

**DEAMINATIVE VINYLATION AND
ARYLATION CROSS-COUPPLING REACTIONS**

by

Diana Lucas Baca

A thesis submitted to the Faculty of the University of Delaware in partial fulfillment of the requirements for the degree of Master of Science in Chemistry and Biochemistry

Fall 2022

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ARYLATION CROSS-COUPPLING REACTIONS**

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ACKNOWLEDGMENTS

I am eternally thankful for the many friendships and support I received while at the University of Delaware. I am especially grateful for my advisor, Mary P. Watson. She has given me unwavering support throughout my years in her research group, and our group members. She never stops fighting for you, she has always believed in me even when I did not at times. Thank you, Mary, for allowing me to express myself and grow into the scientist I am today.

Graduate school is more difficult without an amazing support group. I feel very lucky to have found friends who want to see me succeed. I could not have made it this far without you all. Thank you, Liz, Nam, Bria, and Micah.

My family and partner, thank you for listening to my frustrations and triumphs. Thank you for the pep talks, advice and laughter. I am where I am because of you.

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ABSTRACT

This thesis focuses on nickel-catalyzed vinylation and arylation cross-coupling reactions via C-N bond activation. Chapter 1 describes a vinylation method that was inspired by an analogous alkylation. This method takes advantage of mild reaction conditions and commercially available alkene and alkyne starting materials. This reaction proceeds through a regioselective hydroboration step to form an organoboron intermediate that then participates in the cross-coupling reaction. Excitingly, this reaction has a high functional group tolerance. Regarding the vinylated products, this reaction can install both non-styrenyl groups and tolerates alkyl and benzylic pyridinium salts overcoming limitations of prior methods. We propose this reaction to proceed through a Ni(I)/Ni(III) catalytic cycle based on radical clock and ring-opening experiments. This work was published in *Organic Letters*.

Chapter 2 describes the development of a deaminative reductive cross-coupling reaction using aryl chlorides and alkyl pyridinium salts. This method aims to utilize the more abundant and challenging aryl chlorides in an efficient cross-coupling reaction with unactivated alkyl pyridinium salts. Utilizing High-Throughput Experimentation (HTE), we found 4,4'-di-*tert*-butyl-2,2'-bipyridine ligand to give a decent yield with a nickel (II) chloride hexahydrate catalyst with sodium chloride as the additive. Further examination of the catalyst system is needed to produce efficient yields with a range of aryl chlorides.

Chapter 1

SUZUKI-MIYAURA VINYLATION OF ALKYL PYRIDINIUM SALTS USING ALKYNES

Work described here has been published (Baker, K.; Lucas Baca, D.; Plunkett, S.; Daneker, M. E.; Watson, M. P. *Org. Lett.*, **2019**, 21, 9738 – 9741). Copyright © (2019) American Chemical Society.

1.1 Introduction

The construction of carbon-carbon bonds has been a powerful synthetic tool for the development of organic compounds and elaborate molecular frameworks. The construction of C(sp³)-C(sp³) and C(sp³)-C(sp²) are of great interest in organic synthesis. Development of methods for these bond formations gives access to interesting and exciting bond disconnections that would otherwise be more challenging.¹ Particularly, methods for alkyl-alkyl bond formations are limited due to the more difficult oxidative addition step of the alkyl electrophile, competitive β-hydride elimination, and hydrodehalogenation, which lead to unwanted byproducts.² Efforts in overcoming these challenges explore the use of organometallic reagents in transition metal-catalyzed cross-coupling reactions.^{3,4}

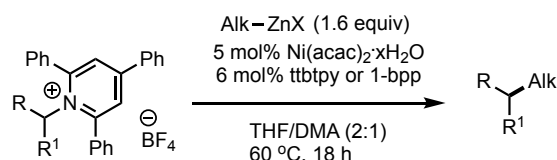
Since Suzuki and co-workers' first alkyl-alkyl cross coupling reaction⁵ significant work has been done by Fu and co-workers to improve the reaction.^{6,7} However they are still limited to alkyl halides as the electrophilic partner, which are not as prevalent as alkyl amines. Our group showed the first alkyl-alkyl cross-coupling

of unactivated alkyl pyridinium salts using a Negishi-type alkylation method (Scheme 1-1A).⁸ This method was able to include primary and secondary alkyl pyridinium salts with a variety of alkyl zinc halides. Despite the impressive scope of the reaction and its selectivity, benzylic and base-sensitive groups were not tolerated due to the harsh alkyl zinc reagents.

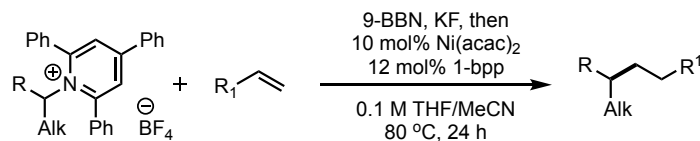
Considering these limitations, my colleague Dr. Kristen Baker was able to develop a Suzuki-Miyaura-type alkylation of alkyl pyridinium salts with organoboron reagents (Scheme 1-1B).⁹ These organoboron compounds can be easily prepared *in situ* from simple alkenes. In addition, boron byproducts have low toxicity and can be easily removed from the reaction mixtures.^{10,11} Dr. Kristen Baker envisioned using alkylboranes, generated by a hydroboration of alkenes using 9-borabicyclo[3.3.1]nonane dimer (9-BBN). This method was successful with primary and secondary alkyl pyridinium salts, and benzylic pyridinium salts which were a prior limitation with the Negishi-type alkylation method. Additionally, this reaction showed tolerance of a variety of base-sensitive functional groups that were previously a limitation in the Negishi coupling method.

Scheme 1-1. Alky-Alkyl Cross-Couplings

A. Negishi-type Alkylation of alkyl pyridinium salts



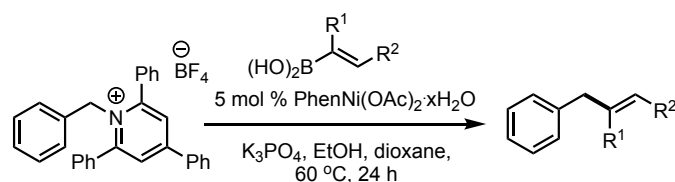
B. Suzuki-Miyaura-type of alkyl pyridinium salts



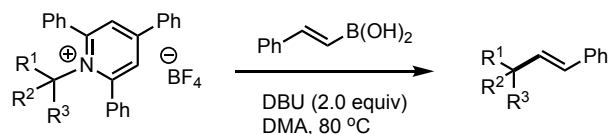
In 2018, our group reported a vinylation of benzylic pyridinium salts with boronic acids in the presence of a nickel catalyst (Scheme 1-2A).¹² The reaction scope showed a broad functional group tolerance with either an alkyl boronic acid or boronic ester as a coupling partner. Despite these exciting results, this reaction is limited to benzylic pyridinium salts. The Loh group has also reported a transitional-metal free vinylation reaction of alkyl pyridinium salts and vinyl boronic acids in the presence of a base.¹³ Their reaction allowed a wide range of primary alkyl amines. However, the reaction is limited to the use of phenylvinyl boronic acid derivatives (Scheme 1-2B).

Scheme 1-2. Vinylation Cross-Couplings

A. Watson's vinylation of benzylic pyridinium salts



B. Loh's metal-free vinylation of alkyl pyridinium salts



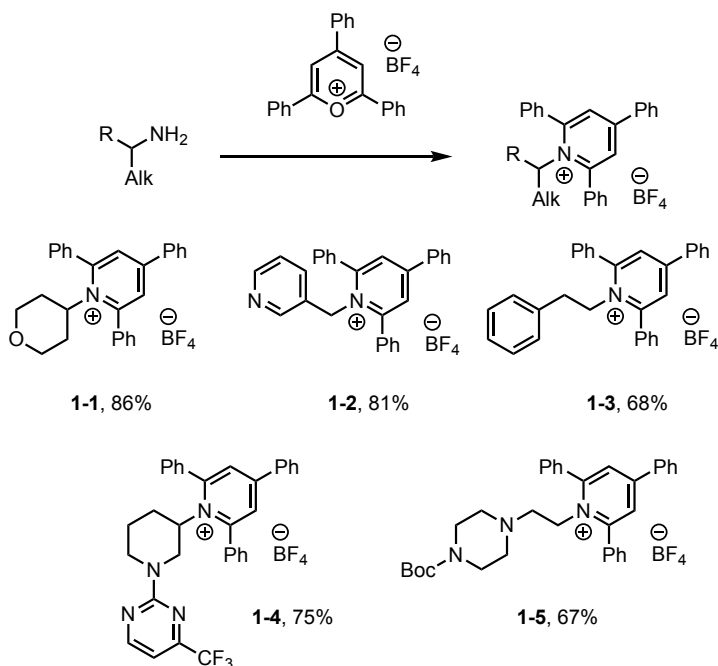
1.2 Results and Discussion

Synthesis of Katritzky alkyl pyridinium salts

When I first joined the group, I began with the synthesis Katritzky pyridinium salts from alkyl amines (Scheme 1-3). Unactivated primary and secondary amines can be converted through treatment of commercially available 2,4,6-triphenylpyrylium tetrafluoroborate to form Katritzky pyridinium salts in one step.¹⁴ I was able to obtain

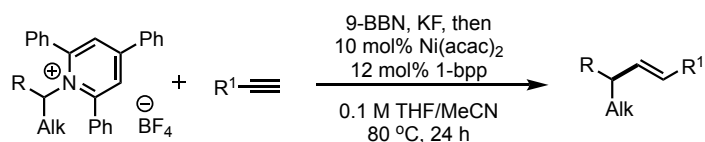
pyridinium salts through suction filtration, no further chromatography isolation needed. Katritzky pyridinium salts are solid, and benchtop stable.

