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Vinylation of Benzylic Amines via C–N Bond Functionalization of Benzylic Pyridinium Salts

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Abstract

Cross-couplings of benzylic pyridinium salts and vinylboronic acids or esters have been developed. Via these benzylic pyridinium intermediates, benzylic amines can be engaged in these cross-couplings via C–N bond functionalization. This method boasts mild reaction conditions and excellent tolerance for heteroaryl substituents and a range of functional groups.

Graphical abstract

Keywords

allyl complexes; amines; benzylation; catalysis; cross-coupling; nickel

In our effort to identify new feedstocks for transition metal-catalyzed cross-couplings, we have been attracted to the use of alkyl amine derivatives. Amines are widely available, easily purified (often without chromatography), and can be easily carried through multi-step sequences in protected form. Thus, they offer opportunities in late-stage functionalization, as well as serving as simple building blocks. In particular, many benzylic amines are commercially available, or can be readily prepared via reduction of benzonitriles, as well as other methods.² We and others have previously shown that benzylic amines can be harnessed in nickel-catalyzed cross-couplings with aryl and vinyl boronic acids via conversion to trimethylammonium triflates (Scheme 1A).³ However, preparation of the ammonium triflate requires two steps from the parent primary amine, and is not compatible with the presence of

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other basic nitrogen atoms in the benzylic amine substrate, limiting the use of this chemistry to prepare heteroaryl-substituted products.

Recently, we developed a new strategy for the activation of amino groups in cross-couplings. By the one-step conversion of alkyl amines into Katritzky pyridinium salts, amines are then poised to undergo cross-coupling (Scheme 1B).⁴ Our initial efforts focused on alkyl amines with *unactivated* alkyl groups (not benzylic, allylic, or strained). Preliminary mechanistic experiments suggested that these nickel-catalyzed cross-couplings proceed via alkyl radical intermediates, likely in a Ni^{I/III} catalytic cycle.⁵ This mechanistic insight suggests that benzylic amines will also be excellent substrates, because they would proceed via stabilized benzylic radical **2** if they follow a similar mechanism as for non-benzylic pyridinium salts (Scheme 1C).

Herein, we describe our development of cross-couplings of benzylic pyridinium salts with vinyl boronic acids. This cross-coupling delivers 1,3-disubstituted allylic molecules, which have proven to be versatile intermediates in the synthesis of complex organic molecules.⁶ In addition, 1,3-diaryl allylic molecules themselves can possess promising biological activity.⁷ By harnessing a benzylic amine, this method offers synthetic opportunities that are complementary to analogous cross-couplings of benzylic halides⁸ and alcohol derivatives,⁹ as well as umpolung strategies that utilize benzylic nucleophiles.^{10,3k, 11, 11l, 12,8g, 13} Specifically, many previous cross-couplings of benzylic substrates largely neglect heteroaryl substitution.^{8a, 8d, 11n, 11w, 11ab, 14}

Because pyridinium formation is selective for primary amines (NH₂ groups), this method is highly tolerant of heteroaryl substituents, including those with basic nitrogen atoms. Additional features include mild reaction conditions, broad functional group tolerance, and the ability to use either boronic acids or boronic esters. Furthermore, although lower yielding than the reactions with a nickel catalyst, a transition metal-free pathway was also observed for this vinylation.^{8g, 13}

For our optimization studies, we prioritized identification of conditions that would enable incorporation of heteroaryl substitution. We selected the cross-coupling of pyridyl-substituted pyridinium salt **3a** with vinyl boronic acid as the model reaction. Under conditions identified in our related studies of a nickel-catalyzed arylation of benzylic pyridinium salts, which uses a single-component catalyst prepared from phenanthroline (Phen) and Ni(OAc)₂·4H₂O,¹⁵ we observed 76% yield of product **4** (Table 1, entry 1). However, we were surprised to find that the reaction also proceeded in the absence of a nickel catalyst, albeit in slightly reduced yield (entry 2). Further investigation showed that base (K₃PO₄) was necessary (entry 3). In an effort to improve the utility of this reaction, we found that only two equivalents of boronic acid are needed (entry 4), and that pinacol boronic ester can also be used as the coupling partner (entry 7). When boronic ester is used, only 2.5 equivalents of base are required (entry 8). The ability to use either boronic acid or ester broadens the pool of commercially available reagents that can be used.

