Supporting Information

Development and Investigation of a Site Selective Palladium-Catalyzed 1,4-Difunctionalization of Isoprene using Pyridine-Oxazoline Ligands

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I. General Considerations:

Anhydrous dimethylformamide (DMF) was purchased from Sigma Aldrich and stored over activated 3 Å molecular sieves (3 Å MS). Pd₂(dba)₃•CHCl₃ was synthesized according to known procedure.¹ Isoprene was purchased from Alfa Aesar and distilled prior to use. Unless otherwise noted all reagents and solvents were purchased from Sigma Aldrich, Frontier Scientific, Acros, or TCI and used without further purification. ¹H NMR spectra were obtained at 500 MHz or 400 MHz, chemical shifts are reported in ppm, and referenced to the CHCl₃ singlet at 7.26 ppm. The abbreviations s, d, t, q, quint, sext, dd, ddd, dt, and m stand for the resonance multiplicities singlet, doublet, triplet, quartet, quintet, sextet, doublet of doublets, doublet of doublets of doublets, doublet of triplet, and multiplet, respectively. ¹³C NMR spectra were obtained at 126 MHz and referenced to the centerline of the CDCl₃ triplet at 77.23 ppm. Flash chromatography was performed using Silicycle SiliaFlash F60 silica gel (230-400 mesh). Gas Chromatography (GC) separations were performed with an HP6890 GC with a flame ionization detector equipped with a DB-5 column using a 50:1 split. Optical rotations were obtained (Na D line) using a Perkin Elmer Model 343 Polarimeter fitted with a micro cell with a 1 dm path length; concentrations are reported in g/100 mL. HPLC separations were performed with a HP series 1100 chromatograph (Agilent ChromSpher 5 Lipids (4.6 x 250 mm)). IR spectra were recorded using a Thermo Nicolet FT-IR. Melting points were obtained on an electrothermal melting point apparatus and are uncorrected. HRMS data were obtained on a Waters LCP Premier XE instrument by ESI/TOF.

II. Preparation of Starting Materials:

cyclohex-1-en-1-yl trifluoromethanesulfonate 1a.

A previously reported procedure was used for the synthesis of **1a** from cyclohexanone.²

3,6-dihydro-pyran-4-yl trifluoromethanesulfonate 1b.

A previously reported procedure was used for the synthesis of **1b** from tetrahydropyran-4-one.²



tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydropyridine-1-carboxylate 1c.

A previously reported procedure was used for the synthesis of 1c from *tert*-butyl-4-oxopiperidine-1-carboxylate.³

(E)-hept-1-en-1-yl trifluoromethanesulfonate 1d.

A previously reported procedure was used for the synthesis of 1d from *n*-butyllithium and acrolein.⁴⁻⁶



(Z)-1-(2-oxodihydrofuran-3-ylidene)ethyl trifluoromethanesulfonate 1e.

A previously reported procedure was used for the synthesis of 1e from 3-acetyldihydrofuran-2-one.⁷

(*E*)-(3-methoxy-3-oxoprop-1-en-1-yl)boronic acid 3b.

A previously reported procedure was used for the synthesis of **3b** from methyl propiolate.⁸

(1-(*tert*-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)boronic acid 3f.

A previously reported procedure was used for the synthesis of **3f** from the pinacol boronic ester.⁹

(*E*)-(5-chloropent-1-en-1-yl)boronic acid 3g.

A previously reported procedure was used for the synthesis of **3g** from the pinacol boronic ester.¹⁰



4-isopropyl-2-(quinolin-2-yl)-4,5-dihydrooxazole L3.

A previously reported procedure was used for the synthesis of L3 from 2-amino-3-methylbutan-1-ol and quinoline-2-carboxylic acid.¹¹



(S)-4-(*tert*-butyl)-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole L4. A previously reported procedure was used for the synthesis of L4 from (S)-tert-leucinol and 5-(trifluoromethyl)pyridine-2-carboxylic acid.¹¹

A. General Procedure for the Synthesis of Quinox and Pyrox Ligands – Anderson Coupling¹¹



To an oven dried 100 mL was added 191 mg (1.0 mmol, 1.0 equiv) of 5-(trifluoromethyl)picolinic acid. The flask was placed under an N₂ atmosphere. Dichloromethane (20 mL) was added by syringe, followed by 0.13 mL (1.2 mmol, 1.2 equiv) *N*-methylmorpholine. The reaction mixture was cooled to 0 °C, then 0.16 mL (1.2 mmol, 1.2 equiv) *iso*-butyl chloroformate was added. The mixture was stirred for 20 min, and then 107 mg (1.2 mmol, 1.2 equiv) 2-amino-2-methylpropan-1-ol was added in dichloromethane (15 mL). The mixture was allowed to warm to room temperature and stirred for 15 h. After completion the reaction mixture was transferred to a separatory funnel with dichloromethane (10 mL) and water (10 mL). The aqueous layer was extracted with dichloromethane (1 x 15 mL), and the combined organic layers were washed with water (1 x 20 mL), and brine (1 x 20 mL), then dried over sodium sulfate. The dried organic mixture was concentrated *in vacuo* and purified by silica gel flash chromatography.



N-(1-hydroxy-2-methylpropan-2-yl)-5-(trifluoromethyl)picolinamide s1.

The general procedure was followed using 1.91 g of 5-(trifluoromethyl)picolinic acid (10 mmol) in dichloromethane (200 mL), 1.27 mL *N*-methylmorpholine (11.5 mmol), 1.57 mL *iso*-butyl chloroformate (12 mmol), and 1.15 mL 2-amino-2-methylpropan-1-ol (12 mmol) in dichloromethane (150 mL). Purification by silica gel flash chromatography (2:1 hexanes:ethyl acetate) afforded **s1** as a white solid (2.37 g, 90%).



(S)-N-(1-hydroxy-3,3-dimethylbutan-2-yl)-4-(trifluoromethyl)quinoline-2-carboxamide s2. The general procedure was followed using 250 mg of 4-(trifluoromethyl)quinolone-2-carboxylic acid (1.04 mmol) in dichloromethane (20 mL), 0.13 mL *N*-methylmorpholine (1.2 mmol), 0.16 mL *iso*-butyl chloroformate (1.24 mmol), and 145 mg (S)-*tert*-leucinol (1.24 mmol) in

dichloromethane (15 mL). Purification by silica gel flash chromatography (2:1 hexanes:ethyl acetate) afforded **s2** as a white solid (290 mg, 82%).



(S)-N-(1-hydroxy-3,3-dimethylbutan-2-yl)-6-(trifluoromethyl)picolinamide s3.