Scheme 1-3. Synthesis of Katritzky Pyridinium Salts



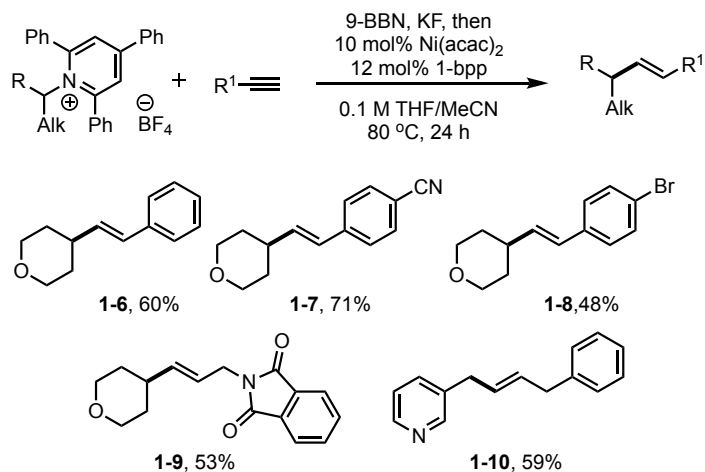
Following on the reaction conditions developed by Dr. Kristen Baker for a deaminative Suzuki-Miyaura alkylation of alkyllpyridinium salts with alkyllboranes (see Scheme 1-1B, above), I demonstrated that these conditions could also be used for vinylation by generating vinylboranes *in situ* from commercially available alkynes (Scheme 1-4).

Scheme 1-4. Suzuki-Miyaura-type Vinylation Using Alkynes



I began my studies with phenylacetylene as the alkyne, to be coupled with a pyran pyridinium salt to form product **1-6** (Scheme 1-5). In my first attempt of this reaction on a 1.0 mmol scale, the yield of my desired product was low compared to the yield in a 0.1 mmol scale. During the initial optimization of the alkylation cross coupling reaction, Dr. Baker observed an extreme sensitivity with the base. Spray-dried potassium fluoride was required to forming the reactive alkyl boronate species *in situ*; otherwise, she observed little to no yield. In the alkylation reaction, the hydroboration/boronate formation step runs for 30 minutes. I hypothesized the low yield could be due to the incomplete hydroboration of the alkyne or the insufficient formation of the boronate species. I decided to run the hydroboration/boronate formation step for 1 hour. The increased time produced the desired product in 60% yield determined by ¹H NMR spectroscopy using an internal standard. Additionally, product **1-7** was formed in an exceptionally low yield of 24% at 1.0 mmol scale. I began investigating the work-up, which utilizes hydrogen peroxide to oxidize unreacted organoboron species suspecting that this work-up was not compatible with the nitrile group. In the absence of hydrogen peroxide, I was able to obtain 71% isolated yield of product **1-7**, consistent with the yield determined by ¹H NMR spectroscopy.

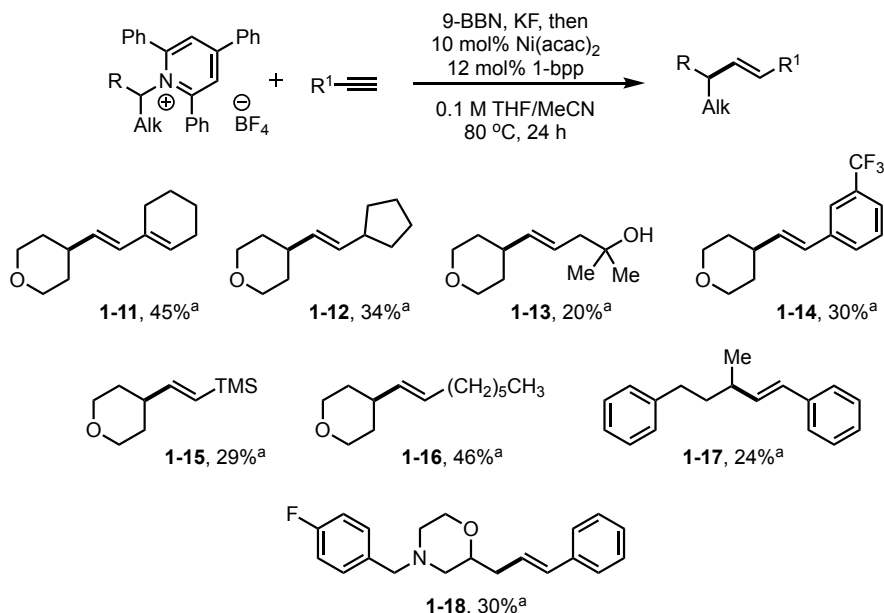
Scheme 1-5. Vinylation Scope



I continued to move forward by investigating the scope of the vinylation by looking at phenylacetylene derivatives. Isolated yields are reported in Scheme 1-5. *Para*-electron-withdrawing substituents such as bromide (**1-8**) and nitrile (**1-7**) groups, resulted in moderate to good yields (Scheme 1-5), whereas *meta*-substituents did not (**1-14**, Scheme 1-6). Furthermore, the reaction was tolerant of phthalimides (**1-9**) and non-styrenyl vinyl (**1-10**) groups as well as benzylic pyridinium salts (**1-10**).

However, broad scope in aliphatic alkynes was not observed, with products **1-11**, **1-16** and **1-18** observed only in low yields (Scheme 1-6). This limitation can be due to the decreased rate of hydroboration compared to aryl alkynes.¹⁰ In addition, vinylation of an acyclic secondary pyridinium salt only proceeded in low yield (**1-17**).

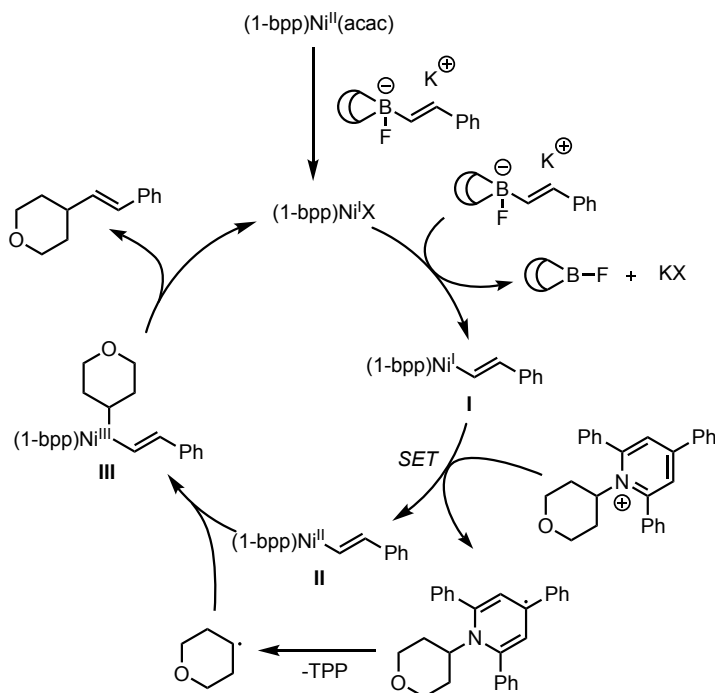
Scheme 1-6. Vinylation Scope Limitations



^aScale: 0.1 mmol alkyl pyridinium salt. Yields determined by H¹ NMR using 1,3,5-trimethoxybenzene.

