Supporting Information

Catalytic Cross-Coupling of Alkylzinc Halides with α -Chloroketones

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Methods and Materials

General. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly purified solvents. Laguna Beach, CA. All reactions were monitored by thin-layer chromatography using E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Gas chromatography (GC) was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with and FID detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies. ^1H and ^{13}C NMR spectra were recorded on Varian Inova-400 or Mercury-300 spectrometers unless otherwise indicated. Chemical shifts are reported relative to internal chloroform (^1H , $\delta = 7.26$, ^{13}C , $\delta = 77.25$) or benzene (^1H , $\delta = 7.16$, ^{13}C , $\delta = 128.1$) as indicated. Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), quin (quintet), sex (sextet) or sep (septet), oct (octet). For signals having multiple coupling patterns, the coupling constants are listed in the same order as the patterns (e.g. dt, $J = 2.0, 4.0$; 2.0 is the coupling constant for the doublet and 4.0 is the coupling constant for the triplet). Infrared spectra were recorded on a Perkin-Elmer 1000 series FTIR. Low resolution mass spectra were acquired on a Shimadzu QP5000 GC/MS or Shimadzu-2010 LC/MS using the indicated ionization method. Chiral HPLC analyses were performed on a Shimadzu LC-10Ai equipped with a diode array detector.

Materials

Diethyl ether (Et_2O) and tetrahydrofuran (THF), methylene chloride and toluene were purified using a solvent purification system purchased from GlassContour, diisopropyl zinc (1M in hexanes), cyclopentyl zinc bromide (0.5 M THF) and Grignard reagents [3.0 M in Et_2O (ethyl magnesium bromide) or 2.0 M in Et_2O] were purchased from Aldrich and used as received. 2-chlorocyclohexanone was purchased from Fisher Scientific and distilled under reduced pressure

prior to use. ZnCl_2 and ZnBr_2 were purchased from Fisher Scientific and were freshly fused under vacuum prior to use. All other commercially obtained reagents were used as received.

Chloroketones **2c** and **2i** were prepared using the method of Brummond and Gesenberg.¹

Chloroketones **2b**, **2d**, **2e**, **2f**, **2g**, and **2h** were prepared via chlorination of the corresponding ketone with *N*-chlorosuccinimide (NCS). The details of this protocol will be reported separately, but briefly: a solution of the ketone (1.00 equiv) and NCS (1.05 equiv) in DMF (1M) was stirred at 25 °C – 50 °C until complete conversion of the ketone was observed. Aqueous workup followed by chromatography on silica gel provided the ketones in 80 – 95% yield.

(+)-2-Chloro-1-phenyl-propan-1-one (2j) was prepared as previously described² in 94% ee as determined by chiral HPLC (Figures S1, S2; Chiralcel OD-H, 10 % IPA in hexanes, $t_r(\text{minor}) = 4.7$ min, $t_r(\text{major}) = 5.3$ min. ¹H NMR (CDCl_3) $\delta = 1.75$ (d, $J = 6.7$, 3H), 5.26 (q, $J = 6.7$, 1H), 7.46-7.52 (m, 2H), 7.57-7.63 (m, 1H), 8.00-8.04 (m, 2H). ¹³C NMR (CDCl_3) $\delta = 20.2$, 53.0, 129.0, 129.2, 134.0, 134.3, 193.8. FTIR (NaCl) 3064, 2985, 2934, 2868, 1694, 1597, 1449, 1377, 1347, 1253, 954 cm^{-1} . $[\alpha]_D^{23} +17.1$ ($c = 1.45$, CH_2Cl_2) lit² $[\alpha] +$.

Trans-4-tert-butyl-2-chloro-cyclohexanone (2k).

