

## A Pyridine-Pyridine Cross-Coupling Reaction via Dearomatized Radical Intermediates.

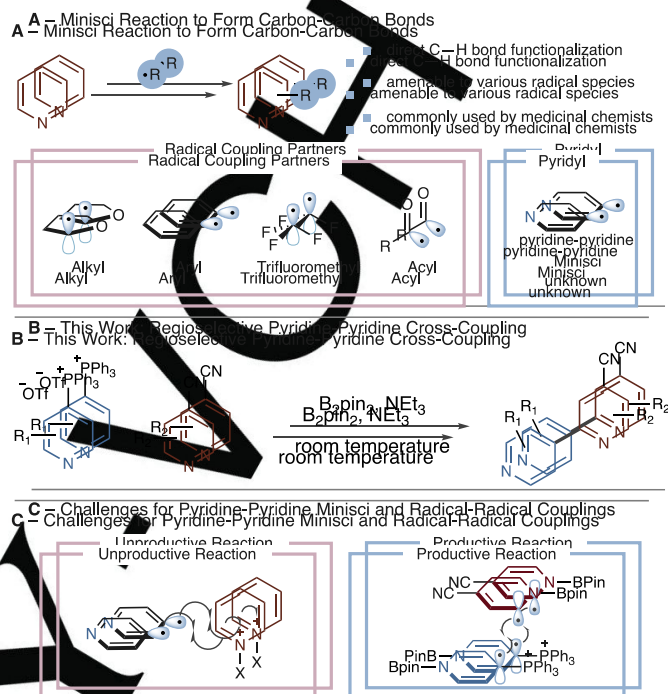
J. Luke Koniarczyk<sup>+</sup>, Jacob W. Greenwood<sup>+</sup>, XXXXXXXX and Andrew McNally<sup>\*</sup>

## Communications

**Abstract:** A pyridine-pyridine coupling reaction has been developed between pyridyl phosphonium salts and cyanopyridines using  $B_2pin_2$  as an electron-transfer reagent. Complete regio- and cross-selectivity are observed when forming a range of valuable 2,4'-bipyridines. Phosphonium salts were found to be the only viable radical precursors in this process, and mechanistic studies indicate that the process does not proceed via Minisci-type coupling involving a pyridyl radical. Instead, a radical-radical coupling process between a boryl phosphonium pyridyl radical and a boryl-stabilized cyanopyridine radical explains the C–C bond-forming step.

Minisci reactions are valuable processes for coupling carbon-bearing groups to azaarenes and are characterized by a mechanistic platform where carbon-centered radicals add to a heteroaromatic  $\pi$ -system.<sup>[1]</sup> Diverse sets of carbon-centered radicals and azaarene C–H precursors can be used interchangeably as coupling partners, including structurally complex variants (Scheme 1A).<sup>[1d]</sup> Recent advances, such as photoredox processes and new radical precursors, have further improved the versatility of these reactions, and they have been widely adopted by medicinal chemists.<sup>[2,3]</sup> Within this reaction class, pyridine arylation reactions have been demonstrated using a variety of aryl radical precursors. However, no examples of cross-coupling between two pyridines have been reported using this manifold. The coupling bipyridines are common motifs in pharmaceuticals and can be challenging to prepare via metal-catalyzed cross-couplings.<sup>[5,6]</sup> We herein report that pyridyl phosphonium salts selectively couple with cyanopyridines using B<sub>2</sub>p<sub>2</sub> to facilitate electron transfer (Scheme 1B). Bipyridines form with complete control of regioselectivity, and mechanistic studies reveal an alternative coupling step to typical Minisci processes involving dearomatized radical intermediates.

Two factors can account for pyridine-pyridine coupling being unfavorable through a Minisci-type reaction pathway. First, pyridyl radical and the  $\pi$ -system of an acceptor pyridine are electronically mismatched making C-C bond formation thermodynamically prohibitive (Scheme 1C).