I propose the vinylation reaction follows a similar mechanism as the alkylation reaction. Displacement of the acetylacetonate ligands with two consecutive transmetallation events with alkyl-(9-BBN) species gives a dialkyl Ni(II) species that can undergo reductive elimination to give Ni(0). The Ni(I) active catalyst is then formed through comproportionation of Ni(II) and Ni(0) complexes.⁴ After transmetallation to form vinyl nickel species **I**, the reaction proceeds through a single electron transfer (SET) event from Ni(I) to the pyridinium salt, **II** which then fragments into the alkyl radical, which recombines with the Ni(II) intermediate **II** to form Ni(III) species **III**. Reductive elimination forms the desired product and closes the catalytic cycle. A TEMPO radical trap and ring opening experiment supports the formation of the alkyl radical, as observed by Mitchell Daneker, and is consistent with our previous work.^{8,9,12,15-17}

Scheme 1-7. Proposed Mechanism



1.3 Conclusion

I have successfully developed a Suzuki-Miyaura-type vinylation using alkylpyridinium salts and easily accessible vinyl organoboron compounds. I was able to expand upon the reaction conditions found by my colleague, Dr. Kristen Baker, for alkylation to include vinyl(9-BBN) compounds and investigate the scope of the reaction. I determined that the hydroboration/boronate formation of alkynes requires a longer time compared to the hydroboration time of alkenes to increase the yields of the vinylation products. This work was published in 2019 in *Organic Letters*.⁹

1.4 Experimental

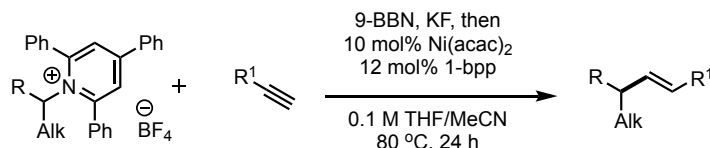
1.4.1 General Information

Reactions were performed in oven-dried Schlenk flasks or in oven-dried, round-bottomed flasks unless otherwise noted. Round-bottomed flasks were fitted

with rubber septa, and reactions were conducted under an atmosphere of N₂. Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed on silica gel 60 (40-63 μm, 60Å) unless otherwise noted. Commercial reagents, including 2,4,6-triphenylpyrylium tetrafluoroborate, were purchased from Sigma Aldrich, Acros, AstaTech, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, AK Scientific, Bide Pharmatech, Oakwood, or Cambridge Isotopes Laboratories and used as received with the following exceptions: MeCN and CH₂Cl₂ were dried by passing through drying columns.¹ MeCN was then degassed by sparging with N₂. Oven-dried potassium carbonate was added to CDCl₃ to remove trace acid. Potassium fluoride for small scale cross-couplings was dried in the oven overnight, passed through a sieve to ensure uniformity throughout the powder, and then stored in a desiccator. 4Å Molecular sieves were purchased and heated at 200 °C under vacuum, then crushed and stored in a desiccator. Proton nuclear magnetic resonance (¹H NMR) spectra, carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on both 400 MHz and 600 MHz spectrometers. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent (CHCl₃ = δ 7.26). Chemical shifts for carbon are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃ = δ 77.16). Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, dd = doublet of doublets, ddd = doublet of doublets of doublets, dt = doublet of triplets), coupling constants in Hertz (Hz), integration. Infrared (IR) spectra were obtained using FTIR spectrophotometers with material loaded onto a KBr plate. The mass spectral data

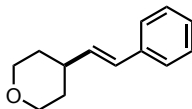
were obtained at the University of Delaware mass spectrometry facility. Melting points were taken on a Thomas-Hoover Uni-Melt Capillary Melting Point Apparatus.

1.4.2 General Procedure: Nickel-Catalyzed Vinylation of Organoboranes with unactivated alkyl Katritzky salts

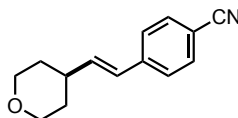


An oven-dried, 25-mL Schlenk flask equipped with a mechanical stirbar was charged with KF (160 mg, 2.75 mmol, 2.75 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and evacuated and backfilled with nitrogen five times. 9-BBN (0.5 M solution in THF, 2.5 mmol, 2.5 equiv, 0.50 mL) and alkyne (2.5 mmol, 2.5 equiv) were added via syringe. The mixture was stirred and heated at 80 °C for 30 min. A second oven-dried, 10-mL Schlenk flask equipped with a mechanical stirbar was charged with Ni(acac)₂ (2.5 mg, 0.10 mmol, 0.10 equiv), 1-bpp (2.6 mg, 0.12 mmol, 0.12 equiv), and pyridinium salt (1.0 mmol, 1.0 equiv). The flask was fitted with a rubber septum and evacuated and backfilled with nitrogen five times. Acetonitrile (5 mL) was added, and the mixture was stirred for 1 hour at room temperature. The catalyst solution was then transferred to the 25-mL Schlenk flask via syringe, and the mixture was stirred at 80 °C for 24 h. The mixture was allowed to cool to room temperature. For nonpolar products that might co-elute with organoborane species, H₂O₂ (0.4 mL) was added, and the mixture was vigorously stirred for 5 min to oxidize the boron species. For nitrile containing products, this oxidation step was skipped. The aqueous layer was washed with EtOAc (3 x 20 mL),

dried (MgSO₄), filtered through a short pad of silica gel, and concentrated. The cross-coupled product was then purified via silica gel chromatography.

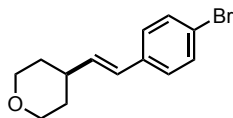


(E)-4-styryltetrahydro-2H-pyran (1-6). Prepared via Vinylation General Procedure using pyridinium salt a. During work-up, the oxidation step with H₂O₂ was used. The crude mixture was purified by silica gel chromatography (10% Et₂O/hexanes) to give 27 (run 1:113 mg, 60%, run 2:118 mg, 63%) as a light yellow oil: ¹H NMR (400 MHz, Chloroform-*d*) δ 7.36 (d, *J* = 7.2 Hz, 3H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.21 (t, *J* = 7.2 Hz, 1H), 6.39 (d, *J* = 16.0 Hz, 1H), 6.16 (dd, *J* = 16.0, 6.8 Hz, 1H), 4.01 (ddd, *J* = 11.3, 4.8, 1.8 Hz, 2H), 3.47 (td, *J* = 11.6, 2.2 Hz, 2H), 2.38 (ddd, *J* = 11.2, 8.9, 5.0 Hz, 1H), 1.74 – 1.67 (m, 2H), 1.63 – 1.51 (m, 2H). ¹³C NMR (101 MHz, Chloroform-*d*) δ 137.64, 134.73, 128.67, 128.37, 127.23, 126.15, 67.89, 38.53, 32.76.

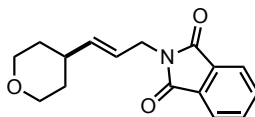


(E)-4-(2-(tetrahydro-2H-pyran-4-yl)vinyl)benzonitrile (1-7). Prepared via Vinylation General Procedure using pyridinium salt a. During work-up, the oxidation step with H₂O₂ was not used. The crude mixture was purified by silica gel chromatography (10% → 15% Et₂O/hexanes) to give 30 (164 mg, 71%) as a light yellow oil: ¹H NMR (400 MHz, Chloroform-*d*) δ 7.66 – 7.54 (m, 2H), 7.49 – 7.37 (m, 2H), 6.39 (d, *J* = 16.1 Hz, 1H), 6.30 (dd, *J* = 16.0, 6.5 Hz, 1H), 4.02 (ddd, *J* = 11.6, 4.5, 1.9 Hz, 2H), 3.47 (td, *J* = 11.7, 2.2 Hz, 2H), 2.42 (dtt, *J* = 10.8, 7.0, 3.7 Hz, 1H), 1.71 (ddd, *J* = 13.2, 4.1, 2.1 Hz, 2H), 1.57 (dtd, *J* = 13.5,

11.6, 4.4 Hz, 3H); ^{13}C NMR (101 MHz, Chloroform-*d*) δ 142.18, 138.80, 132.52, 127.11, 126.67, 119.23, 110.41, 67.73, 38.64, 32.41; FTIR (neat) 2871, 2361, 667 $^{-1}$; HRMS (ESI $^{+}$) $[\text{M}+\text{H}]^{+}$ calculated for $\text{C}_{14}\text{H}_{16}\text{NO}$: 214.1232, found 214.1222.

