Published in final edited form as:

Synthesis (Stuttg). 2010 November ; 2010(21): 3637–3644. doi:10.1055/s-0030-1258237.

Suzuki-Miyaura cross-coupling of 3-pyridyl triflates with 1-alkenyl-2-pinacol boronates

James R. Vyvyan^{*}, Jennifer A. Dell (née Meyer), Toby J. Ligon, Kelsey K. Motanic, and Hayley S. Wall

Department of Chemistry, Western Washington University, 516 High Street, Bellingham, WA 98225-9150

Abstract

Palladium-catalyzed Suzuki-type couplings of 3-pyridyl triflates with alkenyl pinacol boronates proceed in good to excellent yield. Optimized conditions use Pd(PPh₃)₄ (10 mol %) as catalyst with K₃PO₄ (3 equiv) as base in dioxane.

Keywords

boron; cross-coupling; heterocycles; palladium; pyridines

Since its development 30 years ago,¹ the Suzuki-Miyaura cross-coupling of organoboron compounds has become one of the most widely used methods for forming C–C bonds.² Given the myriad examples of Suzuki-Miyaura couplings, and the fact that there are a number of interesting branched 3-alkylpyridine natural products, such as cananodine (**1**)^{3,4} and xestamine C (**2**),⁵ we were surprised to find very few examples of reactions between 3-pyridyl triflates and alkenyl/alkyl boronates.⁶ Similarly, there are few examples of coupling 3-pyridyl boron derivatives with alkenyl halides or triflates.⁷

In a retrosynthetic analysis of cananodine (**1**) and xestamine C (**2**), we identified branched pyridyl alkene **3** as a key intermediate prepared by cross-coupling a 3-pyridyl triflate **4** with alkenyl boronate **6** (Figure 1). Alternatively, the roles of the components could be reversed, such that pyridyl boronate **5** could be coupled with alkenyl triflate **7**. Since preparation of the coupling partners require the same number of synthetic steps, we planned to explore both permutations of the coupling reaction.⁸

Appropriately substituted 3-hydroxypyridines are more readily available than the corresponding 3-halo derivatives, and they are easily converted to the corresponding aryl triflates **4** with Comins' triflimide⁹ in the presence of base. The simple pyridyl triflates **4a** – **4c** are known,¹⁰ and we also desired to examine the cross-coupling reaction with pyridines functionalized at the 2-position to provide a functional group handle for subsequent manipulations (Scheme 1). Triflate **4d** was readily prepared from 3-hydroxy-6-methyl-2-pyridinemethanol (**8**). Selective protection of the primary hydroxyl group as the pivaloate ester using pivaloyl chloride and 4-dimethylaminopyridine (DMAP) provided ester **9**. The 3-hydroxy group was then cleanly converted to the triflate using Comins' triflimide and triethylamine to give **4d** in excellent yield. The preparation of triflate **4e** commenced with

Fax: (360) 650-2826, vyvyan@chem.wvu.edu.

Dedicated to Professor Thomas R. Hoye on the occasion of his 60th birthday.

Supporting Information for this article is available online at <http://www.thieme-connect.de/ejournals/toc/synthesis>.

the protection of the 3-hydroxyl group of **8** as the allyl ether to yield **10**. Reaction of the primary hydroxyl group with *N*-bromosuccinimide and triphenylphosphine provided bromide **11**, which in turn was converted to the sulfone **12** by treatment of the bromide with sodium phenylsulfinate. Cleavage of the allyl ether using standard conditions yielded **13** which was converted to the triflate **4e** with Comins' triflimide as described earlier. Thus, the preparation of **4e** was accomplished in 5 steps in 44% overall yield. Triflate **4f** was synthesized in a more straightforward manner. Reaction of **8** with HBr and thiophenol gave the phenylsulfide that was directly converted to the triflate **4f** in the usual manner.

Despite examining several sets of reaction conditions,¹¹ we were unable to consistently convert the 3-pyridyl triflates **4** to their corresponding pinacol boronates **5**. In some cases, the ¹H NMR spectrum of the crude reaction mixture appeared to contain the desired pyridyl boronate, but **5** could not be isolated after chromatography. Our inability to prepare the 3-pyridyl boronates **5** reliably focused our efforts entirely on the coupling of 3-pyridyl triflates with alkenyl boronates (cf. **4** and **6**, respectively).

Next, we prepared alkenyl boronates with both trisubstituted and monosubstituted pendant alkenes to serve as precursors for planned syntheses of **1** and **2**. Alkenyl triflate **14a**¹² was readily converted to the corresponding alkenyl boronate **15a** under conditions developed by Miyaura (Table 1).¹³ Reaction of triflate **14b** under these conditions, however, produced a complex mixture, and ¹H NMR analysis of the reaction mixture indicated only a small amount of **15b** was formed. Other products observed in the ¹H NMR spectrum included methylenecycloalkenes, produced by intramolecular Heck reaction of the monosubstituted alkene after insertion of the Pd catalyst into the C—O bond of the triflate.¹⁴ Presumably the increased steric bulk of the trisubstituted alkene in **14a** prevents the Heck reaction in that case. Fortunately, boronate **15b** could be produced in excellent yield from 2-bromo-1,5-hexadiene¹⁵ (**14c**) by lithium-bromide exchange followed by addition of the intermediate alkenyllithium species to isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxoborolane.¹⁶ Boronate **15c** was prepared from 2-bromo-1-hexene (**14d**) in a similar fashion and in excellent yield.

Results of the Suzuki-Miyaura coupling between pyridyl triflates **4** and alkenyl boronates **15** are shown in Table 2. Yields for the coupling range from modest to very good. Since the mobilities of the coupled products on silica gel are similar to those of the pyridyl triflates **4**, an excess of **15** (1.2–2 equiv) was used in all cases to ensure complete conversion of the triflate partner.

In head to head comparisons, Pd(PPh₃)₄ was a better catalyst for this transformation than Pd(dppf)Cl₂ (entries 8 vs. 9 and 11 vs. 12) and K₃PO₄ was a better base than potassium acetate in the presence of Pd(dppf)Cl₂ (entry 11 vs. 12). Pyridyl triflates **4a–4c**, lacking substitution at the 2- and/or 6-position, gave lower yields of cross-coupled product in most cases relative to triflate **4d** that has substitution at both the 2- and 6-positions. It is not clear if the reduced yields of the less substituted compounds are truly a result of less efficient cross-coupling, or if product losses during chromatographic purification of the less hindered pyridines on silica gel are responsible.¹⁷

Unfortunately, pyridyl triflates bearing a sulfone (**4e**) or sulfide (**4f**) substituent failed to produce cross-coupled products (entries 13–16). Sulfone **4e** was consumed in the reaction and converted to an unidentified product that appears to arise after deprotonation of the activated CH₂ at the C-2 of the pyridine under the basic reaction conditions. Sulfide **4f** was not consumed under the reaction conditions. Presumably the sulfur substituent poisons the Pd catalyst, perhaps through chelation of Pd between the sulfur and pyridine nitrogen, and prevents the cross-coupling reaction.