Intrigued by the transition metal-free reaction, we probed this possibility further. With the use of only two equivalents of boronic acid, the metal-free reaction proceeds in only 46%

yield (Table 1, entry 6). In addition, these metal-free conditions proved less effective for other substrates. Phenyl-substituted product **5** and imidazole **6** were formed in only 23% and 33% yield, respectively (Scheme 2). These results show that a metal-free pathway is possible, but not as effective as the reaction involving the nickel catalyst. Based on previously reported metal-free vinylations,^{8g, 13} we hypothesize the metal-free variant proceeds via nucleophilic attack of a vinyl boronate to the benzylic pyridinium ion, likely in an S_N2 fashion. With PhenNi(OAc)₂·xH₂O present, a Ni^{I/III} (or Ni^{0/II}) catalytic cycle may also operate, but we cannot exclude the possibility that nickel acts as a Lewis acid with our current data. Because higher yields are observed with all three substrates, we proceeded to investigate the scope of the reaction in the presence of the nickel catalyst. Notably, these conditions are also the less expensive choice. For a 1-mmol scale reaction, the cost of 5 mol % Ni(OAc)₂·4H₂O and 5 mol % Phen (approximately \$0.20 from Sigma Aldrich) is less than an extra equivalent of phenylvinylboronic acid (approximately \$2.00) or pinacol ester (approximately \$10.40).

Under these optimized conditions, we observed broad scope of benzylic pyridinium salts. We prioritized substrates with heteroaryl substituents, and found that both electron-poor (**4–11**) and electron-rich (**12–17**) heteroaryls are well tolerated (Scheme 3). On 1-mmol scale, the product of the model reaction (**4**) was isolated in 80% yield. High yield was also observed when pinacol boronate ester replaced boronic acid (70%). Throughout our scope studies, we used either the boronic acid or ester, depending on which was commercially available. If both were available, the less expensive reagent was used. In addition to 3-pyridyl substitution, 2- and 4-pyridyl were also tolerated (**7, 8**). Quinoline **10** and pyrimidine **11** were also formed in high yields. However, for pyrimidine **11**, isomerization of the alkene was observed, with a 1.3:1 ratio of alkene isomers. For electron-rich heteroaryl groups, imidazole **12**, oxazole **13**, pyrazole **14**, thiadiazole **15**, pyrrole **16**, and thiazole **17** were all successfully formed. However, more electron-rich pyridinium salts were poor substrates; the cross-coupling of the pyridinium salt of 4-methoxybenzylamine resulted in only 26% yield by ¹H NMR analysis. Unfortunately, secondary benzylic pyridinium salts were also poor substrates. Under the conditions of 5 mol % PhenNi(OAc)₂·xH₂O, *trans*-2-phenylvinylboronic acid (3.0 equiv), K₃PO₄ (3.4 equiv), dioxane (0.5 M), 60 °C, 24 h (no EtOH), the vinylation of the pyridinium salt of 1-pyridin-2-yl-ethylamine resulted in only 21% yield by ¹H NMR analysis.