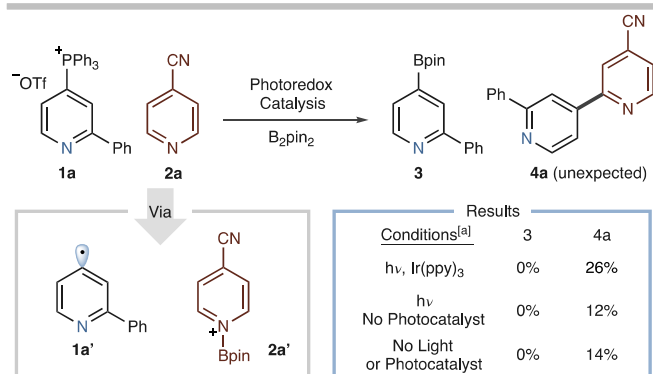
**Scheme 1.** Limitations of Minisci reactions for pyridine-pyridine coupling and a boron mediated method proceeding radical-radical coupling.

Brønsted acid activation of pyridines is common in Minisci reactions and forming pyridinium ions could further exacerbate the electronic incompatibility between donor and acceptor heterocycles. Second, achieving cross-selectivity between two different pyridines is challenging, as pyridyl radicals can conceivably react at comparable rates with their radical precursors and coupling partners. This study reveals an alternative mechanistic platform where the phosphonium group is not expelled to form a pyridyl radical and, instead, bond-formation occurs through a radical-radical coupling process involving a boryl phosphonium radical and a boryl cyanopyridine radical (Scheme 1C).

Our laboratory has shown that pyridines can be converted into phosphonium salts in a 4-selective process and participate in a range of subsequent transformations proceeding through two-electron pathways.<sup>[7,8]</sup> We questioned whether these reagents were also amenable to open-shell pathways via single-electron reduction to pyridyl radicals and hypothesized that a 4-position pyridine borylation was feasible. Two reports from Li and Jiao postulated that a persistent boryl radical forms from 4-substituted pyridines, such as cyano-derivatives (**2a**), and B<sub>2</sub>pin<sub>2</sub>.<sup>[9]</sup> We speculated that reducing pyridyl

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**Scheme 2.** Attempted 4-borylation and unexpected bipyridine formation. [a] Initial reaction conditions: Ir(ppy)<sub>3</sub> (1 mol %), *i*Pr<sub>2</sub>EtN (2.5 equiv), 4-cyanopyridine (2.0 equiv), B<sub>2</sub>pin<sub>2</sub> (1.0 equiv), CH<sub>2</sub>Cl<sub>2</sub> (0.1 M), 34-W Kessil blue LED, rt, 8 h.

phosphonium salt **1a** ( $E_{p/2}^{\text{red}} = -1.51$  V vs SCE) with Ir(ppy)<sub>3</sub> as a photocatalyst and *i*Pr<sub>2</sub>EtN as a sacrificial reductant would form a pyridyl radical (**1a'**) that could react with the putative boryl radical and result in borylated product **3** (Scheme 2). However, no borylation products were observed and, instead, 2,4'-bipyridine **4a** formed with exclusive regioselectivity. Around the time of this finding, further investigations revised the identity of the 4-cyanopyridine-B<sub>2</sub>pin<sub>2</sub> adduct to a delocalized radical in the pyridine ring that may be capable of reducing **1a** to pyridyl radical **1a'**.<sup>[9b,10]</sup> At this juncture, we hypothesized that a Minisci-type coupling between **1a'** and pyridinium **2a'** had occurred and was specific to this reaction system (*vide infra*).

Following the discovery, we set out to optimize the coupling of 2-phenylpyridine phosphonium salt **1a** and 4-cyanopyridine **2a** (Table 1). The yield was improved by increasing the reaction concentration and prolonging the reaction time to 36 hours (entries 1–3). Notably, in the absence of B<sub>2</sub>pin<sub>2</sub>, the desired product was not detected (entry 4). The efficiency of the reaction increased significantly when NEt<sub>3</sub> was used as a base (entries 5–7); product **4a** is still obtained when no base is present but in low yield. Next, other common precursors to carbon centered radicals were examined. Under optimized conditions, 2-phenylpyridines substituted with halides, diazoniums, triflates, and pyridiniums were all unsuccessful in forming **4a**.<sup>[11]</sup> Notably, 4-iodo-2-phenylpyridine, which is known to generate pyridyl radicals under photoredox conditions, was also unsuccessful and further highlights the unique capacity of pyridyl phosphonium salts to serve as coupling partners.