Next, we carried out the cross-coupling with a more functionalized alkenyl boronate to advance our ongoing efforts toward a convergent synthesis of cananodine (**1**).¹⁸ We initially chose an acetone-protected diol group that could eventually serve as a precursor to a trisubstituted epoxide. Formation of the kinetic enolate of ketone **28**¹⁹ using lithium diisopropylamide followed by trapping of the enolate with Comins' triflimide provided alkenyl triflate **29** in modest yield (Scheme 2). Triflate **29** was converted to the alkenyl boronate **30** in good yield using the same conditions¹³ described above for the preparation of **15a**.

Using the optimized cross-coupling conditions, triflate **4d** was coupled with alkenyl boronate **30** to produce cross-coupled product **31** in excellent yield. Compound **31** contains all of the carbon atoms necessary for preparation of the bicyclic core of cananodine (**1**), and diene **16** is a reasonable precursor for the synthesis of xestamine C (**2**).

In summary, we have demonstrated that reaction of 3-pyridyl triflates with 1-alkenyl-2-pinacol boronates produce the cross-coupled product under Suzuki-Miyaura type conditions. Given the accessibility of the precursors and the high yields obtained, this coupling strategy is well-suited to the synthesis of α -branched 3-alkylpyridine targets.

All reactions involving air sensitive materials were carried out in oven-dried glassware under an argon atmosphere. Acetone was dried by stirring with boron oxide (5% w/v) overnight before filtration and distillation.²⁰ Dichloromethane, ether, THF, and toluene were dried by passing the solvent through a column of activated alumina under nitrogen immediately prior to use. Anhydrous DMSO and DMF were used as received from commercial suppliers. 1,4-Dioxane was distilled from sodium benzophenone ketyl under argon. Triethylamine was distilled from CaH₂ (bp 89 °C) and stored over KOH pellets. Methanesulfonyl chloride was distilled from P₂O₅ (bp 57–58 °C @ 18 mmHg). Potassium acetate was dried under vacuum (0.2 mmHg, 100 °C) with a Kugelrohr apparatus immediately prior to use. Comins' triflimide⁹ and KOPh²¹ were prepared as reported in the literature. Pyridyl triflates **4a**, **4b**, and **4c** have been previously reported.¹⁰ Alkenyl triflate **14a**¹² and alkenyl bromides **14c** and **14d**¹⁵ were prepared according to literature procedures.

(3-hydroxy-6-methylpyridin-2-yl)methyl pivaloate (**9**)

DMAP (386 mg, 3.15 mmol) was placed in a 50-mL 2-necked round-bottom flask equipped with a solid addition bulb that contained 3-hydroxy-6-methyl-2-pyridinemethanol (416 mg, 3.00 mmol). The DMAP was dissolved in CH₂Cl₂ (30 mL) and the solution was cooled to 0 °C before pivaloyl chloride (0.37 mL, 362 mg, 3.00 mmol) was added dropwise. The solution was stirred for 30 min, before the 3-hydroxy-6-methyl-2-pyridinemethanol was added at once. The solution was stirred and slowly warmed, and after 2 h TLC analysis indicated complete consumption of the starting material. Water was added, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (2×). The combined organic layers were washed with sat. NaHCO₃. After drying the combined organic layers and evaporating the solvent, purification by flash chromatography (3:1 hexanes: ethyl acetate + 2% EtOH) yielded **9** as a white solid (586 mg, 88%)

Mp 136.5–141.5 °C (dec)

IR (KBr): 2969, 2589, 1721, 1581, 1477, 1458, 1285, 1266, 1156, 1123, 1030, 968, 836 cm⁻¹.

¹H NMR (CDCl₃, 300 MHz): δ 7.15 (d, J = 8.3, 1H), 7.02 (d, J = 8.3, 1H), 5.16 (s, 2H), 2.98 (br. s, 1H), 2.36 (s, 3H), 1.20 (s, 9H).

^{13}C NMR (acetone- d_6 , 125 MHz): δ 178.6, 150.6, 149.2, 142.8, 124.3, 124.0, 64.1, 39.4, 27.6, 23.4.

Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{NO}_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.48; H, 7.38; N, 6.75.

(6-methyl-3-(trifluoromethylsulfonyloxy)pyridin-2-yl)methyl pivaloate (**4d**)

A 10-mL round-bottomed flask was charged with **9** (200 mg, 0.896 mmol) and Comins' triflimide (375 mg, 0.955 mmol). After an argon atmosphere was established, CH_2Cl_2 (5 mL) was added to the flask and the solution was cooled to 0 °C. Triethylamine (0.13 mL, 96 mg, 0.95 mmol) was added dropwise, and the solution was stirred at 0 °C for one hour before the ice bath was removed. After an additional 45 min, TLC analysis indicated complete consumption of the starting material. The solution was washed with 1M NaOH (2 $\times$) and half-saturated K_2CO_3 . After drying the organic layer and evaporating solvent, the crude product was purified by MPLC (6:1 hexanes: ethyl acetate) to afford **4d** as a white solid (308 mg, 97%)

Mp 39.1–40.1 °C

IR (dep. CH_2Cl_2): 2975, 2936, 1737, 1481, 1462, 1427, 1283, 1252, 1218, 1144, 1095, 1040, 936, 871, 831 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 7.52 (d, J = 8.5, 1H), 7.21 (d, J = 8.5, 1H), 5.25 (s, 2H), 2.58 (s, 3H), 1.24 (s, 9H).

^{13}C NMR (CDCl_3 , 75 MHz): δ 177.9, 158.4, 147.5, 143.1, 129.4, 124.2, 118.4 (q, J = 318, CF_3), 62.3, 38.8, 27.1, 23.9.

Anal. Calcd for $\text{C}_{13}\text{H}_{16}\text{F}_3\text{NO}_5\text{S}$: C, 43.94; H, 4.54; N, 3.94; S, 9.02. Found: C, 43.53; H, 4.45; N, 4.20; S, 9.13.

(3-(allyloxy)-6-methylpyridin-2-yl)methanol (**10**)

To a 200-mL round-bottomed flask was added 3-hydroxy-6-methyl-2-pyridinemethanol (3.00 g, 21.5 mmol), K_2CO_3 (5.94 g, 43.0 mmol) and acetone (100 mL). The suspension was stirred vigorously and allyl bromide (2.33 mL, 3.25 g, 26.9 mmol) was added dropwise. A reflux condenser was attached on the flask, and the mixture was heated to reflux. After 3.5 h at reflux, TLC analysis indicated the starting material had been consumed. The solid K_2CO_3 was removed by filtration and the acetone was evaporated under reduced pressure. The solid thus obtained was dissolved in ethyl acetate and water was added. The aqueous layer was extracted with ethyl acetate (2 $\times$). After drying the combined organic layers and removing solvent, **10** (3.65 g, 96%) was obtained as tan crystals.

Mp 51.9–52.8 °C

IR (dep. CDCl_3): 3131, 2920, 2872, 1651, 1481, 1460, 1279, 1140, 1015, 995, 928, 814 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 7.04 (d, J = 8.3, 1H), 6.99 (d, J = 8.3, 1H), 6.01 (ddt, J = 17.1, 10.5, 5.1, 1H), 5.39 (app. dq, J = 17.1, 1.5, 1H), 5.30 (app. dq, J = 10.5, 1.5, 1H), 4.73 (s, 2H), 4.55 (dt, J = 5.1, 1.5, 2H), 2.49 (s, 3H).