A wide range of vinyl groups can be installed via this method (Scheme 3). Both electron-rich and electron-poor phenyl substitution is well tolerated. Thiophene **7** demonstrates that heteroaryls can also be used. In addition, aliphatic alkenes can be formed, including trisubstituted alkene **8**, benzyl-substituted alkene **12**, and *t*-butyl-substituted alkene **17**. Electron-poor α,β-unsaturated ester **9** was formed in 61% yield. In addition to the heteroaryl tolerance, multiple functional groups are compatible, including esters (**9**), ethers (**10, 13**), trifluoromethyl (**11**), fluoride (**14, 15**), and chloride (**16**). However, more bulky vinyl groups, such as in (3-methyl-2-buten-2-yl)boronic ester, 2-methylprop-1-enylboronic ester, or 1-phenylvinylboronic ester, resulted in less than 30% yield. Simple vinylboronic ester also resulted in low yield (17% by ¹H NMR analysis).

In summary, we have developed a coupling of benzylic pyridinium salts with vinyl boronic acids or esters. Via a pyridinium salt intermediate, benzylic amines can be engaged in these vinylations via C–N bond functionalization. Notably, the use of the pyridinium salt enables broad scope of heteroaromatic substituents, including those that would not be amenable to activation via a trimethylammonium triflate. Both boronic acids and boronic esters can be used, increasing the versatility of this method. With respect to the mechanism, a transition metal-free reaction was observed, but provided lower yields than conditions involving a nickel catalyst. Overall, this reaction leverages the wide availability of benzylic amines to enable a new entry to versatile 1,3-disubstituted allylic products.

Reference markers are added by giving the appropriate numbers, in numerical order throughout the manuscript, as superscripts,^{*–3} and should be placed after the relevant punctuation.^{4,5} All references must be cited.^{6–8}

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 a positive pressure of N₂. Stainless steel syringes were used to transfer air- and moisture-sensitive liquids. Silica gel chromatography was performed on silica gel 60 (40–63 μ m, 60Å) unless otherwise noted. Commercial reagents were purchased from Sigma Aldrich, Acros, Fisher, Strem, TCI, Combi Blocks, Alfa Aesar, AK Scientific, Oakwood, or Cambridge Isotopes Laboratories and used as received with the following exceptions: anhydrous ethanol was degassed by sparging with N₂ for 20–30 minutes prior to use in the cross-coupling reactions; dioxane was dried by passing through drying columns, then degassed by sparging with N₂.¹⁶ In some instances oven-dried potassium carbonate was added to CDCl₃ to remove trace acid. PhenNi(OAc)₂·xH₂O and the benzylic pyridinium salts were prepared as previously described.^{4, 15} Proton nuclear magnetic resonance (¹H NMR) spectra, carbon nuclear magnetic resonance (¹³C NMR) spectra, and fluorine nuclear magnetic resonance (¹⁹F 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). Chemical shifts for fluorine were externally referenced to CFCl₃ in CDCl₃ (CFCl₃ = δ 0). 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, h = heptet), 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.

Procedures

General Procedure A: Cross-Coupling of Pyridinium Salts with Boronic Acids

To an oven-dried, 25-mL Schlenk flask equipped with a stir bar was added PhenNi(OAc)₂·xH₂O (20 mg, 0.050 mmol, 5 mol %), pyridinium salt (1.0 mmol, 1.0 equiv), vinylboronic acid (2.0 mmol, 2.0 equiv), and K₃PO₄ (722 mg, 3.4 mmol, 3.4 equiv). The

flask was fitted with a rubber septum, sealed with parafilm, and then evacuated and refilled with N₂ (x 3). Dioxane (2.0 mL) was added, followed by EtOH (0.29 mL, 5.0 mmol, 5.0 equiv). The flask was sealed, and mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with CH₂Cl₂ (4 × 25 mL), and the filtrate was concentrated. The cross-coupled product was then purified via silica gel chromatography.