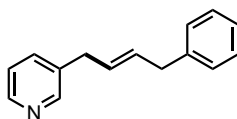


(E)-4-(4-bromostyryl)tetrahydro-2H-pyran (1-8). Prepared via Vinylation General Procedure using pyridinium salt a. During work-up, the oxidation step with H_2O_2 was used. The crude mixture was purified by silica gel chromatography (5% \rightarrow 10% Et_2O /hexanes) to give 28 (127 mg, 48%) as a yellow solid (mp 56-63 $^{\circ}\text{C}$): ^1H NMR (600 MHz, Chloroform-*d*) δ 7.45 – 7.38 (m, 2H), 7.24 – 7.19 (m, 2H), 6.35 – 6.29 (m, 1H), 6.15 (dd, $J = 16.0, 6.8$ Hz, 1H), 4.01 (ddd, $J = 11.7, 4.6, 1.9$ Hz, 2H), 3.46 (td, $J = 11.8, 2.2$ Hz, 2H), 2.37 (ddt, $J = 10.9, 6.9, 3.3$ Hz, 1H), 1.72 – 1.64 (m, 2H), 1.61 – 1.53 (m, 3H); ^{13}C NMR (151 MHz, Chloroform-*d*) δ 136.7, 135.6, 131.75, 127.8, 127.4, 120.9, 67.8, 38.5, 32.7.



(E)-2-(3-(tetrahydro-2H-pyran-4-yl)allyl)isoindoline-1,3-dione (1-9). Prepared via Vinylation General Procedure using pyridinium salt a. During work-up, the oxidation step with H_2O_2 was used. The crude mixture was purified by silica gel chromatography (10% Et_2O /hexanes) to give 29 (106 mg, 53%) as a light yellow solid (mp: 60-65 $^{\circ}\text{C}$): ^1H NMR (600 MHz, Chloroform-*d*) δ 7.85 (dt, $J = 6.4, 3.2$ Hz, 2H), 7.75 – 7.67 (m, 2H), 5.70 (ddt, $J = 15.5, 6.3, 1.4$ Hz, 1H), 5.51 (dtd, $J = 15.4, 6.2, 1.4$ Hz, 1H), 4.25 (dt, $J = 6.2, 1.1$ Hz, 2H), 3.93 (ddd, $J = 11.8, 4.5, 2.0$ Hz, 2H), 3.37 (td, $J = 11.7, 2.2$ Hz, 2H), 2.23 – 2.13 (m, 1H), 1.59

(ddd, $J = 13.3, 4.1, 2.0$ Hz, 2H), 1.43 (dtd, $J = 13.4, 11.6, 4.4$ Hz, 2H).; ^{13}C NMR (151 MHz, Chloroform- d) δ 168.1, 138.9, 134.1, 132.3, 123.4, 121.9, 67.8, 39.7, 37.6, 32.4. FTIR (neat) 2929, 2842, 1771, 1713, 1393, 720 cm^{-1} ; HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{18}\text{NO}_3$: 272.1287, found 272.1275.



(E)-3-(4-phenylbut-2-en-1-yl)pyridine (1-10). Prepared via Vinylation General Procedure using pyridinium salt b. During work-up, the oxidation step with H_2O_2 was used. The crude mixture was purified by silica gel chromatography (5% \rightarrow 10% Et $_2$ O/hexanes) to give 28 (127 mg, 48%) as a yellow solid (mp 56-63 $^\circ\text{C}$): ^1H NMR (600 MHz, Chloroform- d) δ 7.45 – 7.38 (m, 2H), 7.24 – 7.19 (m, 2H), 6.35 – 6.29 (m, 1H), 6.15 (dd, $J = 16.0, 6.8$ Hz, 1H), 4.01 (ddd, $J = 11.7, 4.6, 1.9$ Hz, 2H), 3.46 (td, $J = 11.8, 2.2$ Hz, 2H), 2.37 (ddt, $J = 10.9, 6.9, 3.3$ Hz, 1H), 1.72 – 1.64 (m, 2H), 1.61 – 1.53 (m, 3H); ^{13}C NMR (151 MHz, Chloroform- d) δ 136.7, 135.6, 131.75, 127.8, 127.4, 120.9, 67.8, 38.5, 32.7.

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Chapter 2

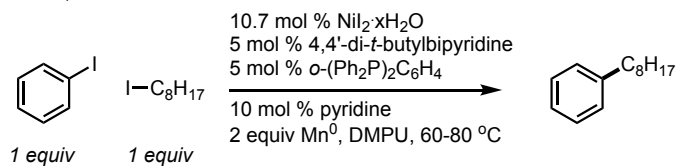
DEAMINATIVE REDUCTIVE CROSS-ELECTROPHILE COUPLING OF ALKYLPYRIDINIUM SALTS AND ARYL CHLORIDES

2.1 Introduction

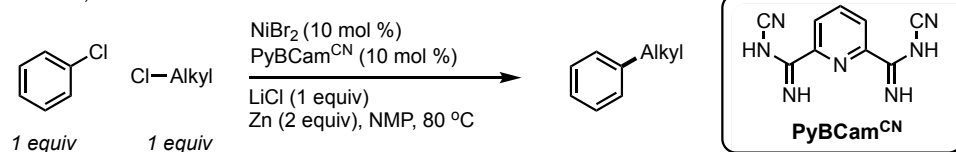
Reductive cross-coupling offers the formation of carbon–carbon bonds using two electrophilic reagents, generally organic halides, which are more commercially abundant, more stable, and easier to handle compared to organometallic reagents.^{1,2} The joining of two readily available electrophiles eliminates the use of stoichiometric strong bases or nucleophiles, which allows for a greater tolerance of functional groups such as electrophilic and base-sensitive groups.¹ The challenge of this reaction is primarily due to the similar chemical reactivity of the substrates, which has been seen to result in low selectivity of the cross-coupled product while forming undesired dimer byproducts.³ Strategies to suppress unwanted homocoupling side reactions have been explored such as (1) adding excess of one coupling partner,^{1,4-6} (2) electronic differentiation of the substrates,^{7,8} (3) utilizing a sterically encumbered catalyst to differentiate the substrates,^{9,10} and (4) radical-chain processes.^{2,11}