^{13}C NMR (CDCl_3 , 125 MHz): δ 149.1, 148.1, 147.2, 132.5, 121.6, 118.6, 117.2, 68.7, 59.8, 23.0.

Anal. Calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.84; H, 7.29; N, 8.26.

3-(allyloxy)-2-(bromomethyl)-6-methylpyridine (11)

PPh₃ (5.39 g, 20.5 mmol) and **10** (3.53 g, 19.5 mmol) were placed in a 100-mL two-necked round-bottomed flask equipped with a solid addition funnel. *N*-bromosuccinimide (NBS) (3.55 g, 19.9 mmol) was placed in the solid addition funnel and an argon atmosphere was established. The solution was cooled to −40 °C (dry ice/acetonitrile) and the NBS was added in small portions over 15 min. After the addition, the cooling bath was removed and the solution was slowly warmed to room temperature. After 2 h, TLC analysis indicated the starting material had been consumed. The solution was diluted with ether and washed with sat. NaHSO₃, sat. NaHCO₃ (3×), and water. After drying the organic layer and removing solvent, bromide **11** was obtained as a bright pink solid (4.08 g, 87%)

Mp 40.0–40.4 °C

IR (KBr): 2904, 1650, 1574, 1472), 1444, 1407, 1382, 1283, 1258, 1207, 1174, 1154, 989, 927, 821 cm^{−1}.

¹H NMR (CDCl₃, 500 MHz): δ 7.08 (d, *J* = 8.5, 1H), 7.03 (d, *J* = 8.5, 1H), 6.04 (ddt, *J* = 17.1, 10.5, 5.1, 1H), 5.45 (app. dq, *J* = 17.1, 1.5, 1H), 5.31 (app. dq, *J* = 10.5, 1.5, 1H), 4.63 (s, 2H), 4.60 (dt, *J* = 5.1, 1.5, 2H), 2.47 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 150.5, 149.4, 145.0, 132.2, 123.8, 120.0, 117.6, 68.8, 29.6, 23.1.

Anal. Calcd for C₁₀H₁₂NOBr: C, 49.61; H, 5.00; N, 5.79. Found: C, 49.88; H, 5.10; N, 5.77.

3-(allyloxy)-6-methyl-2-(phenylsulfonylmethyl)-pyridine (12)

Sodium benzenesulfinate (2.61 g, 15.8 mmol) was added to a 100-mL round-bottomed flask equipped with a reflux condenser. Anhydrous DMSO (75 mL) was used to dissolve **11** (3.48 g, 14.4 mmol) and this solution was then added to the flask with a syringe. The mixture was heated gently for 1.5 h at which time TLC analysis showed complete consumption of the starting material. The hot solution was poured over ice at which time the product began to crystallize. Vacuum filtration of the mixture through a Büchner funnel provided crude **12** which was recrystallized from hexanes:CHCl₃ to give white needles (4.21 g, 96%)

Mp 126.5–128.9 °C

IR (dep. CHCl₃): 2973, 2909, 1573, 1473, 1446, 1303, 1277, 1265, 1144, 1080, 999, 945, 829, 737, 687 cm^{−1}.

¹H NMR (CDCl₃, 500 MHz): δ 7.70 (m, 2H), 7.59 (tt, *J* = 7.7, 1.1, 1H), 7.45 (m, 2H), 7.01 (s, 2H), 5.91 (ddt, *J* = 17.1, 10.5, 5.1, 1H), 5.35 (app. dq, *J* = 17.1, 1.5 1H), 5.28 (app. dq, *J* = 10.5, 1.5, 1H), 4.69 (s, 2H), 4.36 (dt, *J* = 5.1, 1.5, 2H), 2.34 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 151.8, 149.9, 139.4, 137.8, 133.2, 132.4, 128.7, 128.5, 123.8, 119.9, 118.0, 69.2, 59.0, 23.2.

Anal. Calcd for C₁₆H₁₇NO₃S: C, 63.34; H, 5.65; N, 4.62; S, 10.57. Found: C, 62.99; H, 5.47; N, 4.51; S, 10.20.

6-methyl-2-(phenylsulfonylmethyl)pyridin-3-ol (13)

To a 25-mL two-necked round-bottomed flask was added pyridine sulfone **12** (2.87 g, 9.40 mmol) and Pd(PPh₃)₄ (0.105 mg, 0.098 mmol, 1 mol%). An argon atmosphere was established and methanol (65 mL) was added via syringe. The resulting pale yellow solution

was stirred for 5 min before K_2CO_3 (4.01 g, 29.4 mmol) was added. A cloudy white solution resulted. After stirring 3 h, TLC analysis indicated complete consumption of the starting material. The methanol was removed by evaporation under reduced pressure. The residue was then treated with pH 5.2 sodium acetate/acetic acid buffer, extracted with ethyl acetate (3 $\times$), and the organic layers dried over Na_2SO_4 . After removing solvent, recrystallization of the residue from $CHCl_3$:ethanol and ethyl acetate: ethanol yielded **13** as colorless plates (1.95 g, 78%)

Mp 196.9–199.5 °C

IR (diamond ATR): 1575(m), 1492(s), 1449(m), 1302(s), 1283(s), 1264(s), 1141(s), 1081(s), 884(m), 839(s), 785(s), 729(s), 722(s), 682(s) cm^{-1} .

1H NMR ($CDCl_3$, 500 MHz): δ 7.76 (m, 2H), 7.64 (tt, J = 7.3, 1.4, 1H), 7.50 (m, 2H), 7.25 (d, J = 8.3, 1H), 7.02 (d, J = 8.3, 1H), 4.69 (s, 2H), 2.27 (s, 3H).

^{13}C NMR ($CDCl_3$, 125 MHz): 151.3, 150.7, 137.2, 135.7, 134.2, 129.1, 128.4, 127.3, 124.9, 62.0, 23.1.

Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 5.32; S, 12.18. Found: C, 58.92; H, 4.96; N, 5.19; S, 12.03.

6-methyl-2-(phenylsulfonylmethyl)pyridin-3-yl trifluoromethanesulfonate (**4e**)

The procedure was the same as that described for the preparation of **4d**. Sulfone **13** (910 mg, 3.00 mmol), Comins' triflimide (1.21 g, 3.15 mmol), CH_2Cl_2 (15 mL), and Et_3N (0.44 mL, 320 mg, 3.2 mmol) provided triflate **4e** as a slightly yellow solid (1.10 g, 93%)

Mp 117.2–118.6 °C

IR (KBr): 3085, 3010, 2951, 1595, 1465, 1428, 1316, 1253, 1166, 1148, 903, 872, 841, 745 cm^{-1} .

1H NMR ($CDCl_3$, 500 MHz): δ 7.77 (m, 2H), 7.66 (tt, J = 7.6, 1.4, 1H), 7.53 (d, J = 8.8, 1H), 7.52 (m, 2H), 7.21 (d, J = 8.8, 1H), 4.64 (s, 2H), 2.45 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 158.7, 144.1, 141.2, 138.6, 134.0, 129.5, 129.0, 128.6, 124.8, 118.3 (q, J = 320, CF_3), 59.3, 23.8.