The general procedure was followed using 956 mg of 6-(trifluoromethyl)picolinic acid (5 mmol) in dichloromethane (100 mL), 0.63 mL *N*-methylmorpholine (5.75 mmol), 0.78 mL *iso*-butyl chloroformate (6 mmol), and 703 mg (S)-*tert*-leucinol (6 mmol) in dichloromethane (75 mL). Purification by silica gel flash chromatography (2:1 hexanes:ethyl acetate) afforded **s3** as a white solid (1.34 g, 92%).



(S)-N-(1-hydroxy-3,3-dimethylbutan-2-yl)-6-methylpicolinamide s4.

The general procedure was followed using 1.91 g of 6-methylpicolinic acid (13.9 mmol) in dichloromethane, 1.76 mL *N*-methylmorpholine (16 mmol), 2.18 mL *iso*-butyl chloroformate (16.7 mmol), and 1.96 g (S)-*tert*-leucinol (16.7 mmol) in dichloromethane. Purification by silica gel flash chromatography afforded **s4** as a white solid (3.0 g, 91%).

B. General Procedure for the Synthesis of Quinox and Pyrox Ligands – Oxazoline Formation



DAST = diethylaminosulfurtrifloride

To an oven dried 50 mL round bottom flask was added 223 mg (0.85 mmol, 1.0 equiv) of s1 in dichlormethane (12 mL). The flask was placed under an N₂ atmosphere and cooled to -78 °C. To the mixture was added dropwise 0.16 mL (1.19 mmol, 1.4 equiv) of DAST. The mixture was stirred at -78 °C for 1 h before warming to -20 °C and stirring for an additional 1 h. After completion, the mixture was cooled to -78 °C and 236 mg (1.71 mmol, 2.0 equiv) K₂CO₃ was added in one portion. The mixture was warmed to room temperature, diluted with dichloromethane (5 mL) and washed with NaHCO₃ (10 mL) and brine (10 mL). The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Crude products were purified by silica gel flash chromatography.



4,4-dimethyl-2-(5-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole L5.

The general procedure was followed using 1.2 g of **s1** (4.58 mmol) in dichloromethane (61 mL), 0.85 mL DAST (6.41 mmol), and 1.26 g K₂CO₃ (9.16 mmol). Purification by silica gel flash chromatography (5:1 hexanes:acetone) led to the isolation of **L5** as a white solid (834 mg, 75%), mp 90 °C, $R_f = 0.36$ (5:1 hexanes:acetone). ¹H NMR (CDCl₃, 500 MHz): δ 8.95 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 8.02 (dd, J = 8.3, 2.3 Hz, 1H), 4.24 (s, 2H), 1.43 (s, 6H); ¹³C NMR (CDCl₃, 126 MHz): δ 160.4, 150.3, 146.9 (q, J = 3.8), 134.2 (q, J = 3.7), 128.2 (q, J = 33.4), 123.7, 123.3 (q, J

= 273), 80.1, 68.6, 28.6; FTIR (thin film): 2974, 1640, 1573, 1324, 1089, 1013, 869, 788 cm⁻¹; HRMS m/z calculated for C₁₁H₁₁F₃N₂ONa [M+Na]⁺: 267.0721, found 267.0721.



(S)-4-(*tert*-butyl)-2-(4-(trifluoromethyl)quinolin-2-yl)-4,5-dihydrooxazole L6.

The general procedure was followed using 290 mg of **s2** (0.85 mmol) in dichloromethane (12 mL), 0.16 mL DAST (1.19 mmol), and 236 mg K₂CO₃ (1.71 mmol). Purification by silica gel flash chromatography (3:1 hexanes:ethyl acetate) led to the isolation of **L6** as a white solid (230 mg, 84%), mp 98 °C, $R_f = 0.42$ (3:1 hexanes:ethyl acetate). $[\alpha]^{20}{}_D = -94$ (c = 0.284, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 8.54 (s, 1H), 8.37 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.86 (t, *J* = 8.0 Hz, 1H), 7.75 (t, *J* = 8.0 Hz, 1H), 4.56 (dd, *J* = 9.0, 10.5 Hz, 1H), 4.43 (t, *J* = 8.5 Hz, 1H), 4.21 (dd, *J* = 8.5, 10.5 Hz, 1H), 1.02 (s, 9H); ¹³C NMR (CDCl₃, 126 MHz): δ 162.2, 148.6, 146.9, 135.2 (q, *J* = 32.3), 131.5, 130.9, 129.8, 124.2 (q, *J* = 1.9), 123.7, 123.5 (q, *J* = 275), 118.5 (q, *J* = 5.4), 77.0, 70.2, 34.3, 26.2; FTIR (thin film): 2957, 1645, 1325, 1253, 1132, 967, 850, 765 cm⁻¹; HRMS *m*/*z* calculated for C₁₇H₁₇F₃N₂ONa [M+Na]⁺: 345.1191, found 345.1195.



(S)-4-(*tert*-butyl)-2-(6-(trifluoromethyl)pyridin-2-yl)-4,5-dihydrooxazole L7.

The general procedure was followed using 726 mg of **s3** (2.5 mmol) in dichloromethane (33 mL), 0.46 mL DAST (3.5 mmol), and 691 mg K₂CO₃ (5.0 mmol). Purification by silica gel flash chromatography (3:1 hexanes:ethyl acetate) led to the isolation of **L7** as a white solid (509 mg, 75%), mp 122 °C, $R_f = 0.29$ (3:1 hexanes:ethyl acetate). $[\alpha]^{20}_{D} = -89$ (c = 0.334, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 8.35 (d, J = 8.0 Hz, 1H), 7.96 (t, J = 8.0 Hz, 1H), 7.78 (dd, J = 8.0, 1.0 Hz, 1H), 4.50 (dd, J = 8.5, 10.3 Hz, 1H), 4.36 (t, J = 8.5 Hz, 1H), 4.13 (dd, J = 8.5, 10.5 Hz, 1H), 0.97 (s, 9H); ¹³C NMR (CDCl₃, 126 MHz): δ 161.8, 148.3 (q, J = 41), 147.9, 138.2, 127.0, 122.3 (q, J = 2.5), 121.4 (q, J = 275), 76.6, 70.0, 34.2, 26.1; FTIR (thin film): 2966, 1647, 1363, 1185, 1165, 1077, 955, 836 cm⁻¹; HRMS *m*/*z* calculated for C₁₃H₁₅F₃N₂O [M+Na]⁺: 295.1034, found 295.1030.



(S)-4-(tert-butyl)-2-(6-methylpyridin-2-yl)-4,5-dihydrooxazole L8.