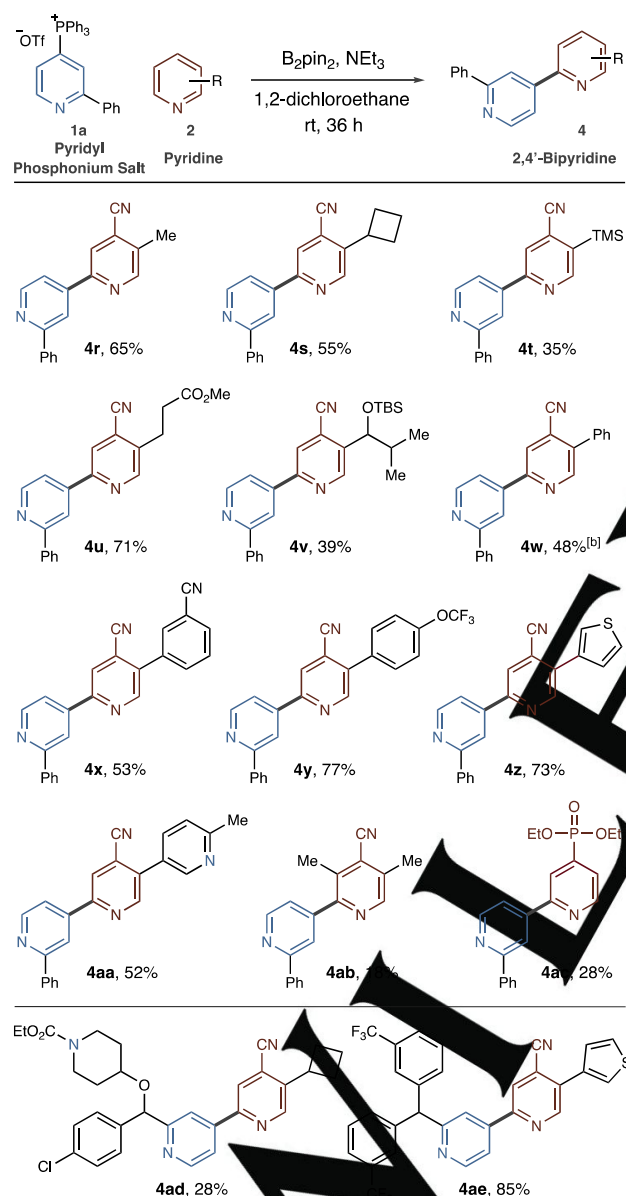
Entry	Base (equiv)	Time [hr]	Concentration [M]	Yield [%] <sup>[b]</sup> <b>4a</b>
1	<i>i</i> Pr <sub>2</sub> NEt (2.5)	8	0.1	14
2	<i>i</i> Pr <sub>2</sub> NEt (2.5)	36	0.2	26
3	<i>i</i> Pr <sub>2</sub> NEt (2.5)	36	0.2	34
4 <sup>[c]</sup>	<i>i</i> Pr <sub>2</sub> NEt (2.5)	36	0.2	0
5	TMP (2.5)	36	0.2	16
6	NEt <sub>3</sub> (2.5)	36	0.2	99
7	None	36	0.2	26
8	NEt <sub>3</sub> (1.25)	36	0.2	97

[a] Phosphonium **1a** (1.0 equiv), **2** (2.0 equiv), B<sub>2</sub>pin<sub>2</sub> (1.0 equiv). [b] Yields by <sup>1</sup>H NMR analysis. [c] B<sub>2</sub>pin<sub>2</sub> omitted from the reaction. [d] Radical precursors (1.0 equiv) used in place of phosphonium **1a**. [e] Reaction conditions: Ir(ppy)<sub>3</sub> (1 mol %), 4-cyanopyridine (1.0 equiv), **2** (2.0 equiv), B<sub>2</sub>pin<sub>2</sub> (1.0 equiv), NEt<sub>3</sub> (1.25 equiv), 1,2-dichloroethane (0.2 M), rt, 96 h. [f] Diazo decomposed under entry 7 conditions.