HRMS-ESI: m/z [$M+H$] calcd for $C_{14}H_{13}F_3NO_5S_2$: 396.0187; found, 396.0207.

6-methyl-2-(phenylthiomethyl)pyridin-3-yl trifluoromethanesulfonate (**4f**)

Diol **8** (1.00 g, 7.20 mmol) was added to a 50-mL two-necked round-bottomed flask equipped with a magnetic stirbar and water-cooled reflux condenser. Concentrated HBr (20 mL) was added followed by thiophenol (0.81 mL, 870 mg, 7.90 mmol). An immediate color change from red/brown to yellow was observed. The mixture was refluxed for 5 h at which time the solution was allowed to cool to room temperature and extracted with ether (3 $\times$). The aqueous layer was brought to pH 8 by the slow, careful addition of solid K_2CO_3 . This solution was then extracted again with ether (3 $\times$). The combined organic layers were washed with water, dried, and concentrated to provide the phenylsulfide as a white solid (1.1 g, 67%) that was used in the next step without further purification.

1H NMR ($CDCl_3$, 500 MHz): δ 7.38 (m, 2H), 7.24 (m, 2H), 7.18 (m, 1H), 7.04 (d, J = 8.3, 1H), 6.93 (d, J = 8.3, 1H), 5.30 (s, 2H), 4.36 (s, 1H), and 2.41 (s, 3H).

The procedure was the same as that described for the preparation of **4d**. The phenylsulfide obtained above (902 mg, 3.90 mmol), Comins' triflimide (1.61 g, 4.10 mmol), CH₂Cl₂ (25 mL), and Et₃N (0.57 mL, 410 mg, 4.1 mmol) provided pyridyl triflate **4f** as a yellow liquid (1.40 g, 100%).

IR (diamond ATR): 3062, 2993, 2928, 1582, 1481(m), 1459, 1422, 1250, 1211, 1135, 1070, 884, 854, 826, 738, 690 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.45 (d, J = 8.3, 1H), 7.40 (m, 2H), 7.3–7.2 (m, 3H), 7.10 (d, J = 8.3, 1H), 4.28 (s, 2H), 2.53 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 158.3, 149.7, 142.7, 134.6, 131.3, 129.2, 128.8, 127.1, 123.2, 118.4 (q, J = 314), 36.2, 23.9.

HRMS-ESI: m/z [M+H] calcd for C₁₄H₁₃F₃NO₃S₂: 364.0289; found, 364.0283.

Anal. Calcd for C₁₄H₁₂F₃NO₃S₂: C, 46.27; H, 3.33; N, 3.85; S, 17.65. Found: C, 46.12; H, 3.31; N, 4.14; S, 17.71.

4,4,5,5-tetramethyl-2-(6-methylhepta-1,5-dien-2-yl)-1,3,2-dioxaborolane (**15a**)

A 25-mL three-necked round-bottomed flask equipped with a reflux condenser, magnetic stirbar, and thermometer was charged with PdCl₂(PPh₃)₂ (45 mg, 0.060 mmol, 3 mol %), PPh₃ (28 mg, 0.12 mmol), bis(pinacolato)diboron (555 mg, 2.18 mmol), and KOPh (401 mg, 3.03 mmol). The flask was evacuated and flushed with argon (6×). Dry toluene (12 mL) was then added with a syringe followed by alkenyl triflate **14a** (521 mg, 2.02 mmol). The solution was heated to 50 °C using a heating mantle. After 2 h, TLC analysis indicated complete consumption of triflate **14a**, so the reaction was cooled to room temperature and water (10 mL) was added. The resulting layers were separated and the aqueous layer was extracted with hexanes (3×). After drying the combined organic layers and removing solvent, the residue was purified by MPLC (12:1 hexanes: ethyl acetate) to yield boronate ester **15a** as a colorless liquid (350 mg, 74%).

IR (neat): 2979, 2926, 2859, 1616, 1437, 1370, 1308, 1144, 911, 734 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 5.76 (d, J = 3.4, 1H), 5.60 (br s, 1H), 5.13 (m, 1H), 2.17 (m, 2H), 2.10 (m, 2H), 1.68 (s, 3H), 1.60 (s, 3H), 1.27 (s, 12H, (CH₃)₄).

¹³C NMR (CDCl₃, 125 MHz): δ 145.8, 131.2, 128.9, 124.3, 83.2, 35.5, 27.9, 25.6, 24.8, 24.74, 24.70, 24.67, 24.6, 17.6.

HRMS-ESI: m/z [M+Na] calcd for C₁₄H₂₆BO₂Na: 259.1845; found, 259.1842.

2-(hexa-1,5-dien-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**15b**)

A 50 mL round-bottomed flask, equipped with thermometer and septum, was charged with bromide **14c** (1.61 g, 10.0 mmol) diluted in THF (15 mL). The flask was then cooled to –78 °C. *tert*-Butyllithium (11.8 mL 1.7 M in pentane, 20.1 mmol) was added dropwise, keeping the reaction temperature below –70 °C. The mixture was stirred for 30 min before adding 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.0 mL, 2.80 g, 15.0 mmol) diluted in THF (10 mL) dropwise. The reaction was warmed slowly to room temperature. Dilute HCl (1.0 M, 10.8 mL) was added while stirring, and the mixture was extracted with dichloromethane (3 × 15 mL). The combined organic extract was dried over magnesium sulfate, the solution was gravity filtered and the filtrate concentrated *in vacuo*. The crude

product was filtered through a plug of Celite eluting with hexanes to yield **15b** as clear colorless oil after solvent removal (2.081 g, 10.0 mmol, 100 %).

IR (NaCl; neat): 2979 (s), 2933 (s), 1638 (m), 1611 (m), 1427 (m), 1370 (s), 1309 (s), 1143 (s) cm^{-1} .

^1H NMR (500 MHz, CDCl_3) δ : 5.83 (ddt, $J = 17.2, 10.2, 6.5$, 1H), 5.79 (d, $J = 3.9$, 1H), 5.61 (br s, 1H), 5.02 (app dq, $J = 17.2, 1.5$, 1H), 4.94 (app dq, $J = 10.2, 1.5$, 1H), 2.21 (m, 4H), 1.27 (s, 12H).

^{13}C NMR (125 MHz, CDCl_3) δ : 141.0 (weak, broad), 138.8, 129.3, 114.4, 83.3, 34.8, 33.5, 24.8.

HRMS-FAB: m/z [M-H] calcd for $\text{C}_{12}\text{H}_{20}\text{BO}_2$: 207.1556; found, 207.1559.