The general procedure was followed using 3.0 g of s4 (12.7 mmol) in dichloromethane, 2.35 mL DAST (17.8 mmol), and 3.51 g K₂CO₃ (25.4 mmol). Purification by silica gel flash chromatography led to the isolation of L8 as a white solid (2.1 g, 70%), mp 71 °C, R_f = 0.44 (2:1 hexanes:acetone). $[\alpha]^{20}_{D} = -83$ (c = 0.262, CHCl₃); ¹H NMR (CDCl₃, 500 MHz): δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 4.45 (dd, *J* = 8.5, 10.5 Hz, 1H), 4.31 (t, *J* = 8.5 Hz, 1H), 4.10 (dd, *J* = 8.5, 10.5 Hz, 1H), 2.63 (s, 3H), 0.97 (s, 9H); ¹³C NMR (CDCl₃, 126 MHz): δ 162.9, 158.8, 146.7, 136.9, 125.4, 121.5, 76.6, 69.6, 34.2, 26.2, 24.9; FTIR (thin film): 2951, 1643, 1461, 1360, 1118, 966, 810 cm⁻¹; HRMS *m*/*z* calculated for C₁₃H₁₈N₂ONa [M+Na]⁺: 241.1317, found 241.1318.

III. Pd-Catalyzed Three-Component Coupling Reactions



To an oven dried 5 mL vial were added 32 mg (0.34 mmol, 1.7 equiv) of KF•2H₂O, 44 mg (0.30 mmol, 1.5 equiv) of **3a**, and 6 mg (3.0 mol%) of Pd₂dba₃•CHCl₃. The vial was equipped with a stirbar and the threads were wrapped with Teflon tape, and then was flushed with N₂ before being sealed with a septum cap. To the solids were added a solution of 69 mg (0.3 mmol, 1.5 equiv) of **1a** in 1.0 mL of DMA containing an internal standard (2-methoxynaphthalene) and 20 μ L (0.2 mmol, 1.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, a ~200 μ L aliquot of the reaction mixture was removed via syringe and filtered through a silica plug, eluting with ethyl acetate. The mixture was analyzed by GC. Yields were calculated using a response factor (¹H NMR spectroscopy was used to measure the response factor to account for varying detector response).

Table S1. Optimization of Reaction																
entry	solvent	conc. (M)	temp.	base	x	У	yield (%)	(<i>E</i>)–4a	:	(<i>Z</i>)–4a	:	5a	:	(<i>E</i>)–6a	:	(<i>Z</i>)–6a
1	DMA	0.2	55	KF•2H ₂ O	1.5	1.0	17	10		0.64		1.9		1.0		1.1
2	DMA	0.2	55	KF•2H ₂ O	1.0	1.0	21	10		0.64		1.8		1.0		1.1
3	DMA	0.2	55	KF•2H ₂ O	1.0	7.0	61	8.5		0.53		1.7		1.0		1.1
4	DMA	0.2	rt	KF•2H ₂ O	1.0	7.0	61	8.0		0.52		1.5		1.0		1.0
5	DMA	0.2	rt	Na ₂ CHO ₃	1.0	7.0	79	7.6		0.72		1.1		1.0		0.97
6	DMF	0.2	rt	Na ₂ CO ₃	1.0	7.0	81	7.0		0.80		0.73		1.0		0.93
7	DMF	0.25	rt	Na ₂ CO ₃	1.0	7.0	80	7.3		0.85		0.64		1.0		0.89
8 ^a	DMF	0.25	rt	Na ₂ CO ₃	1.0	7.0	65	4.5		0.36		1.0		0.05		0.06

В.	Tabular	Summary	of F	Reaction	Optimiza	tion A
hin 04	Ontimization	of Departies				

^a Reaction carried out with 8 mol% L4.



C. Optimized General Procedure A



To an oven dried 10 mL round bottom flask were added 90 mg (0.85 mmol, 1.7 equiv) of Na_2CO_3 , 111 mg (0.75 mmol, 1.5 equiv) of **3a**, and 16 mg (3.0 mol%) of $Pd_2dba_3 \bullet CHCl_3$. The flask was equipped with a PTFE-lined stirbar and a septum, and then was flushed with N_2 . To the solids were added a solution of 115 mg (0.5 mmol, 1.0 equiv) of **1a** in 2.0 mL of DMF and 0.35

mL (3.5 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and filtered through a Celite plug. The organics were washed with H_2O (3 x 10 mL) and brine (1 x 10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Crude products were purified by silica gel flash chromatography. Yields represent a mixture of stereo and regioisomers. HPLC methods and NMR analysis were used to isolate and verify the identity of product isomers. ¹H NMR spectroscopy was used to determine isomeric ratios of the product mixture.

D. General Procedure for Reaction Optimization B



To an oven dried 5 mL vial were added 36 mg (0.34 mmol, 1.7 equiv) of Na₂CO₃, 39 mg (0.3 mmol, 1.5 equiv) of **3b**, and 6 mg (3.0 mol%) of Pd₂dba₃•CHCl₃. The vial was equipped with a stirbar and the threads were wrapped with Teflon tape, and then was flushed with N₂ before being sealed with a septum cap. To the solids were added a solution of 46 mg (0.2 mmol, 1.0 equiv) of **1b** in 0.8 mL of DMF and 0.14 mL (1.4 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and the organics were washed with H₂O (3 x 2 mL) and brine (1 x 2 mL), then dried over magnesium sulfate and concentrated *in vacuo*. ¹H NMR spectroscopy was used to determine isomeric ratios and yields using an internal standard (2-methoxynaphthalene).

entry	x	У	yield (%)	(<i>E</i>)–4b	:	(<i>Z</i>)–4b	:	5b	:	(<i>E</i>)–6b	:	(<i>Z</i>)–6b
1	1.0	1.5	17	8.8		3.4		9.0		1.0		1.1
2	1.0	1.2	28	6.6		2.8		3.8		1.0		1.3
3	1.0	1.0	34	6.8		2.8		3.4		1.0		1.0
4	1.2	1.0	50	5.5		0.74		2.1		1.0		0.95
5	1.5	1.0	57	5.3		1.1		1.8		1.0		0.96
6	2.5	1.0	55	6.4		1.7		1.3		1.0		1.8
7	3.0	1.0	73	12		2.4		4.1		1.0		1.1
8	3.5	1.0	69	12		2.7		3.7		1.0		1.5

E. Tabular Summary of Reaction Optimization B

F. Optimized General Procedure B

Table S2. Optimization of Reaction



To an oven dried 10 mL round bottom flask were added 90 mg (0.85 mmol, 1.7 equiv) of Na_2CO_3 , 65 mg (0.5 mmol, 1.0 equiv) of **3b**, and 16 mg (3.0 mol%) of $Pd_2dba_3 \bullet CHCl_3$. The flask

was equipped with a PTFE-lined stirbar and a septum, and then was flushed with N_2 . To the solids were added a solution of 348 mg (1.5 mmol, 3.0 equiv) of **1b** in 2.0 mL of DMF and 0.35 mL (3.5 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and filtered through a Celite plug. The organics were washed with H₂O (3 x 10 mL) and brine (1 x 10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Crude products were purified by silica gel flash chromatography as noted below. Yields represent a mixture of stereo and regioisomers. HPLC methods and NMR analysis were used to isolate and verify the identity of product isomers. ¹H NMR spectroscopy was used to determine isomeric ratios of the product mixture.