Scheme 2-1. Reductive Cross-Electrophile Couplings

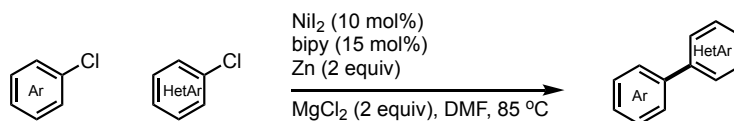
A. Weix, 2010



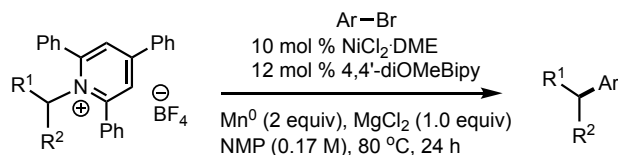
B. Weix, 2020



C. Lautens, 2021



D. Watson, 2019

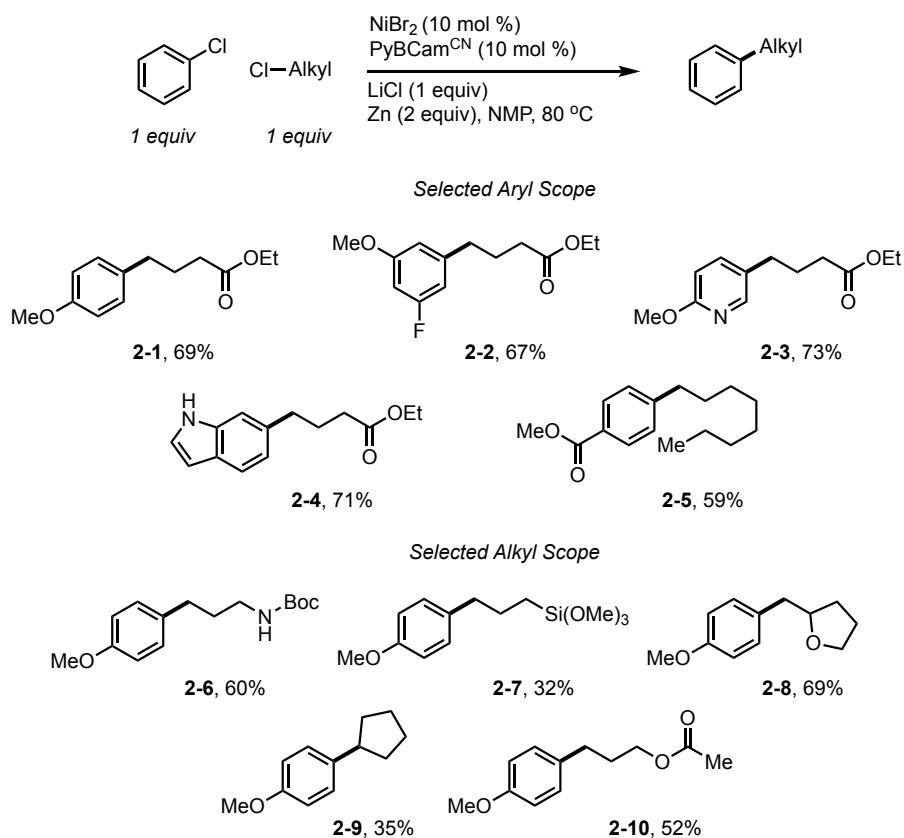


In 2010, the Weix group reported a method for C(sp³)-C(sp²) bond formation that proceeds through a dual-ligand nickel catalyst system and requires only one equivalent of each coupling partner (Scheme 2-1A).¹² This method showed high selectivity for the coupling product while using equimolar amounts of the substrates. Mechanistic studies later revealed that the aryl iodide is selective towards oxidative addition with the nickel(0) species, the while alkyl iodide is proposed to generate an alkyl radical through two self-initiating mechanisms: (1) alkyl iodide undergoes single-electron transfer (SET) with a nickel(I) species to generate a nickel(II) diiodide species and alkyl radical that would then participate in radical recombination with

arylnickel(II) species; (2) alkyl iodide can undergo halogen atom abstraction by arylnickel(II) species, which then reacts with the arylnickel(II) intermediate.^{2,13} Furthermore, the use of a neutral bidentate ligand such as bipyridine is observed to give an efficient nickel catalyst system for reductive cross coupling methods.^{3,12} This work was primarily limited to aryl iodides and bromides with alkyl iodide substrates.

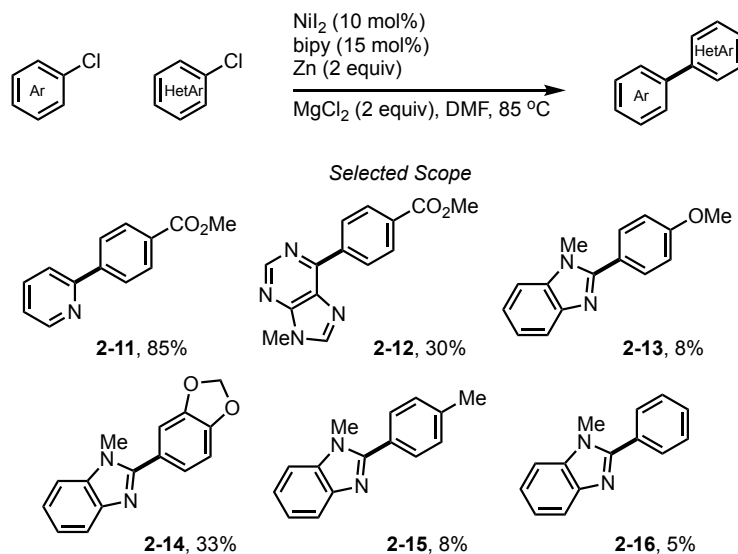
More recently, the Weix group demonstrated a reductive cross-selective coupling of aryl chlorides and primary alkyl chlorides (Scheme 2-1B).¹⁴ This method overcomes the challenge of selectivity between substrates while suppressing dimerization of either substrate through a tridentate nickel catalyst (PyCam^{CN}) and salt additives. They found a strong correlation between productive reaction and the nickel counter-anion being bromide or iodide, proposing that the alkyl chloride is undergoing halogen exchange to form alkyl bromide/iodide. These conditions allowed for a wide scope of both aryl chlorides and alkyl chlorides. (Scheme 2-2). Despite these impressive findings, this method requires this unique catalyst system and is limited to moderate yields for electron-rich aryl chlorides and low yields for secondary alkyl chlorides.

Scheme 2-2. Weix's Nickel-Catalyzed Coupling of Aryl Chlorides with Alkyl Chlorides: Substrate Scope



Similarly, Lautens and co-workers have developed a reductive cross-coupling of heteroaryl chlorides and aryl chlorides (Scheme 2-1C).¹⁵ The challenging selectivity between two C(sp²) electrophiles was overcome by the employment of a nickel catalyst in the presence of iodide ions and magnesium chloride. The magnesium salt is suggested to facilitate the reduction of the nickel catalyst, and the role of iodide ions is unclear. This method was tolerant of various heteroaryl chlorides, including 2-chloropyridines but was limited to electron-poor aryl chlorides. Electron-rich aryl chlorides resulted in low yields due to the more difficult oxidative addition step (Scheme 2-3).

Scheme 2-3. Nickel-Catalyzed Coupling of Heteroaryl Chlorides and Aryl Chlorides



Although alkyl halides are most often used in these reductive cross-couplings, the M. Watson group identified alkyl amine derivatives as a useful, complementary class of starting materials. As described in Chapter 1, the advantage of alkyl amines is their wide abundance in commercially available molecules, as well as advanced drug-like compounds. Specifically, the Watson group demonstrated a deaminative reductive cross-coupling of alkylpyridinium salts and aryl bromides (Scheme 2-1D).^{6,10,16-19} This method introduces alkyl pyridinium salts as efficient coupling partners in reductive conditions. Although high functional group tolerance was demonstrated in the scope and this method allows the use of alkyl amine derivatives as substrates, it is limited to the use of aryl bromides.¹⁶ I sought to overcome this limitation by identifying conditions that would allow aryl chlorides to be used.

Although aryl chlorides present the lowest reactivity for oxidative addition due to the strong carbon-chlorine bond (C-Cl BDE: ~80 kcal/mol vs C-Br BDE: ~67 kcal/mol),²⁰ aryl chlorides comprise a larger pool of commercially available

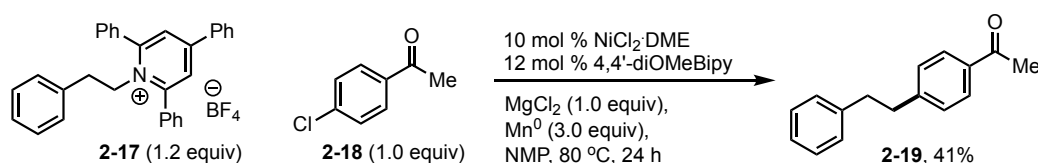
compounds for coupling reactions; they are more abundant and stable than aryl bromides (>1,300,000 aryl chlorides vs <600,000 aryl bromides)²¹ and boronic acids (<100,000 boronic acids).¹⁴ Efforts to utilize aryl chlorides in reductive cross coupling reactions have been made by Weix^{1,14,22} and others^{5,7,23–26} with the most recent method developed by Lautens and co-workers.¹⁵ Although these methods show promising results, yields remain low compared to reductive couplings of bromoarenes, and no examples exist for coupling aryl chlorides with alkyl pyridinium salts.

Herein are my efforts in the optimization of a deaminative reductive cross-coupling reaction of aryl chlorides with unactivated alkylpyridinium salts. Due to the challenging oxidation step of the aryl chloride bond, I hypothesized that using a bidentate electron-rich ligand will help achieve this step as well as promote a single electron transfer (SET) for the activation of the pyridinium salt.

2.2 Results and Discussion

I began the optimization from the initial results that my colleagues Mike Talley and Megan Hoerrner found with primary alkyl Katritzky pyridinium salt **2-17** and aryl chloride **2-18** as the coupling partners (Scheme 2-4). Based on previous studies,³³ I expected primary alkyl pyridinium salts to require different conditions than secondary pyridinium salts. For this reason, they are optimized separately. I focused of my efforts on primary alkyl Katritzky pyridinium salts.

