A Unique Catalyst Effects the Room Temperature Cross-Coupling of Organozinc Reagents with Carboxylic Acid Fluorides, Chlorides, Anhydrides and Thioesters

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Supporting Information

General Methods. All reactions were carried out under an atmosphere of argon in flame-dried glassware with magnetic stirring. THF was degassed with argon and passed through two columns of neutral alumina. Column chromatography was performed on EM Science silica gel 60 (230-400 mesh). Thin layer chromatography was performed on EM Science 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light, KMnO_4 , aqueous ceric ammonium molybdate, or bromocresol green dips followed by heating.

Melting points were measured with a MelTemp II melting point apparatus outfitted with a Fluke 51 thermocouple and are uncorrected. Infrared spectra were obtained on a Nicolet Avatar 320 FT-IR spectrometer. ^1H NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Data are reported as follows: chemical shift in parts per million (δ , ppm) from an internal standard [tetramethylsilane (TMS) or deuterated chloroform (CDCl_3)], multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), integration, and coupling constant (Hz). ^{13}C NMR and spectra were recorded on a Varian 300, 400, or 500 MHz spectrometer at ambient temperature. Chemical shifts are reported in ppm from CDCl_3 taken as 77.0 ppm. Mass spectra were obtained on Fisons VG Autospec.

Standard Procedure for ketone synthesis by the Ni-catalyzed coupling of carboxylic acid fluorides and organozinc compounds

A flame-dried round bottom flask was charged with $\text{Ni}(\text{COD})_2$ (0.10 equiv) and pyphos (0.12 equiv) in an inert atmosphere (N_2) glove box. Upon removal from the glove box, 0.5 ml anhydrous THF was added via syringe under an atmosphere of argon and then the solution was stirred at ambient temperature for 15 minutes. 4-fluorostyrene (0.2 equiv) was introduced via syringe followed by a solution of organozinc (0.55 equiv in 0.5 mL THF) and then a solution of acid fluoride (1 equiv, 0.5 mL THF) *via* cannula. The reaction mixture was then stirred for the time and temperature indicated. The reaction was quenched with 5 ml 1M HCl and extracted with diethyl ether. The layers were separated and the aqueous layer extracted with diethyl ether (2 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The product was purified by silica gel chromatography.

Benzophenone (2). According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μL (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph_2Zn (36.1

mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 53.0 mg (97%) of desired ketone **2** was isolated.

phenyl-(2,4,6-triisopropylphenyl)-methanone (4). According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of Ni(COD)₂ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph₂Zn (36.1 mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 22 h at room temperature. Upon work-up 71.5 mg (77%) of desired ketone **4** was isolated.

Phenyl-(3,4,5-trimethoxyphenyl)methanone (6). According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of Ni(COD)₂ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph₂Zn (36.1 mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 80.0 mg (98%) of desired ketone **6** was isolated.

Phenyl-thiophen-2-yl-methanone (8). According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of Ni(COD)₂ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph₂Zn (36.1 mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 53.0 mg (97%) of desired ketone **8** was isolated.

1-phenyl-pent-4-en-1-one (10). According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of Ni(COD)₂ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph₂Zn (36.1 mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 53.0 mg (97%) of desired ketone **10** was isolated.

Cyclohex-1-enyl-phenyl-methanone (12). According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of Ni(COD)₂ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph₂Zn (36.1 mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 53.0 mg (97%) of desired ketone **12** was isolated.

3-(2-Oxo-2-phenyl-ethyl)-1,4-dioxaspiro[4,5]decan-2-one(14). According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of Ni(COD)₂ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph₂Zn (36.1

mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 53.0 mg (97%) of desired ketone **14** was isolated.

^1H NMR (300 MHz, CDCl_3) δ 7.92 (m, 2H), 7.56 (m, 1H), 7.44 (m, 2H), 4.93 (dd, 1H, $J = 3.0$ Hz, $J = 6.9$ Hz), 3.58 (dd, 1H, $J = 3.3$ Hz, $J = 18.0$ Hz), 3.43 (dd, 1H, $J = 6.9$ Hz, $J = 18.0$ Hz), 1.92-1.22 (m, 10H); ^{13}C NMR (75 MHz, CDCl_3) δ 195.1, 173.5, 136.4, 133.8, 128.9, 128.3, 112.2, 69.8, 40.5, 36.4, 35.5, 24.6, 23.2, 23.2; IR (NaCl, neat) 1791, 1691, 1221, 944 cm^{-1} ; HRMS $[\text{C}_{16}\text{H}_{28}\text{O}_4+\text{H}]^+$ calcd 275.1283. Found 275.1275 (FAB+).

3-Methoxy-1,3-diphenyl-propan-1-one (**16**).