G. Scope and Limitations of the 1,4-Difunctionalization Reaction



((1E,4E)-6-(cyclohex-1-en-1-yl)-4-methylhexa-1,4-dien-1-yl)benzene (E)-4a.

General procedure A was followed using 90 mg of Na₂CO₃ (0.85 mmol), 111 mg of **3a** (0.75 mmol), 16 mg of Pd₂dba₃•CHCl₃(3 mol%), 115 mg of **1a** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (19:1 hexanes:benzene) led to the isolation of **4a**, **5a**, and **6a** as a colorless oil (112 mg, 89% as a 7.3:0.85:0.64:1.0:0.89 mixture of (*E*)-**4a**:(*Z*)-**4a**:5**a**:(*E*)-**6a**:(*Z*)-**6a** isomers respectively), isomeric ratios were determined by GC, $R_f = 0.40$ (19:1 hexanes:benzene). ¹H NMR (CDCl₃, 500 MHz): δ 7.35 (d, J = 7.5 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.20 (t, J = 7.5 Hz, 1H), 6.40 (d, J = 16 Hz, 1H), 6.20 (app. dt, J = 7.0, 16 Hz, 1H), 5.41 (m, 1H), 5.26 (t, J = 7.5 Hz, 1H), 2.89 (d, J = 7.0 Hz, 2H), 2.65 (d, J = 7.5 Hz, 2H), 1.98 (m, 2H), 1.92 (m, 2H), 1.62 (m, 5H), 1.55 (m, 2H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*Z*)-**4a**: ¹H NMR (CDCl₃, 500 MHz): δ 6.14 (app. dt, J = 7.0, 16 Hz, 1H), 2.93 (d, J = 6.5 Hz, 2H), 1.75 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 138.0, 137.3, 134.8, 131.2, 129.3, 128.7, 127.1, 126.3, 123.9, 121.1, 43.5, 36.9, 28.8, 25.5, 23.2, 22.8, 16.4; FTIR (thin film): 3025, 2923, 2833, 1495, 1447, 962, 919, 888, 739, 691 cm⁻¹; HRMS *m*/*z* calculated for C₁₉H₂₄Ag [M+Ag]⁺: 359.0929, found 359.0947.



Methyl-(2E,5E)-7-(3,6-dihydropyran-4-yl)-5-methylhepta-2,5-dienoate (E)-4b.

General procedure B was followed using 90 mg of Na₂CO₃ (0.85 mmol), 65 mg of **3b** (0.5 mmol), 16 mg of Pd₂dba₃•CHCl₃(3 mol%), 348 mg of **1b** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **4b**, **5b**, and **6b** as a colorless oil (63 mg, 53% as a 11:1.2:5.1:1.0:1.0 mixture of (*E*)-**4b**:(*Z*)-**4b**:5**b**:(*E*)-**6b**:(*Z*)-**6b** isomers respectively), $R_f = 0.43$ (3:1 hexanes:EtOAc). ¹H NMR (CDCl₃, 500 MHz): δ 6.95 (app. dt, J = 7.0, 15.5 Hz, 1H), 5.83 (d, J = 15.5 Hz, 1H), 5.41 (m, 1H), 5.24 (t, J = 7.0 Hz, 1H), 4.11 (m, 2H), 3.78, (t, J = 5.5 Hz, 2H), 3.73 (s, 3H), 2.88 (d, J = 7.0 Hz, 2H), 2.70 (d, J = 7.0 Hz, 2H), 2.03 (m, 2H), 1.63 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*Z*)-**4b**: ¹H NMR (CDCl₃, 500 MHz): δ 6.90 (app. dt, J = 6.8, 16 Hz, 1H), 5.33 (t, J = 7.7 Hz, 1H), 2.91 (d, J = 7.1 Hz, 2H), 2.66 (d, J = 7.8 Hz, 2H), 1.73 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 167.2, 147.5, 134.7, 133.7, 124.1, 122.2, 120.1, 65.8, 64.6, 51.7, 42.5, 35.8, 28.9, 16.5; FTIR (thin film): 2951, 1720, 1650, 1434, 1270, 1207, 1165, 1126, 1031, 980, 848 cm⁻¹; HRMS *m/z* calculated for C₁₄H₂₀O₃Na [M+Na]⁺: 259.1310, found 259.1316.



tert-Butyl-4-((2*E*,5*E*)-7-methoxy-3-methyl-7-oxohepta-2,5-dien-1-yl)-3,6-dihydropyridine-1-carboxylate (*E*)-4c.

General procedure B was followed using 90 mg of Na₂CO₃ (0.85 mmol), 65 mg of **3b** (0.5 mmol), 16 mg of Pd₂dba₃•CHCl₃ (3 mol%), 497 mg of **1c** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (4:1 hexanes:EtOAc) led to the isolation of **4c**, **5c**, and **6c** as a colorless oil (142 mg, 85% as a 6.5:0.42:3.4:1.0:1.1 mixture of (*E*)-**4c**:(*Z*)-**4c**:5**c**:(*E*)-**6c**:(*Z*)-**6c** isomers respectively; 127 mg, 76% as a 7.3:0.48:3.3:1.0:1.1 mixture of (*E*)-**4c**:(*Z*)-**4c**:5**c**:(*E*)-**6c**:(*Z*)-**6c** isomers respectively), $R_f = 0.37$ (4:1 hexanes:EtOAc). ¹H NMR (CDCl₃, 500 MHz): δ 6.94 (app. dt, *J* = 7.0, 15.5 Hz, 1H), 5.84 (dt, *J* = 1.5, 16 Hz, 1H), 5.33 (m, 1H), 5.21 (t, *J* = 7.4 Hz, 1H), 3.85 (m, 2H), 3.73 (s, 3H), 3.48 (m, 2H), 2.88 (d, *J* = 7.0 Hz, 2H), 2.69 (d, *J* = 7.0 Hz, 2H), 2.02 (m, 2H), 1.62 (s, 3H), 1.46 (s, 9H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*Z*)-**4c**: ¹H NMR (CDCl₃, 500 MHz): δ 6.89 (app. dt, *J* = 6.5, 15.5 Hz, 1H), 5.82 (dt, *J* = 1.5, 15.5 Hz, 1H), 2.90 (d, *J* = 7.0 Hz, 2H), 2.66 (d, *J* = 7.5 Hz, 2H), 1.72 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 167.2, 155.2, 147.4, 133.7, 128.7, 124.2, 122.2, 118.6, 79.7, 51.7, 43.7, 42.5, 40.0, 35.9, 28.7, 16.5; FTIR (thin film): 2977, 1693, 1415, 1367, 1244, 1209, 1164, 1142, 1062, 871, 769, 611 cm⁻¹; HRMS *m/z* calculated for C₁₉H₂₉NO₄Na [M+Na]⁺: 358.1994, found 358.2007.