Scheme 2-4. Reductive Cross-Coupling Preliminary Results

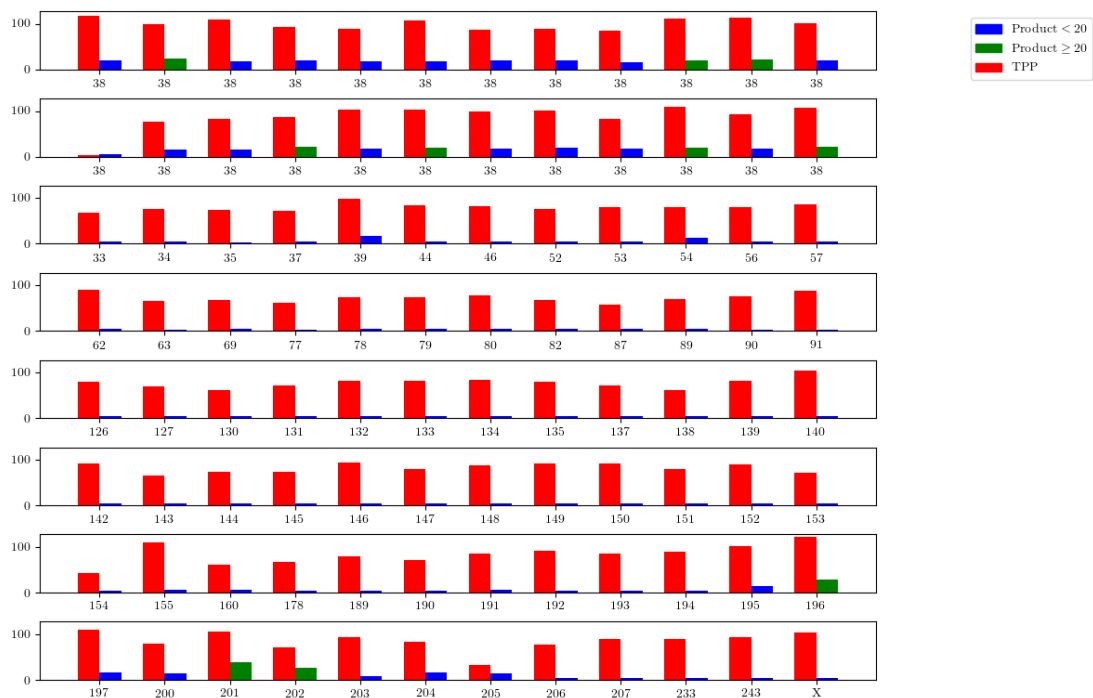
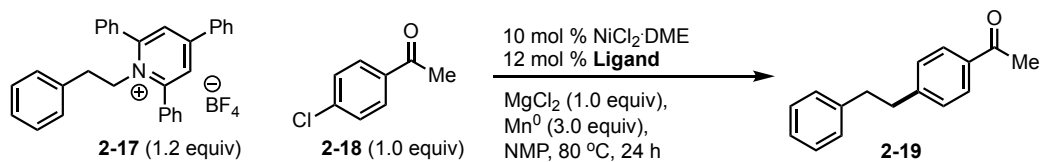


Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

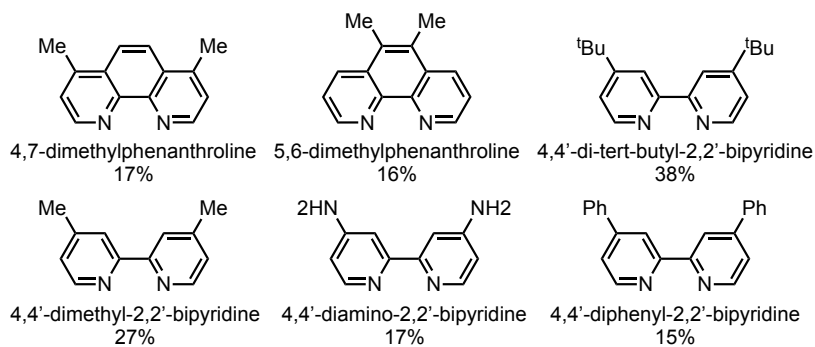
My initial studies focused on investigating ligands, nickel sources, and additives in the cross-coupling reaction of primary alkyl pyridinium salt **2-17** using High-Throughput Experimentation (HTE) techniques (scale: 8.3 μmol of pyridinium salt **2-17**). The first parameter I chose to investigate was ligand due to the large ligand effect seen with previous pyridinium salt cross-couplings. I chose 72 ligands and expected 2,2'-bipyridine and phenanthroline ligands to provide the best yield, because they are efficient in single electron transfer (SET) events and are observed to give the most efficient catalyst system for reductive cross couplings.¹⁹ As expected, the highest yielding ligands from this experiment were electron-rich phenanthroline and 2,2'-bipyridine ligands (Scheme 2-5B).

Scheme 2-5. Highest Yielding Ligands from HTE Ligand Screen

A. Initial HTE 72 Ligand Screen in NMP



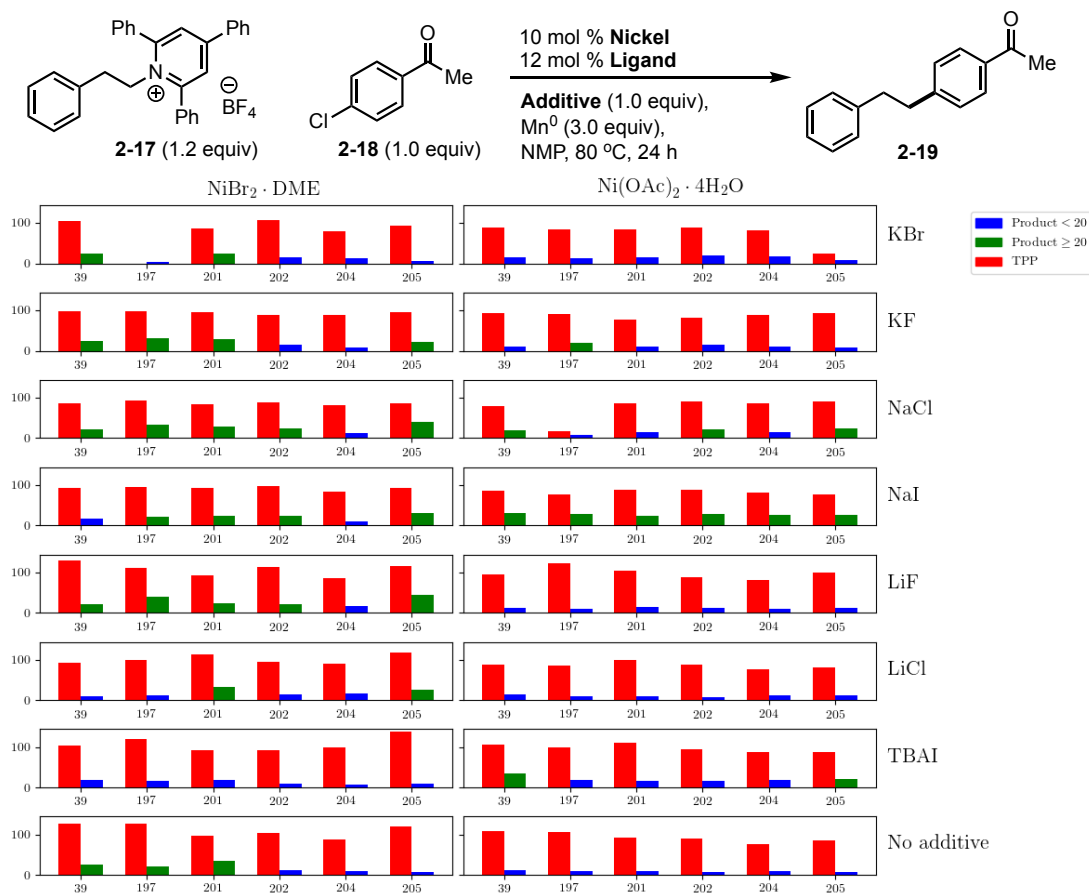
B. Best ligands from initial 72 ligand screen in NMP with NiCl₂·DME.



Yields as determined by LC/MS.

The second parameter I chose to investigate using HTE was additives and two nickel sources along with the ligands in Scheme 2-5B, see Scheme 2-6. In this study, I observed an increase in reactivity with different salt additives with NiBr₂·DME as the nickel catalyst.

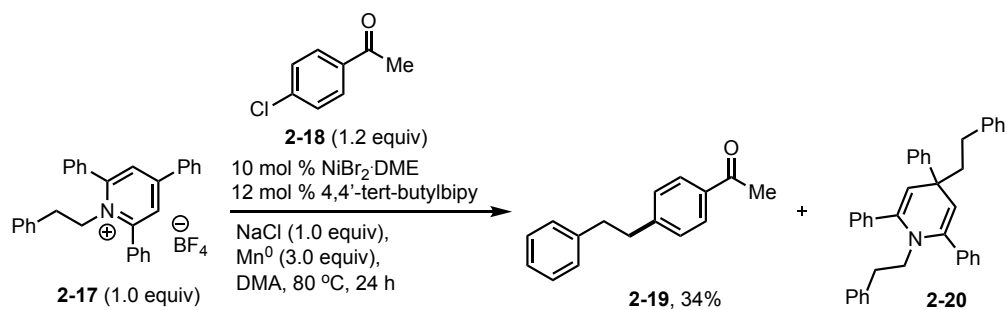
Scheme 2-6. HTE Nickel Source and Salt Additive Screen



From these experiments, 4,4'-di-*tert*-butyl-2,2'-bipyridine (4,4'-di^tBuBpy) as ligand with sodium chloride as additive in NMP produced the highest yielding reaction (38% LC/MS yield). I scaled the reaction to 0.1 mmol scale, which resulted in a drop in yield, and saw a large amount of dihydropyridine byproduct **2-20**, which

presumably formed via excess alkyl radical reacting with an equivalent of **2-17**, followed by another one-electron reduction (Scheme 2-7).

