**Cross-Couplings of Unactivated Secondary Alkyl Halides:
Room-Temperature Nickel-Catalyzed Negishi Reactions
of Alkyl Bromides and Iodides**

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I. General

The following reagents were purchased: pyridine-2,6-dinitrile (Aldrich), (2*S*,3*S*)-isoleucinol (TCI), ZnCl₂ (anhydrous; Cerac), chlorobenzene (anhydrous; Aldrich), Ni(cod)₂ (Strem), *N,N*-dimethylacetamide (DMA; anhydrous; Aldrich), 4-bromopiperidine hydrobromide (Aldrich), pentan-3-ol (Aldrich), 4-chlorobutyrophenone (92%; Aldrich), zinc powder (−140+325 mesh, 99.9%; Alfa-Aesar), iodine (chips, 99+%; Aldrich), *n*-nonyl bromide (Avocado), cycloheptyl bromide (Lancaster), cyclooctyl bromide (Lancaster), cyclopentyl iodide (Aldrich), cyclohexyl iodide (Lancaster), 4-phthalimido-1-bromobutane (Avocado), neopentyl iodide (Aldrich), isoamyl iodide (Aldrich), 3-phenoxypropyl bromide (Aldrich), 2-(2-bromoethyl)-1,3-dioxolane (Avocado), ethyl 5-bromovalerate (Avocado), 3-phenylpropyl bromide (Aldrich). 6-Bromo-*N,N*-diethylhexanamide was prepared according to a literature procedure.¹

The liquid alkyl halides were purged with argon prior to use. All reactions were conducted in oven-dried glassware under an inert atmosphere with magnetic stirring.

II. Preparation of Substrates and Reagents

The yields have not been optimized.

***s*-Bu-Pybox (2,6-bis[(4*S*, 6*S*)-*sec*-butyl-2-oxazolin-2-yl]pyridine) [118949-62-5].²** In a glove box, pyridine-2,6-dinitrile (367 mg, 2.85 mmol), (2*S*,3*S*)-isoleucinol (1.00 g, 8.5 mmol), anhydrous ZnCl₂ (39 mg, 0.29 mmol), and anhydrous chlorobenzene (10.0 mL) were added to a vial. The reaction mixture was stirred at 110 °C for 40 h, and then it was passed through a short pad of silica gel (CH₂Cl₂ washings). The filtrate was then concentrated, and the residue was crystallized from hot hexane/EtOAc (20:1). The resulting white powder was collected by filtration to give 740 mg (79%) of the desired product.

¹H NMR (CDCl₃, 400 MHz): δ 8.22 (d, *J* = 7.8 Hz, 2H), 7.85 (t, *J* = 7.8 Hz, 1H), 4.55-4.48 (m, 2H), 4.30-4.21 (m, 4H), 1.76-1.60 (m, 4H), 1.31-1.20 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 6H), 0.88 (d, *J* = 6.7 Hz, 6H).

¹³C NMR (CDCl₃, 400 MHz): δ 162.4, 147.2, 137.3, 125.9, 71.7, 70.7, 39.3, 26.4, 14.7, 11.7.

4-Bromo-*N*-(*p*-toluenesulfonyl)piperidine [347885-68-1]. 4-Bromopiperidine hydrobromide (1.15 g, 4.7 mmol), *p*-toluenesulfonyl chloride (1.16 g, 6.1 mmol), and pyridine (10 mL) were added to a flask, and the resulting mixture was stirred at r.t. for 18 h. The product was then extracted (CH₂Cl₂/1 N HCl), and the organic layer was concentrated. The residue was dissolved in CH₂Cl₂ and precipitated with hexane to give a white solid (1.15 g, 77%).

¹H NMR (CDCl₃, 400 MHz): δ 7.66 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 8.3 Hz, 2H), 4.28-4.23 (m, 1H), 3.23-3.17 (m, 2H), 3.13-3.07 (m, 2H), 2.46 (s, 3H), 2.24-2.17 (m, 2H), 2.10-2.03 (m, 2H).

¹³C NMR (CDCl₃, 400 MHz): δ 143.9, 133.3, 130.0, 127.8, 48.0, 44.0, 34.8, 21.7.