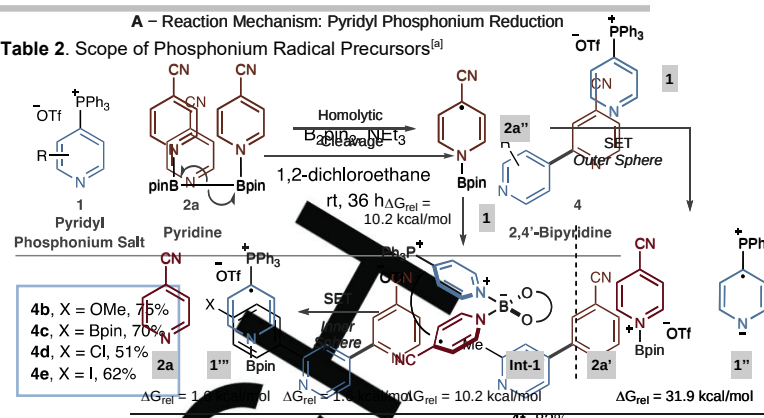
Next, the scope of pyridyl phosphonium salts was examined (Table 2). A range of 2-aryl salts, including functional groups amenable to further transformations, as well as a 2-methyl salt, functioned effectively (**4b–4f**). A chlorine atom is tolerated at the 2-position albeit in lower yield (**4g**). Pyridines substituted at the 3-position are compatible and coupled products are obtained in moderate yield. Fluorine atoms are accommodated as in **4j**, derived from a 2,3-disubstituted salt. Azetidine rings and heteroaromatics can also proceed through the reaction without interference (**4k** & **4l**). Finally, pharmaceuticals and drug analogues were tested to demonstrate that complex structures were applicable to the protocol; examples **4m–4q** show that a range of 2,4'-bipyridine derivatives, with a range of functional groups, can be formed with precise control of regioselectivity.

We then turned our attention to the scope of acceptor pyridines and began with substituted cyanopyridines (Table 3). Simple alkyl and silyl groups at the 3-position are accommodated in products **4r–4t**;

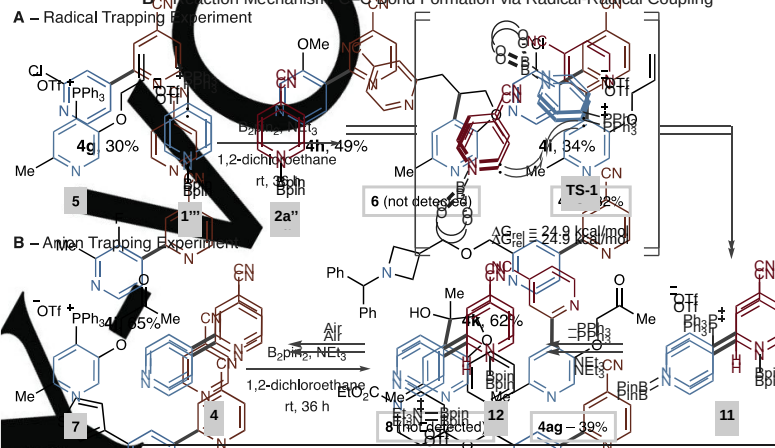
**Table 1.** Pyridine-Pyridine Coupling: Optimization.<sup>[a]</sup>



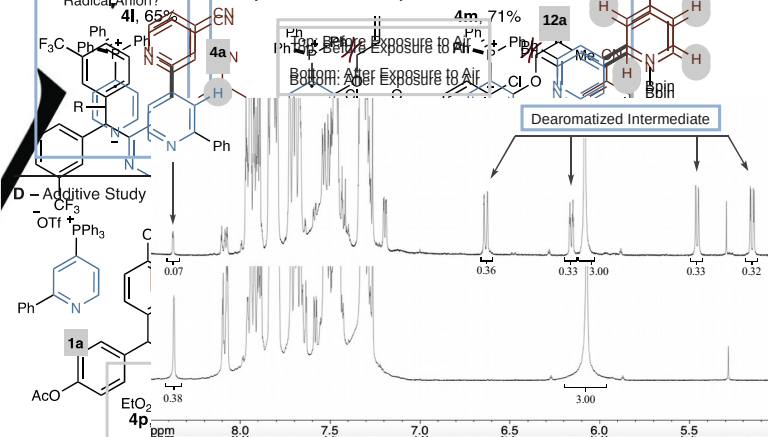
**Table 2.** Scope of Phosphonium Radical Precursors<sup>[a]</sup>



### B - Reaction Mechanism: C-C Bond Formation via Radical-Radical Coupling



C Phosphonium Radical Anion? Observation of Dearomatized Intermediate 13a Cyclization Disfavored by Steric Interactions.