Methyl-(2E,5E,8E)-5-methyltetradeca-2,5,8-trienoate (E)-4d.

General procedure B was followed using 90 mg of Na₂CO₃ (0.85 mmol), 65 mg of **3b** (0.5 mmol), 16 mg of Pd₂dba₃•CHCl₃(3 mol%), 369 mg of 1d (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (19:1 hexanes:EtOAc) led to the isolation of **4d**, **5d**, and **6d** as a colorless oil (77 mg, 62% as a 5.5:1.4:3.0:1.0:1.4 mixture of (E)-4d:(Z)-4d:5d:(E)-6d:(Z)-6d isomers respectively; 67 mg, 54% as a 6.4:1.4:3.3:1.0:1.4 mixture of (E)-4d:(Z)-4d:5d:(E)-6d:(Z)-6d isomers respectively), (Z)-4d and (Z)-6d isomeric ratios are reported as a inseparable mixture, $R_f = 0.27$ (19:1 hexanes:EtOAc). ¹H NMR (CDCl₃, 500 MHz): δ 6.95 (app. dt, J = 7.0, 15.5 Hz, 1H), 5.83 (dt, J = 1.5, 15.5 Hz, 1H), 5.42 (app. dt, J= 6.5, 15.5 Hz, 1H, 5.35 (app. dt, J = 6.0, 15.0 Hz, 1H), 5.22 (t, J = 7.0 Hz, 1H), 3.73 (s, 3H), 2.89 (d, J = 7.0 Hz, 2H), 2.70 (d, J = 7.0 Hz, 2H), 1.97 (q, J = 7.0 Hz, 2H), 1.62 (s, 3H), 1.30 (m, 2H), 1.62 (s, 2H), 1.62 (6H), 0.88 (t, J = 7.0 Hz, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (Z)-4d: ¹H NMR (CDCl₃, 500 MHz): δ 2.90 (d, J = 6.6 Hz, 2H), 2.67 (t, J = 6.6 Hz, 2H), 1.70 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 167.3, 147.7, 132.2, 131.2, 128.2, 125.8, 122.0, 51.6, 42.5, 32.7, 31.7, 31.5, 29.4, 22.8, 16.4, 14.3; FTIR (thin film): 2925, 2855, 1725, 1643, 1434, 1268, 1161, 1040, 968, 893, 725 cm⁻¹; HRMS m/z calculated for C₁₆H₂₆O₂Na [M+Na]⁺: 273.1831, found 273.1824.



Methyl-(2E,5E,8Z)-5-methyl-8-(2-oxodihydrofuran-3-ylidene)nona-2,5-dienoate (E)-4e.

General procedure B was followed using 90 mg of Na₂CO₃ (0.85 mmol), 65 mg of **3b** (0.5 mmol), 16 mg of Pd₂dba₃•CHCl₃(3 mol%), 390 mg of **1e** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **4e**, **5e**, and **6e** as a colorless oil (110 mg, 83% as a 1.4:0.33:0.30:1.0:0.49 mixture of (*E*)-**4e**:(*Z*)-**4e**:**5e**:(*E*)-**6e**:(*Z*)-**6e** isomers respectively; 116 mg, 87% as a 1.6:0.39:0.48:1.0:0.52 mixture of (*E*)-**4e**:(*Z*)-**4e**:**5e**:(*E*)-**6e**:(*Z*)-**6e** isomers respectively), $R_f = 0.32$ (3:1 hexanes:EtOAc).

¹H NMR (CDCl₃, 400 MHz): δ 6.93 (app. dt, J = 6.8, 15.6 Hz, 1H), 5.82 (dt, J = 1.6, 15.6 Hz, 1H), 5.18 (t, J = 7.4 Hz, 1H), 4.30 (t, J = 7.6 Hz, 2H), 3.73 (s, 3H), 3.55 (d, J = 7.2 Hz, 2H), 2.88 (m, 4H), 1.84 (s, 3H), 1.71 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ¹³C NMR (CDCl₃, 126 MHz): δ 170.4, 167.2, 152.6, 147.4, 134.2, 123.5, 122.2, 118.8, 64.4, 51.7, 42.5, 31.5, 28.0, 22.3, 16.8; FTIR (thin film): 2914, 1738, 1716, 1653, 1435, 1269, 1214, 1161, 1031, 987, 847, 754 cm⁻¹; HRMS *m*/*z* calculated for C₁₅H₂₀O₄Na [M+Na]⁺: 287.1259, found 287.1260.



(Z)-3-((4E,7E)-8-(4-methoxyphenyl)-5-methylocta-4,7-dien-2-ylidene)dihydrofuran-2-one (E)-4f.

General procedure A was followed using 90 mg of Na₂CO₃ (0.85 mmol), 134 mg of **3c** (0.75 mmol), 16 mg of Pd₂dba₃•CHCl₃ (3 mol%), 130 mg of **1e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **4f**, **5f**, and **6f** as a colorless oil (126 mg, 81% as a 1.5:0.22:0.44:1.0:0.78 mixture of (*E*)-**4f**:(*Z*)-**4f**:5**f**:(*E*)-**6f**:(*Z*)-**6f** isomers respectively; 136 mg, 84% as a 1.5:0.26:0.47:1.0:0.74 mixture of (*E*)-**4f**:(*Z*)-**4f**:5**f**:(*E*)-**6f**:(*Z*)-**6f** isomers respectively), R_f = 0.30 (3:1 hexanes:EtOAc). ¹H NMR (CDCl₃, 500 MHz): δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 6.33 (d, *J* = 16 Hz, 1H), 6.03 (app. dt, *J* = 7.0, 16 Hz, 1H), 5.20 (t, *J* = 7.4 Hz, 1H), 4.29 (t, *J* = 7.5 Hz, 2H), 3.80 (s, 3H), 3.57 (d, *J* = 7.0 Hz, 2H), 2.87 (m, 4H), 1.85 (t, *J* = 2.0 Hz, 3H), 1.73 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*E*)-**6f**: ¹H NMR (CDCl₃, 500 MHz): δ 5.28 (t, *J* = 7.0 Hz, 1H), 4.36 (t, *J* = 7.5 Hz, 2H), 1.83 (t, *J* = 1.5 Hz, 3H), 1.60 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 170.4, 158.9, 152.1, 134.1, 130.8. 129.4, 127.3, 127.1, 124.6, 120.0, 114.1, 64.3, 55.5, 42.0, 31.7, 28.2, 21.8, 16.0; FTIR (thin film): 2911, 1737, 1606, 1509, 1243, 1172, 1029, 965, 837, 750 cm⁻¹; HRMS *m/z* calculated for C₂₀H₂₄O₃Na [M+Na]⁺: 335.1623, found 335.1633.