General Procedure B: Cross-Coupling of Pyridinium Salts with Pinacol Boronic Esters

To an oven-dried, 10-mL round bottom flask equipped with a stir bar was added PhenNi(OAc)₂·xH₂O (20 mg, 0.050 mmol, 5 mol %), pyridinium salt (1.0 mmol, 1.0 equiv), vinylboronic acid pinacol ester (2.0 mmol, 2.0 equiv), and K₃PO₄ (531 mg, 2.5 mmol, 2.5 equiv). The flask was fitted with a rubber septum, sealed with parafilm, and then purged with N₂ for 20 min. Dioxane (2.0 mL) was added, followed by EtOH (0.29 mL, 5.0 mmol, 5.0 equiv). The flask was sealed, and mixture was stirred at 60 °C for 24 h. The mixture was allowed to cool to room temperature, and then filtered through a small pad of Celite. The filter cake was washed with CH₂Cl₂ (4 × 25 mL), and the filtrate was concentrated. The cross-coupled product was then purified via silica gel chromatography.

3-Cinnamylpyridine (4)

Prepared via General Procedure A using 2,4,6-triphenyl-1-(pyridin-3-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (50% Et₂O/hexanes) to give **4** (156 mg, 80%) as pale yellow oil. The spectral data matches that reported in the literature.¹⁷

¹H NMR (600 MHz, CDCl₃) δ 8.54 – 8.46 (m, 2H), 7.58 – 7.53 (m, 1H), 7.37 – 7.33 (m, 2H), 7.33 – 7.28 (m, 2H), 7.25 – 7.20 (m, 2H), 6.47 (d, *J* = 15.8 Hz, 1H), 6.32 (dt, *J* = 15.8, 6.8 Hz, 1H), 3.56 (d, *J* = 5.4 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 150.3, 147.9, 137.2, 136.3, 135.6, 132.1, 128.7, 127.9, 127.6, 126.3, 123.5, 36.6.

Product **4** was also prepared via General Procedure B. The crude mixture was purified by silica gel chromatography to give **4** (135 mg, 70%).

(*E*)-2-(3-(Thiophen-3-yl)allyl)pyridine (7)

Prepared via General Procedure B using 2,4,6-triphenyl-1-(pyridin-2-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (50% EtOAc/hexanes) to give **7** (146 mg, 72%) as orange oil.

FTIR (neat) 3078, 3007, 2923, 1590, 1472, 1434, 965, 766 cm⁻¹.

¹H NMR (600 MHz, CDCl₃) δ 8.58 – 8.53 (m, 1H), 7.61 (td, *J* = 7.7, 1.8 Hz, 1H), 7.26 – 7.18 (m, 3H), 7.16 – 7.08 (m, 2H), 6.54 (d, *J* = 15.8 Hz, 1H), 6.30 (dt, *J* = 15.7, 7.1 Hz, 1H), 3.70 (dd, *J* = 7.1, 1.4 Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 160.4, 149.6, 140.1, 136.7, 127.6, 126.3, 126.0, 125.2, 123.0, 121.5, 121.4, 42.1.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{12}\text{NS}$: 202.0690, found 202.0687.

4-(Cyclohex-1-en-1-ylmethyl)pyridine (**8**)

Prepared via General Procedure A using 2,4,6-triphenyl-1-(pyridin-4-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 20 $\rightarrow$ 100% EtOAc/hexanes) to give **8** (88 mg, 51%) as yellow oil.

FTIR (neat) 3024, 2926, 2834, 1599, 1559, 1414 cm^{-1} .

^1H NMR (600 MHz, CDCl_3) δ 8.51 – 8.46 (m, 2H), 7.12 – 7.08 (m, 2H), 5.53 – 5.48 (m, 1H), 3.22 (s, 2H), 2.06 – 2.00 (m, 2H), 1.86 – 1.80 (m, 2H), 1.63 – 1.51 (m, 4H).

^{13}C NMR (151 MHz, CDCl_3) δ 149.8, 149.7, 135.6, 124.6, 124.4, 44.1, 28.2, 25.5, 23.0, 22.4.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{12}\text{H}_{16}\text{N}$: 174.1283, found 174.1277.