3-Iodopentane [1809-05-8].³ Imidazole (4.76 g, 70 mmol) and PPh₃ (18.3 g, 70 mmol) were added to a Schlenk tube equipped with a stir bar. The air was removed by evacuating/refilling with argon (three times), and then CH₂Cl₂ (100 mL) was added. The resulting solution was cooled to 0 °C, and iodine chips (17.8 g, 70 mmol) were introduced portion-wise. Pentan-3-ol (4.41 g, 50 mmol) was added dropwise to the 0 °C mixture (brown solution with yellow solids), which was then allowed to warm to r.t. overnight. Hexane was added, and the solids were removed by passing the mixture through silica gel (hexane washings). The resulting solution was concentrated, and the residue was purified by flash chromatography (hexane), which furnished the desired product as a pink oil (3.09 g; 31% yield).

¹H NMR (CDCl₃, 400 MHz): δ 4.10-4.04 (hept, *J* = 4.7 Hz, 1H), 1.93-1.72 (m, 4H), 1.04 (t, *J* = 7.2 Hz, 6H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 44.8, 33.6, 14.3.

4-Iodobutyrophenone [65488-05-3]. 4-Chlorobutyrophenone (1.96 g, 9.9 mmol) and NaI (7.50 g, 50 mmol) were refluxed in acetone (40 mL) for 10 h. The solvent was then removed, and the residue was passed through silica gel (CH_2Cl_2 washings). The filtrate was concentrated, and the residue was purified by flash chromatography (hexane/EtOAc), which provided a colorless oil (2.42 g, 88%) that quickly turned red (and solidified during storage in a refrigerator).

^1H NMR (CDCl_3 , 400 MHz): δ 8.02-8.00 (m, 2H), 7.63-7.59 (m, 1H), 7.52-7.49 (m, 2H), 3.36 (t, J = 6.6 Hz, 2H), 3.17 (t, J = 7.0 Hz, 2H), 2.29 (apparent quintet, J = 6.7 Hz, 2H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 199.0, 137.1, 133.7, 129.1, 128.4, 39.3, 27.9, 7.3.

Preparation of alkylzinc bromide solutions: Representative procedure.⁴ Zinc powder (0.980 g, 15.0 mmol) was added to a 25-mL Schlenk tube, and the air was removed by evacuating/refilling with argon (three times). Iodine chips (127 mg, 0.50 mmol) and *N,N*-dimethylacetamide (DMA; 10.0 mL) were then added, and the resulting mixture was stirred for 2 min at r.t., during which time it changed from a dark-brown suspension to a colorless solution. *n*-Nonyl bromide (2.07 g, 10.0 mmol) was added by syringe, and the reaction mixture was stirred at 80 °C for 3 h, at which time all of the starting material had been consumed (monitored by GC). The purity of the solution was >90%, and the concentration in DMA was ~0.75 M.

Preparation of isoamylzinc iodide. Zinc powder (0.980 g, 15.0 mmol) was added to a 25-mL Schlenk tube, and the air was removed by evacuating/refilling with argon (three times). Iodine chips (127 mg, 0.50 mmol) and DMA (10.0 mL) were then added, and the resulting mixture was stirred for 2 min at r.t., during which time it changed from a dark-brown suspension to a colorless solution. Isoamyl iodide (1.98 g, 10.0 mmol) was added by syringe, and the reaction mixture was stirred at r.t. for 3 h, at which time all of the starting material had been consumed (monitored by GC). The purity of the solution was >90%, and the concentration in DMA was ~0.75 M.

III. Negishi Cross-Coupling Reactions

Procedure for Table 1. In a glove box, yellow Ni(cod)₂ crystals (2.8 mg, 0.010 mmol), *s*-Bu-Pybox (6.6 mg, 0.020 mmol), and DMA (0.40 mL) were added to a vial. The resulting mixture was stirred for 20 min at r.t., and then the resulting deep-blue solution was treated in turn with *n*-C₁₆H₃₄ (internal standard for GC analysis; 29 μ L, 0.10 mmol), a solution of *n*-nonylzinc bromide (0.75 M in DMA; 0.53 mL, 0.40 mmol) and *i*-propyl bromide (24 μ L, 31 mg, 0.25 mmol). The reaction mixture was stirred for 20 h at r.t., and then it was quenched with ethanol (~0.5 mL). The resulting mixture was stirred at r.t. for 10 min, and then an aliquot was passed through silica gel and analyzed by GC.