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph_2Zn (36.1 mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 30 min at room temperature. Upon work-up 53.0 mg (97%) of desired ketone **16** was isolated.

2-(1-Benzyl-2-oxo-2-phenyl-ethyl)-isoindole-1,3-dione (**18**).

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Ph_2Zn (36.1 mg, 0.165 mmol, 0.55 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 30 min at room temperature. Upon work-up 53.0 mg (97%) of desired ketone **18** was isolated. Enantiomeric excess of the ketone was determined using chiral stationary phase HPLC analysis using Chiralpak AS (hexanes:iPrOH 97:3 at 0.3 mL/min): minor 82.9 min, major 87.7 min (ee >99%).

1-Phenyl-ethanone (**19a**)

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Me_2Zn (2M in toluene, 90 μ L, 0.18 mmol), 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 33.2 mg (92%) of desired ketone **19a** was isolated.

1-Phenyl-propan-1-one (**19b**)

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Et_2Zn (18.0 μ L, 0.18 mmol, 0.6 equiv) in 0.5 mL of THF, 33 μ L (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 36.0 mg (90%) of desired ketone **19b** was isolated.

2-Methyl-1-phenyl-propan-1-one (**19c**)

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated

with 7 μL (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, $(i\text{Pr})_2\text{Zn}$ (1M in toluene, 0.16 mL), 33 μL (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 40.5 mg (91%) of desired ketone **19C** was isolated.

4-Oxo-4-phenyl-butyric acid ethyl ester (**19d**)

A Schlenk flask was charged with ZnCl_2 (163.0 mg, 1.2 mmol, 0.4 equiv) from glove box. The flask was evacuated and heated with a burner with swirling until practically all of the salt melted. After the flask cooled down to room temperature, 3 mL of Et_2O was introduced via syringe. The mixture was refluxed gently for 1 h to aid dissolution of the solid state. The flask was cooled. [(1-ethoxycyclopropyl)oxy]trimethylsilane (0.5 g, 0.57 mL, 3.0 mmol) was introduced dropwise. The cloudy mixture was stirred for 1 h at room temperature and then reflux for 30 min. The solvent was removed under vacuum. The residue was redissolved in 3 mL of THF to make ~ 0.32 M solution and used directly for acylation. The estimated yield is about 80%.

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μL (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, 0.32 M $(\text{EtOOCCH}_2\text{CH}_2)_2\text{Zn}$ (0.5 mL, 0.16 mmol), 33 μL (0.3 mmol) of benzoyl fluoride **1** in 0.5 mL THF was added via cannula and the reaction was stirred for 10 min at room temperature. Upon work-up 59.2 mg (95%) of desired ketone **19d** was isolated.

2R-Benzyloxy-1-phenyl-propan-1-one (**21a**)

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μL (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, 36.1 mg (0.165 mmol, 0.55 equiv) of Ph_2Zn , 54.6 mg (0.3 mmol) of acid fluoride in 0.5 mL THF was added via cannula and the reaction was stirred for 30 min at room temperature. Upon work-up 51.8 mg (72%) of desired ketone was isolated. Enantiomeric excess determined by chiral stationary phase HPLC analysis using Chiralpak AS (hexanes:*i*PrOH 97:3 0.2 mL/min): minor 29.7 min; major 32.8 min (ee = 92%). This result was compared to the ee of O-benzyl ethyl lactate (ee = 92%) which was used for the synthesis of the acid fluoride (ester hydrolysis followed by formation of the acid fluoride).

2R-Benzyloxy-pentan-3-one (**21b**)

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of $\text{Ni}(\text{COD})_2$ and 10.4 mg (0.036 mmol, 0.12 equiv) of Pyphos in 0.5 mL of THF were treated with 7 μL (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Et_2Zn (18.0 μL , 0.18 mmol, 0.6 equiv), 54.6 mg (0.3 mmol) of acid fluoride in 0.5 mL THF was added via cannula and the reaction was stirred for 30 min at room temperature. Upon work-up 50.3 mg (87%) of desired ketone was isolated. Enantiomeric excess determined by chiral stationary phase HPLC analysis using Chiralcel OJ (hexanes:*i*PrOH 95:5 0.5 mL/min): major 17.9 min; minor 19.4 min (ee = 92%). This result was compared to the ee of O-benzyl ethyl lactate (ee = 92%) which was used for the synthesis of the acid fluoride (ester hydrolysis followed by formation of the acid fluoride).