Ethyl (*E*)-4-(pyridin-3-yl)but-2-enoate (**9**)

Prepared via General Procedure B using 2,4,6-triphenyl-1-(pyridin-3-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 50 $\rightarrow$ 75% EtOAc/hexanes) to give **9** (117 mg, 61%) as pale yellow oil.

FTIR (neat) 3030, 2982, 2937, 1734, 1160, 1025, 970, 709 cm^{-1} .

^1H NMR (400 MHz, CDCl_3) δ 8.61 – 8.55 (m, 1H), 8.50 – 8.43 (m, 1H), 7.74 – 7.66 (m, 1H), 7.26 – 7.21 (m, 1H), 6.48 (d, J = 16.0 Hz, 1H), 6.38 (dt, J = 16.0, 6.8 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.27 (dd, J = 6.9, 1.2 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, CDCl_3) δ 171.3, 148.8, 148.4, 132.8, 132.6, 130.0, 124.5, 123.6, 61.1, 38.6, 14.4.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{14}\text{NO}_2$: 192.1025, found 192.1020.

(*E*)-6-(3-(4-Methoxyphenyl)allyl)quinoline (**10**)

Prepared via General Procedure A using 2,4,6-triphenyl-1-(quinolin-6-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 5 $\rightarrow$ 50% EtOAc/hexanes) to give **10** (197 mg, 72%) as yellow oil.

FTIR (neat) 3030, 2956, 2834, 1606, 1511, 1247, 1175, 968, 835 cm^{-1} .

^1H NMR (600 MHz, CDCl_3) δ 8.88 (dd, J = 4.2, 1.7 Hz, 1H), 8.13 – 8.08 (m, 1H), 8.08 – 8.03 (m, 1H), 7.67 – 7.60 (m, 2H), 7.38 (dd, J = 8.3, 4.2 Hz, 1H), 7.34 – 7.29 (m, 2H), 6.87 – 6.83 (m, 2H), 6.47 (d, J = 15.7 Hz, 1H), 6.29 (dt, J = 15.7, 6.9 Hz, 1H), 3.80 (s, 3H), 3.72 (d, J = 6.9 Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 159.2, 150.0, 147.5, 139.1, 135.8, 131.31, 131.26, 130.3, 129.7, 128.6, 127.5, 126.6, 126.4, 121.3, 114.2, 55.5, 39.4.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{18}\text{NO}$: 276.1388, found 276.1384.

(E)-2-(3-(4-(Trifluoromethyl)phenyl)allyl)pyrimidine (11a) and (E)-2-(3-(4-(Trifluoromethyl)phenyl)prop-1-en-1-yl)pyrimidine (11b)

Prepared via General Procedure A using 2,4,6-triphenyl-1-(pyrimidin-2-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 8 $\rightarrow$ 70% EtOAc/hexanes) to give **11a** (119 mg, 45%) as yellow oil and **11b** (94 mg, 36%) as yellow oil.

(E)-2-(3-(4-(Trifluoromethyl)phenyl)allyl)pyrimidine (**11a**):

FTIR (neat) 3041, 1563, 1422, 1327, 1164, 1122, 1068 cm^{-1} .

^1H NMR (600 MHz, CDCl_3) δ 8.71 (d, J = 4.9 Hz, 2H), 7.54 (d, J = 8.2 Hz, 2H), 7.47 (d, J = 8.2 Hz, 2H), 7.17 (t, J = 4.9 Hz, 1H), 6.72 – 6.58 (m, 2H), 3.94 (d, J = 6.7 Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 169.4, 157.5, 140.9, 131.2, 129.2 (q, J = 32.3 Hz), 129.1, 126.6, 125.6 (q, J = 3.8 Hz), 124.5 (q, J = 271.7 Hz), 119.0, 43.4.

^{19}F NMR (565 MHz, CDCl_3) δ –62.48.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{N}_2$: 265.0953, found 265.0950.