2-(hex-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**15c**)

A 250 mL round-bottomed flask equipped with thermometer and stir bar was brought under argon atmosphere and then charged with diethyl ether (39 mL) and *tert*-butyllithium (11.8 mL, 1.7 M in pentane, 20.0 mmol). The flask was cooled with a dry ice/isopropanol slurry and after the mixture reached -78°C , bromide **14d** (1.630 g, 10.0 mmol) was diluted in diethyl ether (15 mL) and added dropwise. The mixture was stirred 45 min before 2-Isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (6.16 mL, 5.617 g, 30.0 mmol) diluted in diethyl ether (10 mL) was added dropwise. The reaction was then slowly warmed over the next 3 hours. Dilute HCl (1.0 M, 100 mL) was added and the mixture was stirred for 30 min. The aqueous layer was extracted with diethyl ether (3×50 mL) and the combined organic layers were dried over sodium sulfate. The solution was gravity filtered and the filtrate was concentrated *in vacuo*. The crude product was filtered through a plug of Celite eluting with hexanes to remove the white solid and **15c** was obtained as a clear colorless oil after solvent removal (2.101 g, 10.0 mmol, 100 %).

IR (NaCl; neat): 2928 (s), 1615 (w), 1426 (w), 1370 (s), 1308 (s), 1214 (w), 1144 (s) cm^{-1} .

^1H NMR (300 MHz, CDCl_3) δ : 5.75 (d, $J = 6.0$, 1H), 5.59 (br s, 1H), 2.14 (t, $J = 7.0$, 2H), 1.4–1.2 (4H, m), 1.26 (12H, s), 0.89 (t, $J = 7.0$, 3H).

^{13}C NMR (75 MHz, CDCl_3) δ : 141.1, 128.6, 83.2, 35.0, 31.4, 24.7, 22.3, 14.0.

HRMS-FAB: m/z calcd for $\text{C}_{12}\text{H}_{23}\text{BO}_2$: 210.1791; found, 210.1793.

Typical procedure for cross-coupling of 3-pyridyl triflates and alkenyl boronates

3-(Hexa-1,5-dien-2-yl)pyridine (**16**)

A large screw top culture tube equipped with a stir bar and charged with $\text{Pd}(\text{PPh}_3)_4$ (115 mg, 0.10 mmol) and K_3PO_4 (636 mg, 3.00 mmol) and brought under argon atmosphere. Dioxane (18 mL) was added followed by **4a** (227 mg, 1.00 mmol) and **15b** (260 mg, 1.25 mmol). The septum was replaced with a screw cap and the tube was placed in a hot oil bath (90 – 95°C). The mixture was stirred and heated overnight before water (10 mL) was added and the aqueous layer was extracted with diethyl ether (3×10 mL). The combined organic layers were dried over sodium sulfate and the solution was gravity filtered and concentrated *in vacuo*. Flash chromatography (3:1 hexanes: ethyl acetate) of the residue provided **16** (89 mg, 0.56 mmol, 56 %) as clear, yellow oil.

IR (Diamond ATR; dep. CH₂Cl₂): 3079, 2925, 1639, 1629, 1585, 1565, 1022, 997, 950, 814, 718 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ: 8.65 (d, *J* = 2.4, 1H), 8.51 (dd, *J* = 4.4, 1.4, 1H), 7.67 (dt, *J* = 2.4, 1.4, 1H), 7.25 (dd, *J* = 4.4, 2.4, 1H), 5.82 (ddt, *J* = 17.0, 10.3, 6.5, 1H), 5.34 (d, *J* = 2.4, 1H), 5.17 (d, *J* = 2.4, 1H), 4.99 (m, 2H), 2.59 (t, *J* = 7.3, 2H), and 2.22 (td, *J* = 7.3, 6.5, 2H).

¹³C NMR (125 MHz, CDCl₃) δ: 148.6, 147.6, 144.9, 137.6, 136.6, 133.4, 123.1, 115.1, 114.3, 34.4, 32.2.

HRMS-ESI: *m/z* [M+H] calcd for C₁₁H₁₅N: 160.1126; found, 160.1121.

3-(hex-1-en-2-yl)pyridine (17)

IR (NaCl; neat): 3083, 3033, 2958, 2931, 2861, 1628, 1585, 1566, 1467, 1022, 898, 815, 719 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ: 8.65 (dd, *J* = 2.5 and 1.0, 1H), 8.50 (dd, *J* = 4.9 and 1.5, 1H), 7.67 (dt, *J* = 7.8 and 1.5, 1H), 7.24 (ddd, *J* = 7.8, 4.9 and 1.0, 1H), 5.30 (br s, 1H), 5.15 (app q, *J* = 1.4, 1H), 2.32 (t, *J* = 6.8, 2H), 1.4 (m, 2H), 1.33 (m, 2H), 0.88 (t, *J* = 7.3, 3H).

¹³C NMR (125 MHz, CDCl₃) δ: 148.4, 147.6, 145.7, 136.8, 133.3, 123.1, 113.8, 34.8, 30.2, 22.3, 13.9.

HRMS-ESI: *m/z* [M+H] calcd for C₁₁H₁₆N: 162.1283; found: 162.1277.

Anal. Calcd for C₁₁H₁₅N: C, 81.94; H, 9.38; N, 8.69. Found: C, 82.09; H, 9.07; N, 8.33.

2-methyl-3-(6-methylhepta-1,5-dien-2-yl)pyridine (18)

IR (Diamond ATR; dep. CDCl₃): 2967, 2856, 1565, 1558, 1433, 1376, 903, 807, 740 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ: 8.40 (dd, *J* = 4.8, 1.8, 1H), 7.35 (dd, *J* = 7.5, 1.8, 1H), 7.08 (dd, *J* = 7.5, 4.8, 1H), 5.25 (d, *J* = 1.2, 1H), 5.09 (br t, *J* = 7.5, 1H), 4.92 (d, *J* = 1.2, 1H), 2.52 (s, 3H), 2.37 (t, *J* = 7.0, 2H), 2.07 (dt, *J* = 7.5, 2H), 1.67 (s, 3H), 1.53 (s, 3H).

¹³C NMR (125 MHz, CDCl₃) δ: 155.4, 147.9, 147.4, 137.8, 135.9, 132.1, 123.4, 120.6, 115.1, 37.3, 26.2, 25.6, 22.7, 17.7.

Anal. Calcd for C₁₄H₁₉N: C, 83.53; H, 9.51; N, 6.96. Found: C, 83.78; H, 9.67; N, 6.67.

3-(hexa-1,5-dien-2-yl)-2-methylpyridine (19)

IR (NaCl; neat): 2927, 1712, 1639, 1566, 1432, 1399, 1227, 1205, 1130, 1086, 996, 906, 807, 740 cm⁻¹.

¹H NMR (500 MHz, CDCl₃) δ: 8.41 (dd, *J* = 1.9, 4.6, 1H), 7.36 (dd, *J* = 7.5, 1.9, 1H), 7.08 (dd, *J* = 7.5, 4.6, 1H), 5.80 (m, 1H), 5.25 (d, *J* = 1.4, 1H), 5.03 (dd, *J* = 1.4, 17.1, 1H), 4.99 (dd, *J* = 10.5, 1.4, 1H), 4.96 (d, *J* = 1.4, 1H), 2.52 (s, 3H), 2.44 (t, *J* = 7.5, 2H), 2.15 (td, *J* = 7.5, 6.5, 2H).

¹³C NMR (125 MHz, CDCl₃) δ: 155.4, 147.6, 147.5, 137.8, 136.0, 120.7, 115.4, 115.1, 36.7, 31.8, 22.8.