Procedure for Tables 2 and 3 (with a glove box). In a glove box, yellow Ni(cod)₂ crystals (5.6 mg, 0.020 mmol), *s*-Bu-Pybox (13.2 mg, 0.040 mmol), and DMA (0.80 mL) were added to a vial. The resulting mixture was stirred for 20 min at r.t., and then the resulting deep-blue solution was treated in turn with a solution of the alkylzinc halide (0.75 M in DMA; 1.06 mL, 0.80 mmol) and the alkyl halide (0.50 mmol). The reaction mixture was stirred for 20 h at r.t., and then it was quenched with iodine chips (~100 mg; to iodinate the excess organozinc reagent). After stirring at r.t. for 10 min, the dark-brown mixture was passed through a short pad of silica gel (to remove DMA, inorganic salts, and iodine). The filtrate was then concentrated, and the residue was purified by flash chromatography.

Procedure for Tables 2 and 3 (without a glove box). Yellow Ni(cod)₂ crystals (5.6 mg, 0.020 mmol) and *s*-Bu-Pybox (13.2 mg, 0.040 mmol) were added to a vial. The air was removed by evacuating/refilling with argon (three times), and then DMA (0.80 mL) was added. The resulting mixture was stirred for 20 min at r.t., and then the resulting deep-blue solution was treated in turn with a solution of the alkylzinc halide (0.75 M in DMA; 1.06 mL, 0.80 mmol) and the alkyl halide (0.50 mmol). The reaction mixture was stirred for 20 h at r.t., and then it was quenched with iodine chips (~100 mg; to iodinate the excess organozinc reagent). After stirring at r.t. for 10 min, the dark-brown mixture was passed through a short pad of silica gel (to remove DMA, inorganic salts, and iodine). The filtrate was then concentrated, and the residue was purified by flash chromatography. [Note: Electrophiles that are solids (4-bromo-*N*-(*p*-toluenesulfonyl)piperidine, 4-phthalimido-1-bromobutane, and 4-iodobutyrophenone) were added before DMA.]

Table 2, entry 1. 4-Bromo-*N*-(*p*-toluenesulfonyl)piperidine (159 mg, 0.50 mmol) and isoamylzinc iodide (0.75 M in DMA; 1.6 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/EtOAc 100:10. White powder (glove box: 102 mg, 66%; no glove box: 100 mg, 65%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.63 (d, J = 8.2 Hz, 2H), 7.31 (d, J = 8.2 Hz, 2H), 3.75 (d, J = 11.6 Hz, 2H), 2.42 (s, 3H), 2.18 (td, J = 11.9, 2.1 Hz, 2H), 1.70 (d, J = 11.5 Hz, 2H), 1.44 (hept, J = 6.6 Hz, 1H), 1.31-1.24 (m, 2H), 1.25-1.16 (m, 2H), 1.13-1.08 (m, 3H), 0.83 (d, J = 6.6 Hz, 6H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 143.4, 133.2, 129.6, 127.8, 46.7, 35.9, 35.5, 33.9, 31.7, 28.1, 22.7, 21.6.

IR (KBr pellet): 2945, 2844, 1598, 1466, 1338, 1168 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{17}\text{H}_{27}\text{NNaO}_2\text{S}$ ($\text{M}+\text{Na}$) $^+$ 332.1655. Found: 332.1650.

Table 2, entry 2. Cycloheptyl bromide (90 mg, 0.50 mmol) and 3-phenoxypropylzinc bromide (0.75 M in DMA; 1.06 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/ Et_2O 100:3. Colorless oil (glove box: 70 mg, 60%; no glove box: 74 mg, 64%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.35-7.29 (m, 2H), 6.99-6.92 (m, 3H), 3.98 (t, J = 6.7 Hz, 2H), 1.87-1.39 (m, 15H), 1.29-1.20 (m, 2H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 159.3, 129.6, 120.6, 114.7, 68.4, 39.2, 34.7, 34.6, 28.7, 27.4, 26.7.