(E)-2-(3-(4-(Trifluoromethyl)phenyl)prop-1-en-1-yl)pyrimidine (**11b**):

FTIR (neat) 3037, 2918, 1557, 1421, 1332, 1161, 1105 cm^{-1} .

^1H NMR (600 MHz, CDCl_3) δ 8.66 (d, J = 4.9 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.0 Hz, 2H), 7.32 – 7.26 (m, 1H), 7.09 (t, J = 4.8 Hz, 1H), 6.61 – 6.55 (m, 1H), 3.69 (d, J = 6.6 Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 164.4, 157.0, 143.0, 138.8, 131.3, 129.2, 128.9 (q, J = 32.1 Hz), 125.5 (q, J = 3.8 Hz), 124.3 (q, J = 271.8 Hz), 118.7, 38.7.

^{19}F NMR (565 MHz, CDCl_3) δ –62.43.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{N}_2$: 265.0953, found 265.0951.

(E)-1-(4-(4-Phenylbut-2-en-1-yl)phenyl)-1H-imidazole (12)

Prepared via General Procedure A using 1-(4-(1H-imidazol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 20 $\rightarrow$ 100% EtOAc/hexanes) to give **12** (172 mg, 63%) as yellow oil.

FTIR (neat) 3026, 2899, 1521, 1492, 1303, 1057, 965 cm^{-1} .

^1H NMR (600 MHz, CDCl_3) δ 7.85 – 7.81 (m, 1H), 7.34 – 7.27 (m, 6H), 7.26 – 7.25 (m, 1H), 7.24 – 7.17 (m, 4H), 5.76 – 5.62 (m, 2H), 3.44 – 3.37 (m, 4H).

^{13}C NMR (151 MHz, CDCl_3) δ 140.6, 140.4, 135.8, 135.7, 131.4, 130.5, 130.0, 129.8, 128.7, 128.6, 126.2, 121.8, 118.5, 39.1, 38.5.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{19}\text{N}_2$: 275.1548, found 275.1543.

(E)-5-(4-(3-(3-Methoxyphenyl)allyl)phenyl)oxazole (13)

Prepared via General Procedure B using 1-(4-(oxazol-5-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 10→50% EtOAc/hexanes) to give **13** (220 mg, 76%) as yellow solid (mp 60–63 °C).

FTIR (neat) 3027, 2937, 2833, 1598, 1579, 1490, 1267, 1043, 941 cm^{-1} .

^1H NMR (600 MHz, CDCl_3) δ 7.90 (s, 1H), 7.63 – 7.58 (m, 2H), 7.34 – 7.29 (m, 3H), 7.22 (t, J = 7.9 Hz, 1H), 6.99 – 6.94 (m, 1H), 6.92 – 6.88 (m, 1H), 6.80 – 6.75 (m, 1H), 6.48 – 6.41 (m, 1H), 6.35 (dt, J = 15.7, 6.8 Hz, 1H), 3.81 (s, 3H), 3.58 (d, J = 7.2 Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 160.0, 151.7, 150.4, 141.0, 138.9, 131.6, 129.7, 129.4, 129.0, 126.0, 124.8, 121.3, 119.0, 113.1, 111.6, 55.4, 39.2.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{19}\text{H}_{18}\text{NO}_2$: 292.1338, found 292.1331.

(E)-1-(4-(3-(4-Fluorophenyl)allyl)phenyl)-1H-pyrazole (14)

Prepared via General Procedure A using 1-(4-(1H-pyrazol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 5→20% Et₂O/hexanes) to give **14** (241 mg, 87%) as light yellow solid (mp 80–83 °C).

FTIR (neat) 3037, 2922, 1524, 1507, 1394, 1225, 936, 838, 748 cm^{-1} .