Anal. Calcd for C₁₂H₁₅N: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.22; H, 8.79; N, 7.82.

3-(hex-1-en-2-yl)-2-methylpyridine (20)

IR (NaCl; neat): 3077, 3045, 2958, 2931, 2861, 1636, 1565, 1458, 1432, 1218, 1140, 1106, 902, 809, 742 cm^{-1} .

^1H NMR (500 MHz, CDCl_3) δ : 8.40 (dd, $J = 4.9$ and 1.5 , 1H), 7.35 (dd, $J = 7.8$ and 1.5 , 1H), 7.08 (dd, $J = 7.8$ and 4.9 , 1H), 5.22 (app q, $J = 1.5$, 1H), 4.90 (m, 1H), 2.52 (s, 3H), 2.33 (t, $J = 6.8$, 2H), 1.35 (m, 4H), 0.88 (t, $J = 7.3$, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ : 155.4, 148.4, 147.4, 138.2, 135.9, 120.6, 114.8, 37.2, 29.9, 22.8, 22.4, 13.9.

Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.08; H, 9.67; N, 7.81.

5-(hexa-1,5-dien-2-yl)-2-methylpyridine (21)

IR (NaCl; dep. CH_2Cl_2): 2918, 1627, 1437, 1377, 1120, 909, 731 cm^{-1} .

^1H NMR (500 MHz, CDCl_3) δ : 8.54 (d, $J = 2.0$, 1H), 7.56 (dd, $J = 8.5$, 2.5 , 1H), 7.12 (dd, $J = 8.5$, 2.5 , 1H), 5.81 (ddt, $J = 17.0$, 10.5 , 6.5 , 1H), 5.29 (d, $J = 1.1$, 1H), 5.12 (d, $J = 1.1$, 1H), 4.98 (m, 2H), 2.57 (t, $J = 1.1$ -2H), 2.56 (s, 3H), 2.20 (dt, $J = 7.5$, 6.5 , 2H).

^{13}C NMR (125 MHz, CDCl_3) δ : 157.1, 146.6, 144.8, 137.7, 133.9, 122.8, 115.1, 113.5, 34.4, 32.2, 29.7, 23.9.

HRMS-ESI: m/z [$\text{M}+\text{H}$] calcd for $\text{C}_{12}\text{H}_{16}\text{N}$: 174.1283. found: 174.1277.

5-(hex-1-en-2-yl)-2-methylpyridine (22)

IR (NaCl; neat): 3082, 3013, 2956, 2929, 2860, 1626, 1596, 1556, 1488, 1458, 1378, 1301, 1245, 1140, 1023, 892, 835, 742 cm^{-1} .

^1H NMR (500 MHz, CDCl_3) δ : 8.54 (d, $J = 1.5$, 1H), 7.58 (dd, $J = 8.0$ and 1.5 , 1H), 7.11 (d, $J = 8.0$, 1H), 5.27 (br s, $J = 1.5$, 1H), 5.10 (m, 1H), 2.55 (s, 3H), 2.48 (t, $J = 6.8$, 2H), 1.42 (m, 2H), 1.35 (m, 2H), 0.88 (t, $J = 7.3$, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ : 157.1, 146.8, 145.7, 133.8, 133.7, 122.7, 112.9, 34.8, 30.2, 24.1, 22.3, 13.9.

Anal. Calcd for $\text{C}_{12}\text{H}_{17}\text{N}$: C, 82.23; H, 9.78; N, 7.99. Found: C, 81.89; H, 9.64; N, 7.65.

(6-methyl-3-(6-methylhepta-1,5-dien-2-yl)pyridin-2-yl)methyl pivaloate (23)

IR (Diamond ATR; dep. CDCl_3): 2959, 2930, 2873, 1635, 1731, 1464, 1238, 1151 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 7.36 (d, $J = 7.8$, 1H), 7.08 (d, $J = 7.8$, 1H), 5.24 (d, $J = 1.3$, 1H), 5.12 (s, 2H), 5.07 (app. t, $J = 7.0$, 1H), 4.95 (d, $J = 1.3$, 1H), 2.54 (s, 3H), 2.37 (t, $J = 7.6$, 2H), 2.06 (app. q, $J = 7.6$, 2H), 1.67 (s, 3H), 1.53 (s, 3H), 1.22 (s, 9H).

^{13}C NMR (CDCl_3 , 125 MHz): δ 178.1, 156.6, 151.1, 146.3, 136.6, 135.6, 132.2, 123.4, 122.3, 115.8, 65.6, 38.7, 37.7, 27.2, 26.1, 25.6, 24.1, 17.7.

Anal. Calcd for $\text{C}_{20}\text{H}_{29}\text{NO}_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 76.08; H, 9.57; N, 4.71.

(3-hexa-1,5-dien-2-yl)-6-methylpyridin-2-yl)methyl pivalate (24)

IR (NaCl; neat): 2974 2933 2872 1731, 1593, 1462, 1428, 1397, 1367, 1283, 1218, 1152, 911 cm^{-1} .

^1H NMR (500 MHz, CDCl_3) δ : 7.36 (d, $J = 7.7$, 1H), 7.08 (d, $J = 7.7$, 1H), 5.78 (m, 1H), 5.25 (d, $J = 3.0$, 1H), 5.13 (s, 2H) 5.01 (d, $J = 3.0$, 1H), 4.99 (m, 2H), 2.55 (s, 3H), 2.42 (t, $J = 7.1$, 2H), 2.15 (m, 2H), 1.22 (s, 9H).

^{13}C NMR (125 MHz, CDCl_3) δ : 178.2, 156.8, 151.2, 145.9, 137.6, 136.7, 134.8, 122.4, 117.9, 116.1, 65.7, 38.7, 37.1, 31.7, 27.3, 24.2.

Anal. Calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_2$: C, 75.22; H, 8.77; N, 4.87. Found: C, 75.37; H, 8.87; N, 4.70.

(3-(hex-1-en-2-yl)-6-methylpyridin-2-yl) methyl pivalate (25)

IR (NaCl; neat): 2959, 2930, 2873, 1731, 1464, 1238, 1151 cm^{-1} .

^1H NMR (500 MHz, CDCl_3) δ : 7.36 (d, $J = 7.8$, 1H), 7.08 (d, $J = 7.8$, 1H), 5.21 (d, $J = 1.4$, 1H), 5.12 (s, 2H), 4.92 (d, $J = 1.4$, 1H), 2.55 (s, 3H), 2.32 (t, $J = 6.8$, 2H) 1.33 (m, 2H), 1.22 (s, 9H), 0.88 (t, $J = 7.3$, 3H).

^{13}C NMR (125 MHz, CDCl_3) δ : 178.2, 156.6, 151.1, 146.7, 136.7, 135.9, 122.3, 115.5, 65.7, 38.7, 37.6, 29.8, 27.3, 24.1, 22.4, 13.9.

Anal. Calcd for $\text{C}_{18}\text{H}_{27}\text{NO}_2$: C, 74.70; H, 9.40; N, 4.94. Found: C, 74.57; H, 8.98; N, 5.22.