(Z)-3-((4E,7E)-5-methyl-8-(4-(trifluoromethyl)phenyl)octa-4,7-dien-2-ylidene)dihydrofuran-2-one (E)-4g.

General procedure A was followed using 90 mg of Na₂CO₃ (0.85 mmol), 162 mg of **3d** (0.75 mmol), 16 mg of Pd₂dba₃•CHCl₃ (3 mol%), 130 mg of **1e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **4g**, **5g**, and **6g** as a colorless oil (148 mg, 85% as a 1.2:0.24:0.49:1.0:0.55 mixture of (*E*)-**4g**:(*Z*)-**4g**:**5g**:(*E*)-**6g**:(*Z*)-**6g** isomers respectively; 136 mg, 78% as a 1.3:0.27:0.57:1.0:0.56 mixture of (*E*)-**4g**:(*Z*)-**4g**:**5g**:(*E*)-**6g**:(*Z*)-**6g** isomers respectively), $R_f = 0.31$ (3:1 hexanes:EtOAc). ¹H NMR (CDCl₃, 500 MHz): δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.2 Hz, 2H), 6.42 (d, *J* = 16 Hz, 1H), 6.29 (app. dt, *J* = 7.0, 16 Hz, 1H), 5.21 (t, *J* = 7.5 Hz, 1H), 4.30 (t, *J* = 7.5 Hz, 2H), 3.57 (d, *J* = 7.5 Hz, 2H), 2.88 (m, 4H), 1.85 (t, *J* = 1.5 Hz, 3H), 1.74 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); ¹³C NMR (CDCl₃, 126 MHz): δ 170.4, 152.9, 141.3, 135.9, 131.7, 130.2, 129.2, 128.9, 126.4, 125.6 (q, *J*_{C-F} = 3.8 Hz), 124.5 (q, *J*_{C-F} = 272.2 Hz), 122.4, 118.7, 64.4, 43.4, 31.6, 28.0, 22.3, 16.8; FTIR (thin film): 2918, 1739, 1322, 1161, 1109, 1065, 968, 838, 755 cm⁻¹; HRMS *m*/z calculated for C₂₀H₂₁F₃O₂Na [M+Na]⁺: 373.1391, found 373.1395.



(Z)-3-((E)-5-methyl-7-phenylocta-4,7-dien-2-ylidene)dihydrofuran-2-one (E)-4h.

General procedure A was followed using 90 mg of Na₂CO₃ (0.85 mmol), 111 mg of 3e (0.75 mmol), 16 mg of Pd₂dba₃•CHCl₃ (3 mol%), 130 mg of 1e (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of 4h, 5h, and 6h as a colorless oil (81 mg, 57% as a 1.4:0.20:0.22:1.0:0.42 mixture of (E)-4h:(Z)-4h:5h:(E)-6h:(Z)-6h isomers respectively; 78 mg, 55% as a 1.6:0.20:0.11:1.0:0.42 mixture of (E)-4h:(Z)-4h:5h:(E)-6h:(Z)-6hisomers respectively), $R_f = 0.40$ (3:1 hexanes:EtOAc). ¹H NMR (CDCl₃, 400 MHz): δ 7.38 (m, 2H), 7.27 (m, 3H), 5.37 (s, 1H), 5.17 (m, 1H), 5.07 (s, 1H), 4.27 (t, J = 7.6 Hz, 2H), 3.51 (d, J = 7.6 Hz, 2H), 3.19 (s, 2H), 2.81 (t, J = 7.6 Hz, 2H), 3.19 (s, 2H), 2.81 (t, J = 7.6 Hz, 2H), 3.19 (s, 2H),7.6 Hz, 2H), 1.66 (s, 3H), 1.62 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (E)-6h: ¹H NMR (CDCl₃, 400 MHz): δ 5.32 (s, 1H), 5.27 (t, J = 7.5 Hz, 1H), 4.32 (m, 2H), 3.54 (s, 2H), 3.21 (d, J = 7.5 Hz, 2H), 2.87 (t, J = 7.6 Hz, 2H), 1.71 (s, 3H), 1.60 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 170.4, 153.4, 146.3, 141.4, 135.4, 128.3, 127.4, 126.5, 123.5, 118.3, 114.4, 64.4, 45.9, 31.4, 28.0, 21.9, 16.4; FTIR (thin film): 2912, 1737, 1655, 1443, 1373, 1269, 1187, 1029, 968, 896, 778, 755, 704 cm⁻¹; HRMS m/z calculated for C₁₉H₂₂O₂Na [M+Na]⁺: 305.1526, found 305.1517.



tert-butyl-4-((2*E*,5*Z*)-2-methyl-5-(2-oxodihydrofuran-3-ylidene)hex-2-en-1-yl)-3,6-dihydropyridine-1-carboxylate (*E*)-4i.

General procedure A was followed using 90 mg of Na₂CO₃ (0.85 mmol), 170 mg of **3f** (0.75 mmol), 16 mg of Pd₂dba₃•CHCl₃ (3 mol%), 130 mg of **1e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **4i**, **5i**, and **6i** as a colorless oil (148 mg, 81% as a 1.5:0.09:0.14:1.0:0.60 mixture of (*E*)-**4i**:(*Z*)-**4i**:5**i**:(*E*)-**6i**:(*Z*)-**6i** isomers respectively; 162 mg, 90% as a 1.5:0.21:0.13:1.0:0.61 mixture of (*E*)-**4i**:(*Z*)-**4i**:5**i**:(*E*)-**6i**:(*Z*)-**6i** isomers respectively), $R_f = 0.32$ (3:1 hexanes:EtOAc). ¹H NMR (CDCl₃, 500 MHz): δ 5.37 (m, 1H), 5.15 (t, *J* = 7.0 Hz, 1H), 4.30 (t, *J* = 7.5 Hz, 2H), 3.86 (m, 2H), 3.55 (d, *J* = 7.0 Hz, 2H), 3.45 (m, 2H), 2.88 (t, *J* = 7.8 Hz, 2H), 2.67 (s, 2H), 1.93 (m, 2H), 1.84 (t, *J* = 2.0 Hz, 3H), 1.61 (s, 3H), 1.46 (s, 9H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*E*)-**6i**: ¹H NMR (CDCl₃, 500 MHz): δ 5.19 (t, *J* = 6.5 Hz, 1H), 2.91 (t, *J* = 8.0 Hz, 2H), 2.70 (d, *J* = 7.5 Hz, 2H), 1.80 (t, *J* = 1.5 Hz, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 170.5, 155.3, 153.1, 135.2, 130.0, 123.1, 119.6, 118.5, 79.7, 64.4, 48.1, 43.8, 40.0, 31.6, 28.7, 28.0, 22.2, 16.1; FTIR (thin film): 2913, 1742, 1691, 1415, 1364, 1238, 1166, 1036, 966, 864, 755 cm⁻¹; HRMS *m/z* calculated for C₂₁H₃₁NO₄Na [M+Na]⁺: 384.2151, found 384.2148.



