproduct was removed easily. The reaction retained the yields and bromoarene compatibility observed when using 99, while greatly expanding the thiol scope. Apart from thiophenol and benzylthiol derivatives, virtually any thiol (primary, secondary, or tertiary) could be employed. Thiols containing protic, and even acidic, moieties, as well as those possessing epimerizable chiral centers, were well-tolerated.

## 3. SUMMARY AND OUTLOOK

In only two years, single-electron transmetalation has emerged as a powerful paradigm for reliably forging  $C_{sp^3}$ – $C_{sp^2}$  bonds. Operating within this new mechanistic framework has resulted in methods that, although still in their adolescent stages, frequently equal or surpass the capabilities of conventional protocols in the cross-coupling of readily available and bench stable  $sp^3$ -hybridized nucleophiles. We anticipate that progress in this realm will continue, affording methods that demonstrate even greater functional group tolerance with amenability to applications with new classes of substrates, including aryl- and alkenyl pseudo(halides), aryl chlorides,  $sp^3$ -hybridized electrophiles, and challenging heterocyclic systems. As already witnessed in the development of alkylsilicate cross-couplings, the development of



**Figure 15.** Cross-coupling of (hetero)aryl bromides with thiols via silicate-mediated HAT.

novel radical progenitors will likely continue to be instrumental to the advancement of these methods, allowing access to complementary substructures and potentially improving practical elements, such as atom economy, waste handling, and synthetic accessibility. Philosophically, the success of the single-electron transmetalation paradigm stands as a reminder of the powerful potential of *de novo* catalysis design in solving longstanding synthetic challenges. Ultimately, we hope that the lessons learned in the realization of photoredox/nickel dual catalysis will lead to further advances in cross-coupling technology, propelling organic synthesis to new heights.

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### Author Contributions

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### Notes

The authors declare no competing financial interest.

### Biographies

**John C. Tellis** is a Bristol Myers-Squibb Graduate Fellow in the laboratory of Professor Gary Molander at the University of Pennsylvania. He received a B.S. from Elizabethtown College, supplemented by a summer REU at Vanderbilt University. After

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**Christopher B. Kelly** is an NIH NRSA postdoctoral fellow at the University of Pennsylvania working in the laboratory of Professor Gary Molander. He is currently investigating organosilicates and other radical precursors for application in dual catalytic photoredox cross-coupling. After obtaining his B.S. in biochemistry from Stonehill College, he received a Ph.D. from the University of Connecticut in 2015 under Dr. Nicholas Leadbeater, developing new synthetic methods in organofluorine chemistry and novel oxidative reactions utilizing oxoammonium salts.

**David N. Primer** received his B.Sc. from Emory University working with Professor Huw Davies. He is currently a graduate student in the laboratory of Professor Gary Molander where he has pioneered the development of radical mediated cross-coupling through the exploration of novel methods and reagents.

**Mathieu Jouffroy** obtained his Ph.D. from the University of Strasbourg in 2014 on the synthesis of cyclodextrin-based ligand scaffolds under the supervision of Dr. D. Matt and Professor D. Armspach. That same year, he moved to Tokyo Tech as a JSPS postdoctoral fellow under Professor K. Osakada and Dr. D. Takeuchi, working on copolymerization using monophosphine Pd(II) complexes. He is currently a postdoctoral researcher at the University of Pennsylvania under Prof. G. Molander investigating organosilicates for Ni catalyzed photoredox cross-coupling.

**Niki R. Patel** received her B.S. in Chemistry from Temple University. She obtained her Ph.D. from Lehigh University under the supervision of Professor Robert Flowers, investigating the mechanisms of silver-catalyzed SET pathways. She is currently a postdoctoral researcher in the laboratory of Professor Gary Molander, developing new methods for organosilicate cross-couplings.

**Gary A. Molander** completed his undergraduate studies at Iowa State University under the tutelage of Professor Richard Larock. He earned his Ph.D. at Purdue University under the direction of Professor Herbert Brown and undertook postdoctoral training with Professor Barry Trost at the University of Wisconsin, Madison. He began his academic career at the University of Colorado, Boulder, moving to the University of Pennsylvania in 1999, where he is currently the Hirschmann–Makineni Professor of Chemistry.

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