($\pm$)-4-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)but-1-en-2-yl trifluoromethanesulfonate (29)

Ketone acetone **2818** (1.003 g, 5.0 mmol) in THF (30 mL) was added dropwise to a cold (-78°C) solution of LDA [prepared from diisopropylamine (0.88 mL, 0.637 g, 6.3 mmol) and *n*-BuLi (2.5 M in hexanes, 2.4 mL, 6.0 mmol) in THF (15 mL)] such that the temperature of the reaction mixture was kept below -60°C . After 30 min, Comins' triflimide (2.376 g, 6.0 mmol) dissolved in THF (10 mL) was added quickly dropwise (the temperature of the reaction mixture rose to -58°C during the addition). The mixture was warmed slowly overnight. At that point, TLC analysis indicated the presence of unreacted ketone, so the mixture was re-cooled to -78°C and additional LDA (3.0 mmol) was added dropwise. After 80 min, additional Comins' triflimide (0.894 g, 2.3 mmol) as added as a solution in THF (5 mL). The mixture was slowly warmed to room temperature before quenching with sat. NaHCO_3 and extracting with ether (3 $\times$). The combined ether layers were washed with brine and dried over MgSO_4 . Solvent removal and flash chromatography (gradient elution 9:1 hexanes: ethyl acetate to 1:1 hexanes: ethyl acetate) of the residue provided **29** as a colorless oil (0.567 g, 34%).

IR (neat): 2938, 2936, 1670, 1419, 1371, 1214, 1141, 1004, 951, 896 857 cm^{-1} .

^1H NMR (CDCl_3 , 500 MHz): δ 5.15 (d, $J = 3.6$, 1H), 5.01 (d, $J = 3.6$, 1H), 3.69 (dd, $J = 10.3$, 2.9, 1H), 2.64 (ddd, $J = 16.1$, 10.0, 4.9, 1H), 2.44 (ddd, $J = 16.1$, 9.3, 7.0, 1H), 1.71 (dddd, $J = 13.0$, 10.3, 9.3, 4.9, 1H), 1.65 (dddd, $J = 13.0$, 10.0, 7.0, 2.9, 1H), 1.42 (s, 3H), 1.34 (s, 3H), 1.26 (s, 3H), 1.11 (s, 3H).

^{13}C NMR (CDCl_3 , 75 MHz): δ 156.0, 118.4 (q, $J = 320$, CF_3), 106.9, 104.7, 81.6, 80.0, 31.5, 28.4, 26.8, 25.9, 25.8, 22.9.

Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{F}_3\text{O}_5\text{S}$: C, 43.37; H, 5.76; S, 9.65. Found: C, 43.04; H, 5.45; S, 9.26.

($\pm$)-4,4,5,5-tetramethyl-2-(4-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)but-1-en-2-yl)-1,3,2-dioxaborolane (30)

To a large culture tube was added bis(pinacolato)diboron (616 mg, 2.42 mmol), $\text{PdCl}_2(\text{PPh}_3)$ (49 mg, 0.070 mmol), PPh_3 (37.5 mg, 0.132 mmol), and KOPh (443 mg, 3.35

mmol). An argon atmosphere was established, before toluene (15 mL) and triflate ($\pm$)-**29** (730 mg, 2.20 mmol) were added. The solution was heated to 60 °C in an oil bath and stirred for 1.5 hr at which time TLC analysis indicated complete consumption of the starting material. The reaction was quenched with water and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2 $\times$). The combined organic layers were washed with sat. NaHCO₃. After drying and solvent removal, the crude product was purified by flash chromatography (9:1 hexanes: ethyl acetate) to give ($\pm$)-**30** as a colorless oil (496 mg, 73%).

IR (neat): 2979, 2934, 2866, 1617, 1370, 1310, 1216, 1143, 1002, 860 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 5.82 (d, J = 2.9, 1H), 5.66 (br. m, 1H), 3.70 (dd, J = 9.3, 3.9, 1H), 2.39 (ddd, J = 14.6, 9.7, 4.8, 1H), 2.20 (ddd, J = 14.6, 9.1, 6.5, 1H), 1.67 (m, 1H), 1.55 (m, 1H), 1.42 (s, 3H), 1.32 (s, 3H), 1.27 (s, 12H), 1.24 (s, 3H), 1.10 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 141(br), 129.5, 106.3, 83.3, 82.4, 80.0, 32.3, 28.5, 28.4, 26.8, 26.0, 24.7, 24.6, 22.8.

HRMS-ESI: m/z [M+Na] calcd for C₁₇H₃₁BO₄Na: 333.2213; found, 333.2211.

($\pm$)-{6-Methyl-3-[4-(2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)but-1-en-2-yl]pyridin-2-yl}methyl pivaloate (31**)**

The procedure used for the preparation of **16** was followed. Pyridyl triflate **4d** (343 mg, 0.958 mmol), Pd(PPh₃)₄ (110 mg, 0.0958 mmol, 10 mol %), and anhydrous K₃PO₄ (624 mg, 2.87 mmol) were reacted with alkenyl boronate ($\pm$)-**30** (357 mg, 1.15 mmol) in anhydrous 1,4-dioxane (8 mL) at 100 °C. Workup and purification by flash chromatography yielded **31** as a pale yellow oil (321 mg, 86 %).

IR (neat): 2979, 2934, 2870, 1731, 1593, 1465, 1370, 1282, 1217, 1152, 1003 cm⁻¹.

¹H NMR (CDCl₃, 500 MHz): δ 7.38 (d, J = 7.8, 1H), 7.09 (d, J = 7.8, 1H), 5.28 (br. s, 1H), 5.13 (s, 2H), 4.99 (br. s, 1H), 3.67 (dd, J = 9.8, 2.9, 1H), 2.61 (ddd, J = 15.6, 10.5, 4.8, 1H), 2.55 (s, 3H), 2.39 (ddd, J = 15.6, 10.3, 5.8, 1H), 1.64 (dddd, J = 14.2, 10.3, 9.8, 4.8, 1H), 1.47 (dddd, J = 14.2, 10.5, 5.8, 2.9, 1H), 1.40 (s, 3H), 1.30 (s, 3H), 1.22 (s, 9H), 1.21 (s, 3H), 1.06 (s, 3H).

¹³C NMR (CDCl₃, 125 MHz): δ 178.1, 156.8, 151.1, 145.8, 136.6, 135.4, 122.3, 116.0, 106.6, 82.6, 80.0, 65.6, 38.7, 35.0, 28.5, 27.3, 27.2, 26.8, 25.9, 24.1, 22.9.

Anal. Calcd for C₂₃H₃₅NO₄: C, 70.92; H, 9.06; N, 3.60. Found: C, 70.54; H, 8.85; N, 3.87.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work was supported by the National Cancer Institute, National Institutes of Health (R15 CA122084).

References

1. Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* 1979. p. 3437
2. Selected reviews: (a) Miyaura N. *Bull Chem Soc Jpn.* 2008; 81:1535. (b) Suzuki A. *Chem Commun.* 2005:4759. (c) Miyaura N, Suzuki A. *Chem Rev.* 1995; 95:2457.