IR (thin film): 2922, 2852, 1601, 1497, 1245 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{16}\text{H}_{24}\text{O}$ ($\text{M}+\text{Na}$) $^+$ 232.1822. Found: 232.1818.

Table 2, entry 3. Cyclooctyl bromide (96 mg, 0.50 mmol) and 2-(1,3-dioxolan-2-yl)ethylzinc bromide (0.75 M in DMA; 1.6 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/ Et_2O 100:3. Colorless oil (glove box: 74 mg, 70%; no glove box: 69 mg, 65%).

^1H NMR (CDCl_3 , 400 MHz): δ 4.84 (t, J = 4.8 Hz, 1H), 3.99-3.93 (m, 2H), 3.90-3.84 (m, 2H), 1.70-1.42 (m, 15H), 1.36-1.24 (m, 4H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 105.2, 65.0, 37.4, 32.5, 32.4, 32.1, 27.5, 26.5, 25.7.

IR (thin film): 2910, 2856, 1728, 1474, 1447, 1145 cm^{-1} .

HRMS (EI): Calcd for $\text{C}_{13}\text{H}_{23}\text{O}_2$ ($\text{M}-\text{H}$) $^+$: 211.1693. Found: 211.1701.

Table 2, entry 4. 3-Iodopentane (99 mg, 0.50 mmol) and 4-ethoxycarbonylbutylzinc bromide (0.75 M in DMA; 1.6 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/ Et_2O 100:3. Colorless oil (glove box: 61 mg, 61%; no glove box: 62 mg, 62%).

^1H NMR (CDCl_3 , 400 MHz): δ 4.12 (q, J = 7.1 Hz, 2H), 2.30 (t, J = 7.6 Hz, 2H), 1.61 (quintet, J = 7.5 Hz, 2H), 1.33-1.13 (m, 12H), 0.83 (t, J = 7.5 Hz, 6H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 174.2, 60.4, 40.4, 34.6, 32.5, 26.5, 25.6, 25.5, 14.5, 11.1.

IR (thin film): 2962, 2934, 1739, 1462, 1167 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{12}\text{H}_{24}\text{NaO}_2$ ($\text{M}+\text{Na}$) $^+$ 223.1669. Found: 223.1677.

Table 2, entry 5. Cyclopentyl iodide (98 mg, 0.50 mmol) and 5-diethylaminocarbonylpentylzinc bromide (0.75 M in DMA; 1.6 mL, 0.80 mmol) were

used. Solvent for chromatography: hexane/EtOAc 100:15. Colorless oil (glove box: 92 mg, 77%; no glove box: 94 mg, 79%).

^1H NMR (CDCl_3 , 400 MHz): δ 3.39-3.27 (m, 4H), 2.28 (t, J = 7.1 Hz, 2H), 1.72-1.47 (m, 9H), 1.30 (br s, 6H), 1.18-1.05 (m, 8H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 172.5, 42.1, 40.3, 40.2, 36.2, 33.3, 32.9, 30.0, 28.8, 25.7, 25.3, 14.6, 13.3.

IR (thin film): 2934, 2857, 1644, 1461, 1428, 1266 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{29}\text{NNaO}$ ($\text{M}+\text{Na}$) $^+$ 262.2141. Found: 262.2139.

Table 2, entry 6. [170661-44-6] Cyclohexyl iodide (106 mg, 0.50 mmol) and 3-phenylpropylzinc bromide (0.75 M in DMA; 1.6 mL, 0.80 mmol) were used. Solvent for chromatography: hexane. Colorless oil (glove box: 88 mg, 87%; no glove box: 89 mg, 88%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.32-7.28 (m, 2H), 7.22-7.18 (m, 3H), 2.61 (t, J = 7.9 Hz, 2H), 1.75-1.62 (m, 7H), 1.30-1.25 (m, 6H), 0.94-0.85 (m, 2H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 143.2, 128.6, 128.4, 125.8, 37.8, 27.4, 36.5, 33.6, 29.0, 27.0, 26.7.