Scheme 2-7. HTE Reaction Conditions at 0.1 mmol Scale

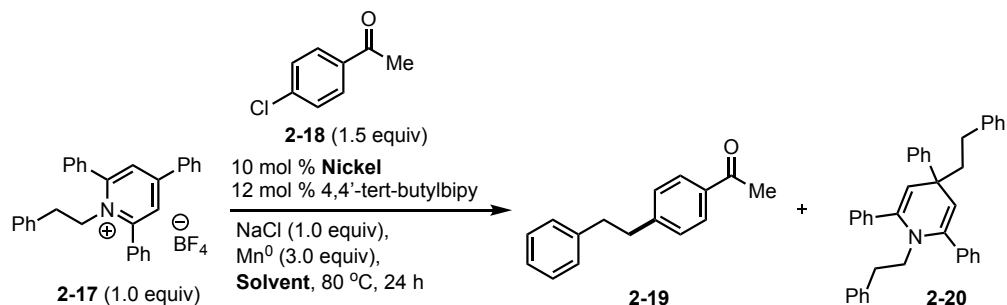


Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

To solve this, I reduced the equivalents of pyridinium salt **2-17** and increased aryl chloride **2-18** to 1.0 equivalents and 1.5 equivalents, respectively. Because the reductant is also able to reduce the pyridinium salt, I decreased the equivalents of manganese(0) to 2.0 equivalents. These changes resulted in an increase in yield (54% yield as determined by ¹H NMR spectroscopy).

To further examine the reaction, I decided to investigate the effect of solvent as well as nickel sources (Table 2-1). I found that dimethylacetamide (DMA) produced higher yield and a reasonable mass balance with low yield of undesired dihydropyridine byproduct **2-20**.

Table 2-1. Investigation of Solvent and Nickel Sources



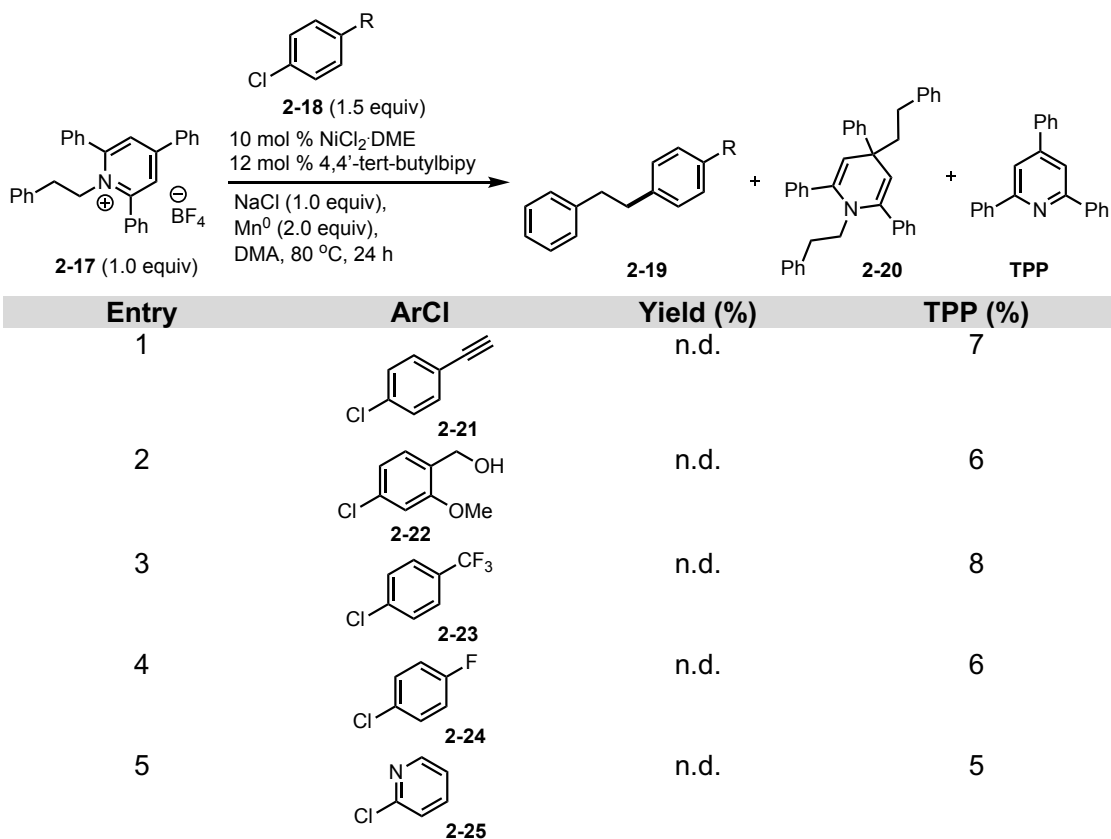
Entry	Nickel Source	Solvent	Yield (%)	TPP (%)	2-21 (%)
1	NiCl ₂ ·DME	NMP	47	65	5
2	NiCl ₂ ·DME	DMA	64	74	4
3	NiCl ₂ ·DME	MeCN	-	72	-
4	NiCl ₂ ·DME	DMF	56	69	6
5	NiCl ₂ ·DME	DMSO	19	45	10
6	NiCl ₂ ·DME	Dioxane	3	42	-
7	NiBr ₂ ·DME	DMA	54	76	4
8	NiI ₂	DMA	55	78	6
9	NiBr ₂	DMA	49	74	7
10	NiCl ₂ ·6H ₂ O	DMA	69	80	3
11	Ni(OAc) ₂ ·4H ₂ O	DMA	19	67	12
12	Ni(acac) ₂	DMA	39	54	17

Yields determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.

Moving forward with DMA as the solvent, I then screened nickel sources (Table 2-1, entries 8-12). I was excited to observe a yield of 69% (as determined by ¹H NMR spectroscopy) with nickel (II) chloride hexahydrate.

With these promising conditions in hand, I examined a small scope of aryl chlorides. This study is important because the optimization used an electron-deficient aryl chloride, which often participates in oxidation addition more readily compared to electron-rich aryl chlorides. Thus, I expected electron-rich and neutral aryl chlorides to result in lower yields compared to aryl chloride **2-18**. However, as shown in Table 2-2, there seems to be no reactivity of any of these aryl chlorides. It is also surprising to see very little triphenylpyridine (TPP) produced, an indication of C-N bond cleavage.

Table 2-2. Aryl Chloride Scope



Yields determined by ¹H NMR using 1,3,5-trimethoxybenzene as internal standard.
n.d. = not detected.

This observation can suggest that oxidative addition is not occurring. The small amounts of triphenylpyridine could be from manganese reduction of the alkylpyridinium salt, however <1% of dihydropyridine byproduct **2-21** was observed in all entries. Aryl chloride starting material was unclear in ¹H NMR spectra. Clearly, this method requires more optimization. Reexamination of the nickel/ligand catalyst is necessary for this reaction to proceed with various aryl chlorides.

2.3 Conclusion

I have made significant efforts in optimizing a reductive cross-electrophile coupling of aryl chlorides and unactivated alkyl Katritzky pyridinium salts. I was able to identify a nickel/ligand catalyst system using High-Throughput Experimentation that resulted in higher yields of desired product. Upon investigation of solvents and additives, I found dimethylacetamide (DMA) to be the superior solvent and sodium chloride to be a beneficial additive. In the model reaction, these conditions gave a reproducible yield of 69% as determined by ^1H NMR spectroscopy. However, further optimization is required to broaden the scope to include electron-rich and neutral aryl chlorides. Mechanistically, the oxidative addition of the aryl chloride is difficult to achieve efficiently, therefore the catalyst would need to be reoptimized using a more challenging aryl chloride.