(Z)-3-((4E,7E)-11-chloro-5-methylundeca-4,7-dien-2-ylidene)dihydrofuran-2-one (E)-4j. General procedure A was followed using 90 mg of Na₂CO₃ (0.85 mmol), 111 mg of 3g (0.75 mmol), 16 mg of Pd₂dba₃•CHCl₃ (3 mol%), 130 mg of 1e (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of 4j, 5j, and 6j as a colorless oil (64 mg, 46% as a 1.1:0.33:0.38:1.0:0.87 mixture of (E)-4j:(Z)-4j:5j:(E)-6j:(Z)-6j isomers respectively; 76 mg, 54% as a 1.0:0.33:0.30:1.0:0.81 mixture of (E)-4j:(Z)-4j:5j:(E)-6j:(Z)-6j isomers respectively), $R_f = 0.40$ (3:1 hexanes:EtOAc).

¹H NMR (CDCl₃, 500 MHz): δ 5.41 (app. dt, J = 6.5, 16 Hz, 2H), 5.12 (t, J = 7.2 Hz, 1H), 4.29 (t, J = 7.5 Hz, 2H), 3.53 (m, 4H), 2.87 (t, J = 7.0 Hz, 2H), 2.67 (d, J = 6.5 Hz, 2H), 2.16 (q, J = 7.0 Hz, 2H), 1.82 (m, 5H), 1.67 (s, 3H); (The stereochemistry was confirmed by NOESY1D NMR spectroscopy); The following signals can be assigned to (*E*)-6j: ¹H NMR (CDCl₃, 500 MHz): δ 5.19 (t, J = 6.0 Hz, 1H), 2.92 (t, J = 7.7 Hz, 2H), 2.71 (d, J = 6.8 Hz, 2H), 1.80 (m, 3H), 1.54 (s, 3H); ¹³C NMR (CDCl₃, 126 MHz): δ 170.4, 153.3, 136.8, 130.0, 121.3, 121.1, 118.4, 64.4, 44.6, 43.1, 32.4, 31.5, 29.8, 28.0, 22.2, 16.6; FTIR (thin film): 2913, 1738, 1657, 1441, 1373, 1162, 1035, 967, 753, 646 cm⁻¹; HRMS *m/z* calculated for C₁₆H₂₃ClO₂Na [M+Na]⁺: 305.1284, found 305.1286.

H. General Procedure for 1,4-Difunctionalization Ligand Screens



To an oven dried 5 mL vial were added 36 mg (0.34 mmol, 1.7 equiv) of Na₂CO₃, 52 mg (0.2 mmol, 1.0 equiv) of **1e**, 53 mg (0.3 mmol, 1.5 equiv) of **3c**, 2 mg (8 mol%) **L1**, and 6 mg (3.0 mol%) of Pd₂dba₃•CHCl₃. The vial was equipped with a stirbar and the threads were wrapped with Teflon tape, and then was flushed with N₂ before being sealed with a septum cap. To the solids were added 0.8 mL of DMF and 0.14 mL (1.4 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and the organics were washed with H₂O (3 x 2 mL) and brine (1 x 2 mL), then dried over magnesium sulfate and concentrated *in vacuo*. ¹H NMR spectroscopy was used to determine isomeric ratios and yields using an internal standard (2-methoxynaphthalene). Alkene insertion selectivity is defined as the ratio of **4f** + **5f** to (*E*)-**6f**.

Table 53.					
Ligand	yield	(<i>E</i>)₋4f	: 5f :	(<i>E</i>)₋6f	Suzuki
none	82%	1.5	0.45	1.0	16%
L1	77%	1.3	0.36	1.0	15%
L2	83%	1.6	0.43	1.0	19%
L3	25%	2.1	1.0	1.0	30%
L4	62%	7.7	2.4	1.0	13%
L5	35%	3.3	2.6	1.0	36%
L6	67%	1.3	0.67	1.0	19%
L7	75%	1.3	0.77	1.0	16%
L8	47%	1.7	1.9	1.0	35%
N F	$L^{2h} \xrightarrow{O}_{N} \xrightarrow{O}_{N}$	L		F ₃ C	
F ₃ C) N N		3 O 	R _ N	0 N = CF ₃ \/
L5		L	.6 /	L8 R	= Me

I. Tabular Summary of 1,4-Difunctionalization Ligand Screen

Table S	4.					_
			pred.	meas.		
			$\Delta\Delta G^{\ddagger}$	$\Delta\Delta G^{\ddagger}$	meas. alkene	
entry	R	Х	(kcal/mol)	(kcal/mol)	insertion selectivty	_
1	н	4-H	0.74	0.79	3.81	
2	н	4-CI	0.72	0.66	3.06	
3	Н	$5-CF_3$	0.70	0.76	3.58	
4	Me	$5-CF_3$	0.99	0.94	4.91	~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
5	Ph	5-CF ₃	1.09	1.13	6.72	
6	Bn	$5-CF_3$	1.28	1.31	9.19	
7	<i>i</i> -Pr	4-H	1.23	1.05	5.91	$N \rightarrow N$
8	<i>i</i> -Pr	4-CI	1.21	1.27	8.59	N-/
9	<i>i</i> -Pr	5-CF ₃	1.19	1.17	7.19	R
10	<i>t-</i> Bu	4-H	1.48	1.46	11.8	
11	<i>t-</i> Bu	4-CI	1.46	1.68	17.0	
12	<i>t-</i> Bu	$5-CF_3$	1.44	1.59	14.6	
13	<i>t</i> -Bu	4-Me	1.49	1.44	11.3	
14	<i>t-</i> Bu	5-CN	1.42	1.36	9.98	
15	<i>t-</i> Bu	5-NO ₂	1.41	1.25	8.29	_

J. Training Set Data for Pyrox Ligand Library

K. General Procedure of Reaction Optimization C



To an oven dried 5 mL vial were added 36 mg (0.34 mmol, 1.7 equiv) of Na₂CO₃, 52 mg (0.2 mmol, 1.0 equiv) of **1e**, 53 mg (0.3 mmol, 1.5 equiv) of **3c**, 4 mg (8 mol%) **L4**, and 6 mg (3.0 mol%) of Pd₂dba₃•CHCl₃. The vial was equipped with a stirbar and the threads were wrapped with Teflon tape, and then was flushed with N₂ before being sealed with a septum cap. To the solids were added 0.8 mL of DMF and 0.14 mL (1.4 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h. After completion, the mixture was diluted with MTBE and the organics were washed with H₂O (3 x 2 mL) and brine (1 x 2 mL), then dried over magnesium sulfate and concentrated *in vacuo*. ¹H NMR spectroscopy was used to determine isomeric ratios and yields using an internal standard (2-methoxynaphthalene).