The method of Brummond and Gesenberg¹ was used to prepare chloroketone **2k**. To a solution of diisopropylamine (4.02 mL, 21.5 mmol) in THF (45 mL) under an N_2 atmosphere at -78 °C, *n*-butyl lithium (13.4 mL 1.6 M in hexane, 21.5 mmol) was added and the reaction solution was stirred for 20 min. To the reaction solution, a solution of 4-*tert*-butyl-cyclohexanone (3.00 g, 19.5mmol) in THF (90 mL) was added and the reaction solution was stirred for 20 min at -78 °C. Finally, *p*-toluenesulfonyl chloride (4.08 g, 21.5 mmol) in THF (45 mL) was added and the reaction solution was stirred for 10 min at -78 °C. The solution was allowed to warm to room

temperature and stirring was continued for 1 h. The reaction mixture was filtered through a pad of silica gel, which was then washed with Et₂O (2 x 75 mL). The solvent was evaporated under reduced pressure and the crude mixture was purified by chromatography on silica gel (gradient elution; 20% to 35% CH₂Cl₂ in hexanes). The *trans*- α -chloroketone (**2k**) was recovered as a pale yellow oil (2.1 g, 57% yield). ¹H NMR (CDCl₃) δ 0.93 (s, 9H), 1.39-1.50 (m, 1H), 1.88 (ddd, *J* = 3.6, 12.0, 14.2, 1H), 2.00 (tt, *J* = 2.7, 12.0, 1H), 2.11 (dtd, *J* = 3.1, 6.2, 12.0, 1H), 2.29-2.35 (m, 2H), 2.99 (dt, *J* = 6.2, 14.3, 1H), 4.24-4.26 (m, 1H). ¹³C NMR (CDCl₃) δ = 27.8, 27.9, 32.3, 36.1, 36.2, 40.3, 60.6, 205.7. FTIR (NaCl) 2963, 2872, 1728, 1368 cm⁻¹. MS (EI) 188 [M]⁺.

***Cis*-4-*tert*-butyl-2-chloro-cyclohexanone (**2l**).**

To a solution of *trans*-4-*tert*-butyl-2-chloro-cyclohexanone (**2k**) (1.50 g, 7.96 mmol) in CHCl₃ (130 mL), was added DBU (0.16 mL, 1.04 mmol). The reaction solution was stirred at 25 °C for 30 min. The solvent was evaporated under reduced pressure and the mixture purified by chromatography on silica gel (gradient elution; 20% to 35% CH₂Cl₂ in hexanes). The *cis*- α -chloroketone (**2l**) was recovered as a white solid (0.90 g, 60% yield). ¹H NMR (CDCl₃) δ = 0.95 (s, 9H), 1.47-1.56 (m, 1H), 1.68 (tt, *J* = 2.8, 12.2, 1H), 1.77 (q, *J* = 12.3, 1H), 2.14 (dtd, *J* = 3.0, 6.0, 13.2, 1H), 2.39 (ddt, *J* = 0.9, 6.0, 14.0, 1H), 2.56-2.63 (m, 1H), 2.66 (ddd, *J* = 2.7, 4.2, 14.1, 1H), 4.54 (ddd, *J* = 0.9, 6.0, 12.8, 1H). ¹³C NMR (CDCl₃) δ = 27.8, 28.2, 32.8, 40.4, 40.5, 47.7, 64.5, 202.8. FTIR (NaCl) 2963, 2872, 1734, 1368 cm⁻¹. Additionally, the *trans*- α -chloroketone (**2k**) was recovered as a pale yellow oil (0.47 g, 31% yield). Structural assignment of **2l** based on the coupling constants for the proton on the chlorine-bearing carbon (one axial-axial, one axial-equatorial).

General procedure for the cross coupling of alkylzinc halides with α -chloroketones (Table 2). Alkylzinc halide reagents were prepared by adding the alkylmagnesium halide (1.0 equiv) as a solution in Et₂O to a solution of freshly fused ZnCl₂ or ZnBr₂ (1.0 equiv) in Et₂O (such that [RZnX•MgX₂] = 0.2 M) at 0 °C. The resulting suspension was stirred vigorously for 30 min at 0 °C. The RZnX•MgX₂ suspension (15 mL, 1.5 equiv or 20 mL, 2.0 equiv, as indicated below) was added via syringe to a suspension of chloroketone (2.0 mmol) and Cu(acac)₂ (0.1 mmol, 0.05 equiv, 26 mg) in THF or Et₂O (4.0 mL) as indicated below at 25 °C. Stirring was maintained for 14 h at which time the reaction mixture was diluted with Et₂O (200 mL) and extracted with sat. NH₄Cl_(aq) (200 mL). The organic layer was separated, dried over MgSO₄, filtered, concentrated under reduced pressure and purified using silica gel chromatography.