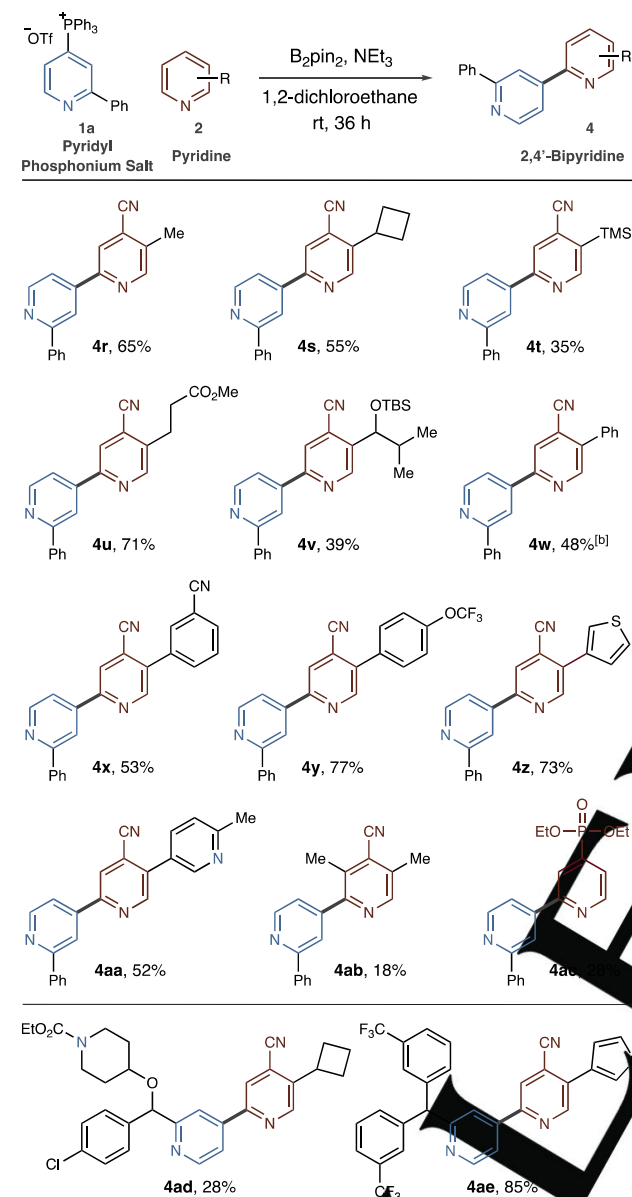


[a] Isolated yields of single regioisomers. Conditions: phosphonium **1** (1.0 equiv), **2a** (2.0 equiv), B-pin<sup>+</sup> (1.0 equiv), 1,2-dichloroethane (0.2 M), rt, 36 h.  
[b] Yield determined by <sup>1</sup>H NMR analysis.

single regioisomers, apart from one example, were obtained despite the possibility of C–C bond formation at other sites. Esters and protected alcohols were also tolerated under the reaction conditions, and substituted aromatic groups enable rapid assembly of tri(hetero)aryl products (**4u–4z**). Tripyridyl product **4aa** demonstrates that site-selective coupling occurs on cyano- over alkyl-substituted pyridines. A substituent adjacent to the site of C–C bond formation is tolerated, although steric effects appear to decrease yields significantly (**4ab**). Despite assuming that a cyano group is important for radical stabilization, a phosphonate ester could also serve this role (**4ac**). Aryl groups at the 4-position were not

effective, however, an ester formed the coupled product in low yields.<sup>[12]</sup>

**Table 3.** Scope of Pyridine Acceptors<sup>[a]</sup>



[a] Isolated yields of single regioisomers. Conditions: phosphonium **1a** (1.0 equiv), **2** (2.0 equiv), B<sub>2</sub>pin<sub>2</sub> (1.0 equiv), 1,2-dichloroethane (0.2 M), rt, 36 h. [b] 17:1 regioisomeric ratio.