5S-(1R-Benzyl-2-oxo-2-phenyl-ethyl)-2S-tert-butyl-[1,3]dioxolan-4-one (23a)

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of Ni(COD)₂ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, 36.1 mg (0.165 mmol, 0.55 equiv) of Ph₂Zn and 88.2 mg (0.3 mmol) of acid fluoride in 0.5 mL THF was added via cannula and the reaction was stirred for 1 h at room temperature. Upon work-up 99.3 mg (94%) of desired ketone was isolated. Diastereomeric ratio of products was determined by ¹H NMR and correlated based on the dr observed in the formation of **23b** (see below).

¹H NMR (300 MHz, CDCl₃) δ 7.72 (m, 2H), 7.51 (m, 1H), 7.38 (m, 2H), 7.24-7.14 (m, 5H), 5.10 (d, 1H, J = 1.2 Hz), 4.53 (dd, 1H, J = 1.2 Hz, J = 8.1 Hz), 4.13 (m, 1H), 3.45 (dd, 1H, J = 5.4 Hz, J = 13.5 Hz), 3.22 (dd, 1H, J = 9.0 Hz, J = 13.5 Hz), 0.89 (s, 9H). ¹³C NMR (75 MHz, CDCl₃)

δ 199.7, 172.7, 137.9, 137.7, 133.3, 129.3, 128.7, 128.6, 128.4, 126.8, 109.5, 74.8, 49.6, 34.4, 34.3, 23.6; IR (NaCl, neat) 1800, 1684, 1200, 958, 744, 696 cm⁻¹; HRMS [C₂₂H₂₄O₄+H]⁺ calcd 353.1753. Found 353.1761 (FAB+).

5S-(1R-Benzyl-2-oxo-butyl)-2S-tert-butyl-[1,3]dioxolan-4-one (23b)

According to the general procedure, 8.0 mg (0.03 mmol, 0.1 equiv) of Ni(COD)₂ and 10.4 mg (0.036 mmol, 0.12 equiv) of pyphos in 0.5 mL of THF were treated with 7 μ L (0.06 mmol, 0.2 equiv) of 4-fluorostyrene, Et₂Zn (18.0 μ L, 0.18 mmol, 0.6 equiv), 88.2 mg (0.3 mmol) of acid fluoride as an 88:8:3:1 mixture of isomers (as judged by GC-MS) in 0.5 mL THF was added via cannula and the reaction was stirred for 1 h at room temperature. Upon work-up 96.1 mg (97%) of desired ketone was isolated, as an 89:8:3 mixture of isomers (as judged by GC-MS).

¹H NMR (300 MHz, CDCl₃) δ 7.37-7.17 (m, 5H), 5.12 (d, 1H, J = 1.2 Hz), 4.37 (dd, 1H, J = 1.2 Hz, J = 8.1 Hz), 3.51-3.17 (m, 1H), 3.08-2.96 (m, 1H), 2.45-2.25 (m, 1H), 2.11-1.98 (m, 1H), 0.99 (s, 9H, major), 0.90 (t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 210.0, 172.7, 138.0, 129.2, 128.9, 127.0, 109.5, 74.7, 54.4, 38.6, 34.4, 33.9, 23.7, 7.2; IR (NaCl, neat) 1796, 1717, 1203, 963, 702 cm⁻¹; HRMS [C₁₈H₂₄O₄+H]⁺ calcd 305.1753. Found 305.1750 (FAB+).

Procedure for the coupling of Et₂Zn and benzoyl fluoride using Ni(II) precatalyst: A flame-dried round bottom flask equipped with a magnetic stir bar was charged with 0.104 g (0.403 mmol, 1 mol%) of anhydrous Ni(acac)₂ and 0.141 g (0.48 mmol, 1.2 mol%) of Pyphos. The reaction flask was then placed under vacuum for five minutes and then refilled with dry argon. After 3 vacuum/argon cycles the flask was placed under a static argon atmosphere. 65 mL of dry THF were added via syringe followed by addition of 96.0 μ L (0.806, 2.0 mol% mmol) of 4-fluorostyrene via syringe. 2.48 mL (24.18 mol, 0.6 equiv) of neat Et₂Zn was then added dropwise via syringe at room temperature. The mixture became light red. Last, 5.0 g (40.3 mmol) of benzoyl fluoride in 10 mL of THF was then introduced via syringe to the light red reaction mixture. The reaction mixture became very warm. TLC revealed that all starting material disappeared after 3 min. After the mixture was cooled down to room temperature, the reaction mixture was then quenched with 20 mL 1M HCl and diluted with 100 mL of ether. The layers were separated and the aqueous layer extracted with ether (2 x 30 mL). The combined organic

extracts were washed with brine, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield 5.03 g (93%) of the desired ketone 1-phenyl-propan-1-one.

saydIII-488

saydIII-488-Cl3

sasydIV-96

sasydIV-96-Cl3

aaydiv-98

aaydiv-98-C13

HPLC trace of **18** and *rac*-**18**.