L. Tabular Summary of Reaction Optimization C

Table S5.							
x (mol%)	temp.	yield (%)	(<i>E</i>)₋4f	5f	:	(<i>E</i>)_6f	Suzuki (%)
8	rt	52	8.0	4.0		1.0	16
7	rt	59	7.7	3.6		1.0	15
7	45 °C	66	6.8	3.1		1.0	11

M. Optimized General Procedure C



To an oven dried 10 mL round bottom flask were added 90 mg (0.85 mmol, 1.7 equiv) of Na_2CO_3 , 130 mg (0.5 mmol, 1.0 equiv) of **1e**, 134 mg (0.75 mmol, 1.5 equiv) of **3c**, 10 mg (7.0 mol%) of **L4**, and 16 mg (3.0 mol%) of Pd₂dba₃•CHCl₃. The flask was equipped with a PTFE-lined stirbar and a septum, and then was flushed with N₂. To the solids were added a solution of in 2.0 mL of DMF and 0.35 mL (3.5 mmol, 7.0 equiv) of isoprene. The mixture was stirred for 16 h at 45 °C. After completion, the mixture was diluted with MTBE and filtered through a Celite plug. The organics were washed with H₂O (3 x 10 mL) and brine (1 x 10 mL), then dried over magnesium sulfate and concentrated *in vacuo*. Crude products were purified by silica gel flash chromatography. Yields represent a mixture of stereo and regioisomers. HPLC methods and NMR analysis were used to isolate and verify the identity of product isomers. ¹H NMR spectroscopy was used to determine isomeric ratios of the product mixture.

N. Scope and Limitations of the 1,4-Difunctionalization Reaction with Ligand



tert-Butyl-4-((2*E*,5*E*)-7-methoxy-3-methyl-7-oxohepta-2,5-dien-1-yl)-3,6-dihydropyridine-1-carboxylate (*E*)-4c.

General procedure C was followed using 90 mg of Na₂CO₃ (0.85 mmol), 65 mg of **3b** (0.5 mmol), 10 mg of **L4** (7.0 mol%), 16 mg of Pd₂dba₃•CHCl₃(3 mol%), 497 mg of **1c** (1.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (4:1 hexanes:EtOAc) led to the isolation of **4c**, **5c**, and **6c** as a colorless oil (84 mg, 50% as a 9.2:1.3:5.9:1.0:0.79 mixture of (*E*)-4c:(*Z*)-4c:5c:(*E*)-6c:(*Z*)-6c isomers respectively; 95 mg, 57% as a 8.6:1.3:5.2:1.0:1.0 mixture of (*E*)-4c:(*Z*)-4c:5c:(*E*)-6c:(*Z*)-6c isomers respectively).



(Z)-3-((4E,7E)-8-(4-methoxyphenyl)-5-methylocta-4,7-dien-2-ylidene)dihydrofuran-2-one (E)-4f.

General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 134 mg of **3c** (0.75 mmol), 16 mg of Pd_2dba_3 •CHCl₃(3 mol%), 130 mg of **1e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **4f**, **5f**, and **6f** as a colorless oil (120 mg, 77% as a 7.2:1.0:2.7:1.0:0.75 mixture of (*E*)-**4f**:(*Z*)-**4f**:(**Z**)-**6f**:(*Z*)-**6f** isomers respectively).



(Z)-3-((4E,7E)-5-methyl-8-(4-(trifluoromethyl)phenyl)octa-4,7-dien-2-ylidene)dihydrofuran-2-one (E)-4g.

General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 162 mg of **3d** (0.75 mmol), 16 mg of Pd_2dba_3 •CHCl₃(3 mol%), 130 mg of **1e** (0.5 mmol), and 0.35 mL of isoprene

(3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of 4g, 5g, and 6g as a colorless oil (142 mg, 81% as a 6.6:0.97:4.1:1.0:0.60 mixture of (*E*)-4g:(*Z*)-4g:5g:(*E*)-6g:(*Z*)-6g isomers respectively).



(Z) - 3 - ((E) - 5 - methyl - 7 - phenylocta - 4, 7 - dien - 2 - ylidene) dihydrofuran - 2(3H) - one (E) - 4h.

General procedure A was followed using 90 mg of Na₂CO₃ (0.85 mmol), 111 mg of **3e** (0.75 mmol), 16 mg of Pd₂dba₃•CHCl₃(3 mol%), 130 mg of **1e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **4h**, **5h**, and **6h** as a colorless oil (62 mg, 44% as a 4.2:0.92:1.1:1.0:0.43 mixture of (*E*)-**4h**:(*Z*)-**4h**:**5h**:(*E*)-**6h**:(*Z*)-**6h** isomers respectively; 69 mg, 49% as a 4.3:0.87:0.97:1.0:0.36 mixture of (*E*)-**4h**:(*Z*)-**4h**:**5h**:(*E*)-**6h**:(*Z*)-**6h** isomers respectively).



tert-butyl-4-((2*E*,5*Z*)-2-methyl-5-(2-oxodihydrofuran-3-ylidene)hex-2-en-1-yl)-3,6-dihydropyridine-1-carboxylate (*E*)-4i.

General procedure A was followed using 90 mg of Na_2CO_3 (0.85 mmol), 170 mg of **3f** (0.75 mmol), 16 mg of Pd_2dba_3 •CHCl₃(3 mol%), 130 mg of **1e** (0.5 mmol), and 0.35 mL of isoprene (3.5 mmol) in 2.0 mL of DMF. Purification by flash chromatography (3:1 hexanes:EtOAc) led to the isolation of **4i**, **5i**, and **6i** as a colorless oil (126 mg, 70% as a 9.0:1.1:3.3:1.0:0.67 mixture of (*E*)-**4i**:(*Z*)-**4i**:(*Z*)-**6i**:(*Z*)-**6i** isomers respectively).

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