^1H NMR (600 MHz, CDCl_3) δ 7.90 (d, J = 2.4 Hz, 1H), 7.72 (d, J = 1.7 Hz, 1H), 7.66 – 7.61 (m, 2H), 7.35 – 7.29 (m, 4H), 7.02 – 6.96 (m, 2H), 6.48 – 6.39 (m, 2H), 6.28 (dt, J = 15.8, 6.8 Hz, 1H), 3.57 (dd, J = 6.8, 1.4 Hz, 2H).

^{13}C NMR (151 MHz, CDCl_3) δ 162.3 (d, $J_{\text{C-F}}$ = 246.1 Hz), 141.1, 138.8, 138.5, 133.6 (d, $J_{\text{C-F}}$ = 3.4 Hz), 130.4, 129.8, 128.7 (d, $J_{\text{C-F}}$ = 2.2 Hz), 127.7 (d, $J_{\text{C-F}}$ = 8.0 Hz), 126.8, 119.6, 115.6 (d, J = 21.2 Hz), 107.6, 38.8.

^{19}F NMR (565 MHz, CDCl_3) δ -115.13.

HRMS (ESI+) $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{18}\text{H}_{16}\text{FN}_2$: 279.1298, found 279.1292.

(E)-5-(4-(3-(2,4-Difluorophenyl)allyl)phenyl)-1,2,3-thiadiazole (15)

Prepared via General Procedure B using 1-(4-(1,2,3-thiadiazol-5-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel

chromatography (step gradient: 1→10% Et₂O/hexanes) to give **15** (163 mg, 52%) as yellow solid (mp 117–120 °C).

FTIR (neat) 3094, 2931, 1589, 1503, 1427, 1223, 970, 846, 809 cm⁻¹.

¹H NMR (600 MHz, CDCl₃) δ 8.62 (s, 1H), 8.03 – 7.98 (m, 2H), 7.43 – 7.37 (m, 3H), 6.85 – 6.75 (m, 2H), 6.62 – 6.55 (m, 1H), 6.39 (dt, *J* = 15.9, 6.9 Hz, 1H), 3.63 (d, *J* = 6.3 Hz, 2H).

¹³C NMR (101 MHz, CDCl₃) δ 162.9, 162.3 (dd, *J* = 196.6, 11.9 Hz), 159.8 (dd, *J* = 199.2, 11.9 Hz), 141.4, 131.0 (dd, *J* = 4.7, 2.3 Hz), 129.8, 129.6, 129.1, 128.1 (dd, *J* = 9.5, 5.5 Hz), 127.7, 123.2 (dd, *J* = 3.0, 1.4 Hz), 121.5 (dd, *J* = 12.5, 4.0 Hz), 111.5 (dd, *J* = 21.3, 3.7 Hz), 104.1 (t, *J* = 25.7 Hz), 39.6.

¹⁹F NMR (565 MHz, CDCl₃) δ -111.66 (d, *J*_{F-F} = 7.1 Hz), -114.30 (d, *J*_{F-F} = 7.1 Hz).

HRMS (ESI+) [M+H]⁺ calculated for C₁₇H₁₃F₂N₂S: 315.0768, found 315.0759.

(*E*)-1-(2-(3-(4-Chlorophenyl)allyl)phenyl)-1*H*-pyrrole (**16**)

Prepared via General Procedure B using 1-(2-(1*H*-pyrrol-1-yl)benzyl)-2,4,6-triphenylpyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 1→10% toluene/hexanes) to give **16** (220 mg, 75%) as colorless oil.

FTIR (neat) 3028, 1502, 1491, 1327, 1093, 764, 727 cm⁻¹.

¹H NMR (600 MHz, CDCl₃) δ 7.38 – 7.28 (m, 4H), 7.25 – 7.19 (m, 4H), 6.82 – 6.78 (m, 2H), 6.34 – 6.30 (m, 2H), 6.21 (d, *J* = 15.9 Hz, 1H), 6.14 (dt, *J* = 15.8, 6.4 Hz, 1H), 3.40 (d, *J* = 6.4 Hz, 2H).