3. Hsieh TJ, Chang FR, Chia YC, Chen CY, Chiu HF, Wu YC. *J Nat Prod.* 2001; 64:616. [PubMed: 11374955]
4. Total synthesis of (+)-cananodine: Craig D, Henry GD. *Eur J Org Chem.* 2006:3558.
5. (a) Sakemi S, Totton LE, Sun HH. *J Nat Prod.* 1990; 53:995. (b) Wang Y, Dong X, Larock RC. *J Org Chem.* 2003; 68:3090. [PubMed: 12688777] (c) Corbet M, de Greef M, Zard SZ. *Org Lett.* 2008; 10:253. [PubMed: 18161980]
6. (a) Torrado A, López S, Alvarez R, de Lera AR. *Synthesis.* 1995:285. (b) Ohe T, Miyaura N, Suzuki A. *J Org Chem.* 1993; 58:2201.
7. (a) Ishikura M, Kamada M, Ohta T, Terashim M. *Heterocycles.* 1984; 22:2475. (b) Gøsig TM, Sjøberg LS, Lindhardt AT, Jensen KL, Skrydstrup T. *J Org Chem.* 2008; 73:3404. [PubMed: 18380442] (c) Chelucci G, Badino S. *Tetrahedron Lett.* 2008; 49:2738. (d) Chelucci G, Badino S, Pinna GA, Sechi B. *Tetrahedron Lett.* 2008; 49:2839. (e) Chelucci G, Capitta F, Badino S, Pinna GA. *Tetrahedron Lett.* 2007; 48:6514.
8. Prieto M, Zurita E, Rosa E, Munoz L, Lloyd-Williams P, Giralt E. *J Org Chem.* 2004; 69:6812. [PubMed: 15387606]
9. Comins DL, Dehghani A, Foti CJ, Joseph SP. *Org Synth Coll.* 1998; 9:165.
10. (a) Draper TL, Bailey TR. *Synlett.* 1995:157. (b) Guthrie RW, Kaplan GL, Mennona FA, Tilley JW, Kierstead RW, Mullin JG, LeMahieu RA, Zawoiski S, O'Donnell M, Crowley H, Yaremk B, Welton AF. *J Med Chem.* 1989; 32:1820. [PubMed: 2754709]
11. (a) Broutin P-E, era I, Campaniello M, Leroux F, Colobert F. *Org Lett.* 2004; 6:4419. [PubMed: 15548040] (b) Kahnpure SP, Garvey DS. *Tetrahedron Lett.* 2004; 45:5283. (c) Ishiyama T, Ishida K, Miyaura N. *Tetrahedron.* 2001; 57:9813. (d) Murata M, Oyama T, Watanabe S, Masuda Y. *J Org Chem.* 2000; 65:164. [PubMed: 10813911] (e) Ishiyama T, Itoh Y, Kitano T, Miyaura N. *Tetrahedron Lett.* 1997; 38:3447. (f) Iimura S, Wu W. *Tetrahedron Lett.* 2010; 51:1353.
12. (a) Kamikubo T, Ogasawara K. *Chem Commun.* 1996:1679. (b) Miller MW, Johnson CR. *J Org Chem.* 1997; 62:1582. (c) Graham AE, Taylor RJK. *J Chem Soc, Perkin Trans 1.* 1997:1087. (d) Vyvyan JR, Loitz C, Looper RE, Mattingly CS, Peterson EA, Staben ST. *J Org Chem.* 2004; 69:2461. [PubMed: 15049646]
13. (a) Takagi J, Takahashi K, Ishiyama T, Miyaura N. *J Am Chem Soc.* 2002; 124:8001. [PubMed: 12095344] See also: (b) Murata M, Oyama T, Watanabe S, Masuda Y. *Synthesis.* 2000:778. (c) Gopalarathnam A, Nelson SG. *Org Lett.* 2006; 8:7. [PubMed: 16381554]
14. Innitzer A, Brecker L, Mulzer J. *Org Lett.* 2007; 9:4431. [PubMed: 17900129]
15. Peterson PE, Nelson DJ, Risener R. *J Org Chem.* 1986; 51:2381.
16. Moran WJ, Morken JP. *Org Lett.* 2006; 8:2413. [PubMed: 16706539]
17. Handy ST, Wilson T, Muth A. *J Org Chem.* 2007; 72:8496. [PubMed: 17918901]
18. (a) Meyer, JA. MS Thesis. Western Washington University; Bellingham, WA: 2006. (b) Ligon, TJ. MS Thesis. Western Washington University; Bellingham, WA: 2009.
19. Brimble M, Rowan D, Spicer J. *Synthesis.* 1995:1263.
20. Burfield D, Smithers R. *J Org Chem.* 1978; 43:3966.
21. Kornblum N, Lurie AP. *J Am Chem Soc.* 1959; 81:2705.
22. (a) Wu Y, Gao J. *Org Lett.* 2008; 10:1533. [PubMed: 18338900] (b) Morrill C, Grubbs RH. *J Org Chem.* 2003; 68:6031. [PubMed: 12868943] (c) Hall LW, Odom JD, Ellis PD. *J Am Chem Soc.* 1975; 97:4527.

Figure 1.

Scheme 1.
Preparation of pyridyl triflates

Scheme 2.

Table 1

Preparation of Alkenyl Boronates **15**

Y	R ³	Conditions ^a	Yield (%)
14a	OTf	prenyl Pd	15a 74
14b	OTf	allyl Pd	15b Complex mixture
14c	Br	allyl Li	15b >99
14d	Br	propyl Li	15c >99

^aPd conditions: Pd(PPh₃)₂Cl₂ (3 mol %), PPh₃ (6 mol %), bispinacolatodiboron (1.1 equiv), KOPh (1.5 equiv), toluene, 50 °C. Li conditions: *tert*-BuLi (2.1 equiv), ether, −78 °C, then isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.5–3.0 equiv).

Table 2

Suzuki-Miyaura Cross-Coupling of 3-Pyridyl Triflates with Alkenyl Boronates

Entry	Pyridyl triflate	Alkenyl Boronate	Conditions ^a	Product	Yield ^b (%)
1	4a	15b	A	16	56
2	4a	15c	A	17	47
3	4b	15a	A	18	86
4	4b	15b	A	19	74
5	4b	15c	A	20	43
6	4c	15b	A	21	59
7	4c	15c	A	22	55
8	4d	15a	A	23	79
9	4d	15a	B	23	50
10	4d	15b	A	24	84
11	4d	15c	A	25	83
12	4d	15c	C	25	60
13	4e	15a	A	26	0 ^c
14	4e	15a	B	26	0 ^c
15	4f	15a	A	27	0 ^d
16	4f	15a	B	27	0 ^d

^a Conditions: A = Pd(PPh₃)₄ (10 mol %), K₃PO₄ (3 equiv), dioxane, 80–100 °C; B = Pd(dppf)Cl₂ (10 mol %), K₃PO₄ (3 equiv), dioxane, 80–100 °C; C = Pd(dppf)Cl₂ (3 mol %), dppf (3 mol %), KOAc (3 equiv), dioxane, 80 °C

^b Isolated yield of analytically pure material.

^c Pyridyl triflate **4e** was consumed, alkenyl boronate **15a** was recovered.

^d Both pyridyl triflate **4f** and alkenyl boronate **15a** recovered.