Table 3, entry 1. [151921-82-3] 4-Phthalimido-1-bromobutane (141 mg, 0.50 mmol) and 3-phenylpropylzinc bromide (0.75 M in DMA; 1.6 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/EtOAc 100:7. Colorless oil (glove box: 99 mg, 64%; no glove box: 102 mg, 66%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.87-7.84 (m, 2H), 7.74-7.70 (m, 2H), 7.31-7.27 (m, 2H), 7.28-7.20 (m, 3H), 3.70 (t, J = 7.3 Hz, 2H), 2.61 (t, J = 7.8 Hz, 2H), 1.73-1.61 (m, 4H), 1.38 (br s, 6H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 168.6, 142.9, 134.0, 132.3, 128.5, 128.4, 125.7, 123.3, 38.2, 36.0, 31.5, 29.3, 29.2, 28.7, 26.9.

Table 3, entry 2. 4-Iodobutyrophenone (137 mg, 0.50 mmol) and 2-(1,3-dioxolan-2-yl)ethylzinc bromide (0.75 M in DMA; 1.6 mL, 0.80 mmol) were used. Solvent for chromatography: hexane/EtOAc 100:10. White solid (glove box: 93 mg, 75%; no glove box: 91 mg, 73%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.97-7.95 (m, 2H), 7.57-7.53 (m, 1H), 7.48-7.44 (m, 2H), 4.85 (t, J = 4.8 Hz, 1H), 3.98-3.92 (m, 2H), 3.89-3.83 (m, 2H), 2.98 (t, J = 7.5 Hz, 2H), 1.80-1.73 (m, 2H), 1.71-1.66 (m, 2H), 1.53-1.41 (m, 4H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 200.5, 137.1, 133.0, 128.7, 128.2, 104.7, 65.0, 38.6, 33.9, 29.4, 24.3, 24.0.

IR (KBr pellet): 2940, 2894, 2860, 1684, 1449, 1231 cm^{-1} .

HRMS (ESI): Calcd for $\text{C}_{15}\text{H}_{20}\text{NaO}_3$ ($\text{M}+\text{Na}$) $^+$ 271.1305. Found: 271.1305.

Table 3, entry 3. [130986-02-6] Neopentyl iodide (99 mg, 0.50 mmol) and 3-phenylpropylzinc bromide (0.75 M in DMA; 1.6 mL, 0.80 mmol) were used. Solvent for chromatography: hexane. Colorless oil (glove box: 68 mg, 72%; no glove box: 70 mg, 74%).

^1H NMR (CDCl_3 , 400 MHz): δ 7.38-7.34 (m, 2H), 7.28-7.24 (m, 3H), 2.70 (t, $J = 7.7$ Hz, 2H), 1.68 (quintet, $J = 7.0$ Hz, 2H), 1.44-1.36 (m, 2H), 1.32-1.27 (m, 2H), 0.96 (s, 9H).

^{13}C NMR (CDCl_3 , 400 MHz): δ 143.2, 128.6, 128.4, 125.7, 44.2, 36.3, 32.7, 30.5, 29.6, 24.6.

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5291

8.235
8.216
7.872
7.852
7.832
7.269

4.551
4.532
4.515
4.499
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4.476
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4.261
4.250
4.235
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1.709
1.687
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1.655
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1.635
1.623
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1.312
1.294
1.276
1.260
1.242
1.222
1.20
1.033
0.982

s-Bu-Pybox

4-Bromo-N-toluenesulfonylpiperidine

6073a

3-Iodopentane

2029

4-Iodobutyrophenone

6087b

7.641
7.621
7.323
7.303
7.284

3.762
3.733
2.423
2.218
2.212
2.188
2.183
2.159
2.153
1.795
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1.460
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1.394
1.310
1.300
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1.271
1.250
1.240
1.217
1.210
1.200
1.184
1.176
1.168

Table 2, entry 1

6099a

Table 2, entry 2

6071b

Table 2, entry 3

6081a

Table 2, entry 4

6075a

7.283

Table 2, entry 5

Table 2, entry 6

6103d1

Table 3, entry 1

61131

Table 3, entry 2

6091d

7.378
7.359
7.341
7.284
7.275
7.257
7.237

2.722
2.703
2.683
1.714
1.697
1.677
1.658
1.639
1.441
1.423
1.418
1.407
1.400
1.389
1.381
1.370
1.363
1.356
1.324
1.316
1.310
1.298

Table 3, entry 3