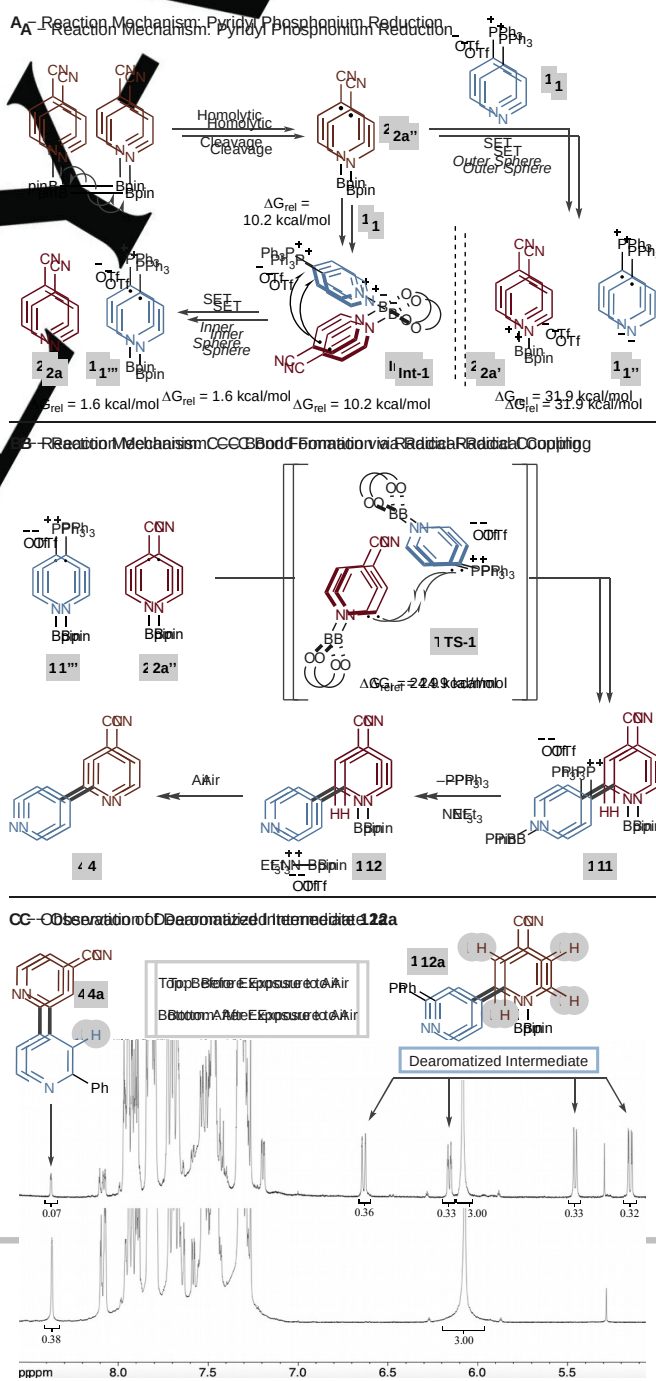
Inductively withdrawing groups, such as halides and trifluoromethyl groups, at the 4-position were not effective as coupling partners and support a pyridyl radical ion intermediate in the reaction mechanism (*vide infra*). Finally, complex phosphonium salts and acceptor pyridines were shown as efficient coupling partners (e.g., **4a**).

We then performed a series of experiments to investigate the mechanism of the reaction. First, a radical trapping experiment was designed to provide evidence of an intermediate pyridyl radical (Figure 1A). When allyloxy-substituted salt **5** was subjected to the reaction conditions cyclized product **6** was not observed, and

significant amounts of bipyridine **4af** formed. As 5-exo-trig radical cyclizations in similar systems proceed with fast kinetics (rate constants:  $7.87 \times 10^7$  to  $9.6 \times 10^9 \text{ s}^{-1}$ ),<sup>[13]</sup> this result suggested that an alternative mechanism was operative. Second, we considered that a putative pyridyl radical could be reduced again to form a pyridyl anion, and that bond-formation occurs via a two-electron pathway.

**Figure 1.** (A) Pyridyl radical trap experiment; (B) Pyridyl anion trap experiment; (C) Potential for radical anions as intermediates and sterically disfavoured cyclizations. (D) Effect of additives on the coupling process. [a] Yield calculated by <sup>1</sup>H NMR analysis of the crude reaction mixture using 1,3,5-trimethoxybenzene as an internal standard.