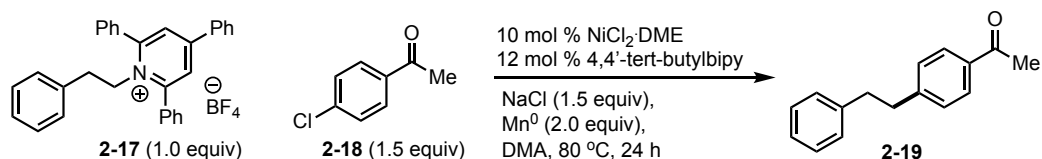
2.4 Experimental

2.4.1 General Information

Reactions were performed in oven-dried Schlenk flasks or in oven-dried, round-bottomed flasks unless otherwise noted. Round-bottomed flasks were fitted with rubber septa, and reactions were conducted under an atmosphere of N_2 . Stainless steel syringes or cannulae were used to transfer air- and moisture-sensitive liquids. Flash chromatography was performed on silica gel 60 (40-63 μm , 60 \AA) unless otherwise noted. Commercial reagents, including 2,4,6-triphenylpyrylium tetrafluoroborate, were purchased from Sigma Aldrich, Acros, AstaTech, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, AK Scientific, Bide Pharmatech, Oakwood, or Cambridge Isotopes Laboratories and used as received with the following exceptions: MeCN and CH_2Cl_2 were dried by passing through drying columns.¹ MeCN was then

degassed by sparging with N₂. Oven-dried potassium carbonate was added to CDCl₃ to remove trace acid. Potassium fluoride for small scale cross-couplings was dried in the oven overnight, passed through a sieve to ensure uniformity throughout the powder, and then stored in a desiccator. 4Å Molecular sieves were purchased and heated at 200 °C under vacuum, then crushed and stored in a desiccator. Proton nuclear magnetic resonance (¹H NMR) spectra, carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on both 400 MHz and 600 MHz spectrometers.

2.4.2 General Procedure: Nickel-Catalyzed Reductive Coupling of Aryl Chlorides with Alkyl Pyridinium Salts



An oven-dried, 25-mL Schlenk flask equipped with a mechanical stirbar was charged with NiCl₂·6H₂O (24 mg, 0.1 mmol, 0.1 equiv), 4,4'-tert-butylbipyridine (32 mg, 0.12 mmol, 0.12 equiv), sodium chloride (88 mg, 1.5 mmol, 1.5 equiv), manganese(0) (110mg, 2.0 mmol, 2.0 equiv) and alkyl Katritzky pyridinium salt (500 mg, 1.0 mmol, 1.0 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and evacuated and backfilled with nitrogen five times. Aryl chloride (0.15 mL, 1.5 mmol, 1.5 equiv) and DMA (0.17 M, 6 mL) were added via syringe. The mixture was stirred and heated at 80 °C for 24 hours. The aqueous layer was washed with EtOAc (3 x 20 mL), combined organic layers were concentrated under reduced pressure, and isolated via silica gel chromatography.

2.4.3 General Procedure: High-Throughput Experimentation

In a N₂-atmosphere glovebox, 250- μ L vials containing pre-plated ligands (1 μ mol of ligand in each, 12 mol %) were charged with a stir bar and placed in a 96-well reaction plate. Stock solutions of nickel source NiBr₂·DME (30 μ g, 0.83 μ mol, 10 mol %) and NiCl₂·DME (22 μ g, 0.83 μ mol, 10 mol %), and pyridinium salt 2-17 (5 mg, 10 μ mol, 1.2 equiv) were added as stock solutions in NMP, such that the total amount of NMP was 40 μ L. Then, a solution of additive (10 μ L, 8.3 μ mol, 1.0 equiv), reductant (25 μ mol, 3.0 equiv), and aryl chloride (20 μ L, 1.0 equiv) was added to each vial. The reaction plate was sealed, and the mixtures were stirred at 80 °C overnight in the glovebox. The plate was then removed from the glovebox. LCMS grade acetonitrile (100 μ L) was added to each vial. 30 μ L of each reaction mixture was then transferred to a second 96-well plate and diluted with 500 μ L of MeOH. Using a centrifuge, any solids were deposited, before GC analysis.

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Appendix A

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Engaging Alkenes and Alkynes in Deaminative Alkyl-Alkyl and Alkyl-Vinyl Cross-Couplings of Alkylpyridinium Salts



Author: Kristen M. Baker, Diana Lucas Baca, Shane Plunkett, et al

Publication: Organic Letters

Publisher: American Chemical Society

Date: Dec 1, 2019

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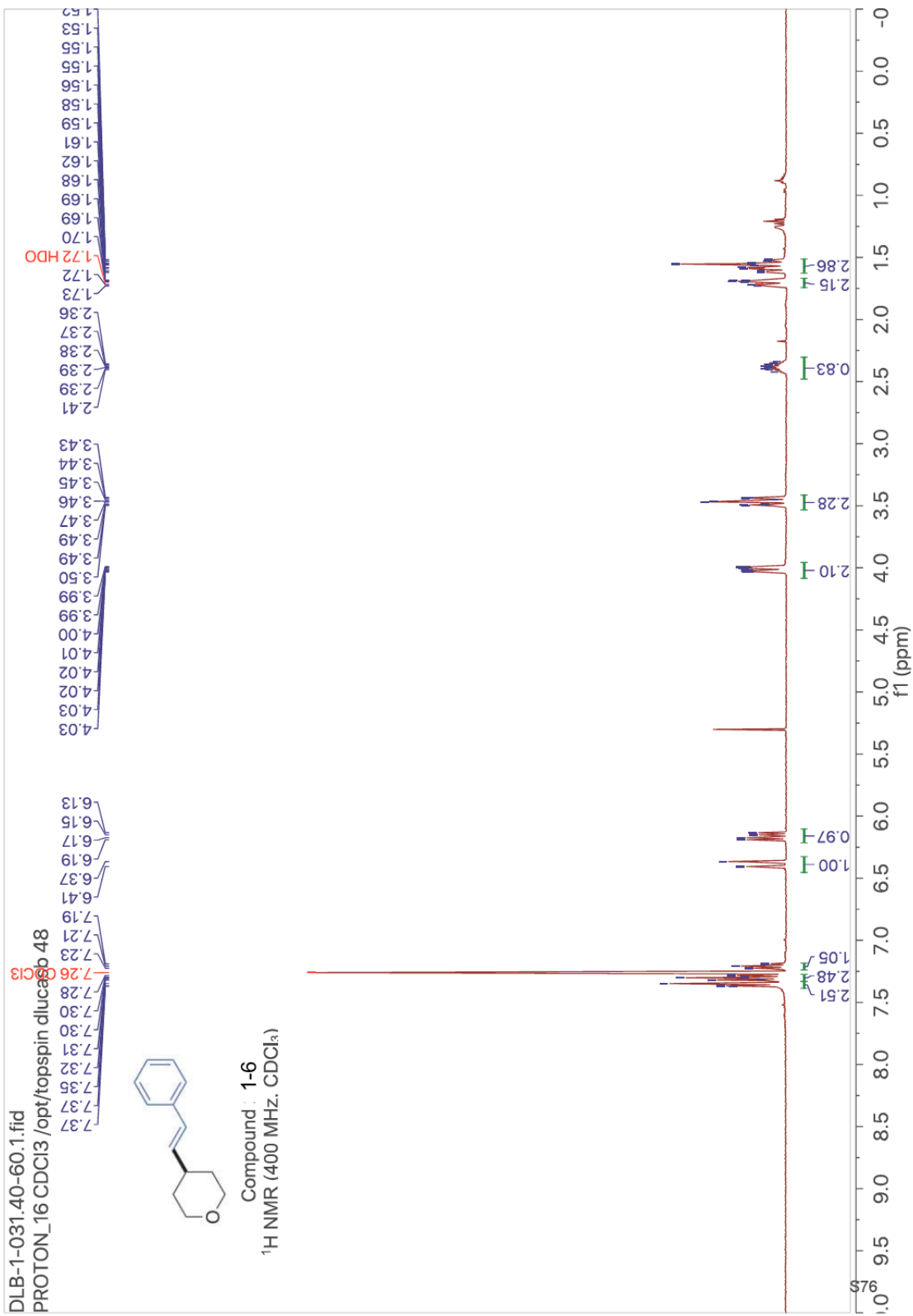
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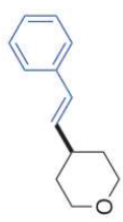
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Appendix B

SPECTRAL DATA FOR CHAPTER 1



DLB-1-102_pdt.2.fid
C13CPD256 CDC13 /opt/topspin bakekr 13



Compound 1-6
¹³C NMR (100 MHz, CDCl₃)