¹³C NMR (151 MHz, CDCl₃) δ 140.6, 136.1, 136.0, 132.9, 130.6, 130.4, 129.3, 128.8, 128.1, 127.5, 127.4, 127.3, 122.5, 109.1, 34.8.

HRMS (ESI+) [M+H]⁺ calculated for C₁₉H₁₇ClN: 294.1050, found 294.1041.

(*E*)-2-(4,4-Dimethylpent-2-en-1-yl)thiazole (**17**)

Prepared via General Procedure A using 2,4,6-triphenyl-1-(thiazol-2-ylmethyl)pyridin-1-ium tetrafluoroborate. The crude mixture was purified by silica gel chromatography (step gradient: 2→20% EtOAc/hexanes) to give **17** (91 mg, 50%) as light yellow oil.

FTIR (neat) 3081, 2959, 2902, 2866, 1501, 1363, 973, 720 cm⁻¹.

¹H NMR (600 MHz, CDCl₃) δ 7.69 (d, *J* = 3.3 Hz, 1H), 7.20 (d, *J* = 3.3 Hz, 1H), 5.75 – 5.69 (m, 1H), 5.58 (dt, *J* = 15.5, 6.9 Hz, 1H), 3.71 (dd, *J* = 6.9, 1.3 Hz, 2H), 1.04 (s, 9H).

¹³C NMR (151 MHz, CDCl₃) δ 171.4, 145.9, 142.6, 120.5, 118.6, 36.9, 33.3, 29.6.

HRMS (ESI+) [M+H]⁺ calculated for C₁₀H₁₆NS: 182.1003, found 182.0998.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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A. Prior art: benzylic substrates reported for vinylations

B. Our previous cross-coupling of alkyl pyridinium salts

C. This work

Scheme 1.

Cross-coupling of benzylic substrates for the synthesis of 1,3-diaryl allylic compounds.

Scheme 2.

Comparison of reactions with and without the nickel catalyst. Conditions: Salt **3** (0.1 mmol), $\text{PhenNi}(\text{OAc})_2 \cdot x\text{H}_2\text{O}$ (0 or 5 mol %), boronic acid (2.0 equiv), K_3PO_4 (3.4 equiv), EtOH (5 equiv), dioxane (0.5 M), 60 °C, 24 h. Yields determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.

Scheme 3.

Scope of the vinylation. Conditions: Salt **3** (1.0 mmol), $\text{PhenNi}(\text{OAc})_2 \cdot x\text{H}_2\text{O}$ (5 mol %), boronic acid (2.0 equiv), K_3PO_4 (3.4 equiv), EtOH (5.0 equiv), dioxane (0.5 M), 60 °C, 24 h, unless noted otherwise. Isolated yields. ^aPinacol boronate ester (2.0 equiv), K_3PO_4 (2.5 equiv). ^bAlkene isomers readily separated via silica gel chromatography and isolated in 45% and 36% yield.

Table 1

Optimization^a

entry	modification from original conditions	yield (%) ^b
1	none	76
2	no PhenNi(OAc) ₂ ·xH ₂ O	62
3	no K ₃ PO ₄	0
4	2 equiv boronic acid	74
5	2 equiv boronic acid, 2.5 equiv K ₃ PO ₄	54
6	no PhenNi(OAc) ₂ ·xH ₂ O, 2 equiv boronic acid	46
7	 (2.0 equiv)	73
8	 (2.0 equiv), 2.5 equiv K ₃ PO ₄	74
9	 (3.0 equiv), no PhenNi(OAc) ₂ ·xH ₂ O	46

^a Conditions: Salt **3a** (0.1 mmol), PhenNi(OAc)₂·xH₂O (5 mol %), boronic acid (3.0 equiv), K₃PO₄ (3.4 equiv), EtOH (5 equiv), dioxane (0.5 M), 60 °C, 24 h.

^b Determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as internal standard.