However, ketone **7** showed no evidence of cyclization to tertiary alcohol **8** and bipyridine **4af** was again observed as the major product (Scheme 1B). At this point, we considered that C–C bond-formation could be occurring





**Figure 2.** (A) SET reduction of pyridyl phosphonium ions; (B) Radical-radical coupling between pyridyl boryl radical coupling partners; (C) Evidence of dearomatized intermediate by  $^1\text{H}$  NMR and its conversion to rearomatized product after exposure to air (peak at 6.08 ppm is 1,3,5-trimethoxybenzene used as an internal standard). ADD DFT stuff here

via a pyridyl phosphonium radical anion (or a related derivative) and that that large phosphonium ion precludes cyclization in both of the resonance forms shown in Figure 1C. Figure 1D shows that pyridine-pyridine coupling is only marginally perturbed by including a Hantzsch ester and C–H abstraction had not occurred to form **9**. In the presence of  $\text{D}_2\text{O}$ , phosphonium salt **x** is largely converted into **9** and **10** (9:91) and no coupled product was observed. Although we obtained useful information from the experiments in Figure 1, the unusual nature of the putative phosphonium pyridyl radical anion, as well as the exact role of  $\text{B}_2\text{pin}_2$  in the reaction, prompted us to investigate the mechanism computationally.

Figure 2 shows a proposed mechanism supported by computational and spectroscopic studies. First, we questioned how single-electron reduction of a pyridyl phosphonium salt occurs. Li and Jiao proposed that two equivalents of pyridine **2a** react with  $\text{B}_2\text{pin}_2$  and subsequent homolytic cleavage of the B–B bond results in boryl radical adduct **2a''** (Figure 2A).<sup>[9,10]</sup> An outer sphere single-electron transfer **2a''** to phosphonium salt **1** would form phosphonium radical anion **1a''** and **2a**. However, the process is endergonic by ca. 30 kcal/mol and, therefore, thermodynamically unfavorable. Alternatively, an inner sphere transfer via bridged boronate complex **Int-1** is feasible; the overall process is endergonic (ca. 10 kcal/mol) due to the entropic cost of forming **Int-1**, but subsequent electron transfer is spontaneous. The cyanopyridine can then disengage from the boron center and release boryl pyridyl radical **1a'''** where most of the spin density is located at the 2- and 4-positions. Second, to determine the pathway for C–C bond-formation, we modeled several combinations of **1a'''** with **2a** and **2a'** via one and two electron processes, but none of these pathways were energetically feasible (See SI for details). Instead, the most favorable pathway is a radical-radical coupling of **1a'''** and boryl cyanopyridine radical **2a''** to form adduct **11** (Figure 2B). The process is rendered feasible by losing  $\text{PPh}_3$ , and deborylation likely occurs using  $\text{NEt}_3$  to form dearomatized intermediate **12**. Forming the bipyridine product **4** requires a final oxidation; part of the reaction protocol involves opening the vessel to air, and we often observe a color change to the solution. We could identify dearomatized intermediate **12a** by  $^1\text{H}$  NMR and LCMS, while exposing the reaction to air results in conversion to bipyridine **4a** (Figure 1C). Further details

of the reaction mechanism are described in the Supporting Information.

In conclusion, we report a pyridine-pyridine cross-coupling reaction unique to heterocyclic phosphonium salts. Mechanistic investigations point to a radical-radical coupling reaction rather than a Minisci-type radical pathway. Further study of the structure and properties of pyridyl phosphonium radical anion derivatives are ongoing in our laboratory.

## Acknowledgements

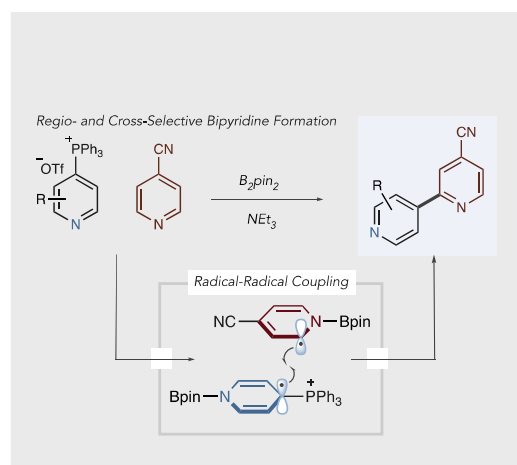
This work was supported from startup funds from Colorado State University and partial support from the National Science Foundation under Grant No. 1753087. We would like to acknowledge Romea Castillo from the Shores laboratory for his valuable assistance running CV experiments.

**Keywords:** Bipyridines • radical anions • phosphonium salts • radical ylides • pyridine • Minisci

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- [14] UV-Vis spectra did not indicate the formation of a discrete charge-transfer complex (see Supporting Information for details).

## COMMUNICATION



pathway.

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s and B2pin2 to form 2,4-bipyridines with complete regiocontrol. Mechanistic between two boryl-stabilized pyridyl radical anions rather than a Minisci-type