2-isopropyl-cyclohexanone³ (Table 2, entry 1): Alkylzinc halide: *i*-PrMgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: THF. Chromatography on silica gel (5% Et₂O in petroleum ether) provided 265 mg (95 % yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 0.86 (d, *J* = 6.4, 3H), 0.88 (d, *J* = 6.4, 3H), 1.46-2.08 (m, 7H), 2.11 (sep, *J* = 6.6, 1H), 2.24 (dddd, *J* = 1.0, 5.5, 10.5, 13.5, 1H), 2.33 (dtd, *J* = 1.4, 5.2, 13.6, 1H). ¹³C NMR (CDCl₃) δ = 19.2, 21.3, 24.4, 26.5, 28.2, 29.4, 42.2, 57.4, 213.8. MS (ES+) 141 [M+H]⁺, 173 [M+MeOH+H]⁺.

2-Butyl-Cyclohexanone⁴ (Table 2, entry 2): Alkylzinc halide: (*n*-C₄H₉)MgCl + ZnBr₂ (2.0 equiv). Reaction cosolvent: Et₂O. Chromatography on silica gel (5% Et₂O in petroleum ether) provided 261 mg (85 % yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 0.85 (t, *J* = 7.1, 3H), 1.11-1.41 (m, 6H), 1.55-1.68 (m, 2H), 1.68-1.85 (m, 2H), 1.93-2.11 (m, 2H), 2.17-2.30 (m, 2H), 2.31-2.38 (m, 1H). ¹³C NMR (CDCl₃) δ = 14.1, 23.0, 24.9, 28.2, 29.2, 29.5, 33.9, 42.1, 50.8, 213.7. MS (ES+) 155 [M+H]⁺, 187 [M+MeOH+H]⁺.

2-Cyclohexyl-Cyclohexanone³ (Table 2, entry 3): Alkylzinc halide: (*c*-C₆H₁₁)MgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: THF. Chromatography on silica gel (2.5% Et₂O in hexanes) provided 346 mg (96% yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 0.80-1.19 (m, 3H), 1.20-1.36 (m, 2H), 1.46-1.96 (m, 12H), 2.02-2.12 (m, 1H), 2.25 (dddd, *J* = 1.1, 5.6, 9.8, 13.2, 1H), 2.31-2.40 (m, 1H). ¹³C NMR (CDCl₃) δ = 24.2, 26.6, 26.7, 28.2, 29.5, 29.6, 31.8, 36.2, 42.1, 56.8, 213.9. MS (ES+) 181 [M+H]⁺, 213 [M+MeOH+H]⁺, 235 [M+Na+MeOH]⁺.

2-Cyclopentyl-Cyclohexanone (Table 2, entry 4): Alkylzinc halide: (*c*-C₅H₉)MgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: THF. Chromatography on silica gel (gradient elution; 20 to 30% CH₂Cl₂ in petroleum ether) provided 306 mg (92% yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 0.94-1.12 (m, 2H), 1.40-1.66 (m, 6H), 1.66-2.20 (m, 8H), 2.20-2.40 (m, 2H). ¹³C NMR (CDCl₃) δ = 24.2, 25.1, 25.2, 28.4, 30.2, 31.2, 32.4, 39.4, 41.9, 56.8, 214.0. FTIR (NaCl) 2943, 2863, 1708, 1449 cm⁻¹. MS (ES+) 167 [M+H]⁺, 208 [M+CH₃CN+H]⁺.

2-Isopropyl-1-indanone (Table 2, entry 5): Alkylzinc halide: *i*-PrMgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: Et₂O. Chromatography on silica gel (7.5% Et₂O in petroleum ether) provided 242 mg (70% yield) of a pale yellow oil. ¹H NMR (CDCl₃) δ = 0.78 (d, *J* = 6.7, 3H), 1.05 (d, *J* = 7.0, 3H), 2.41 (dsep, *J* = 4.3, 7.0, 1H), 2.67 (ddd, *J* = 4.0, 4.3, 7.9, 1H), 2.92 (dd, *J* = 4.0, 17.4, 1H), 3.14 (dd, *J* = 8.0, 17.4, 1H), 7.35 (dt, *J* = 0.8, 7.5, 1H), 7.47 (td, *J* = 0.9, 7.7, 1H), 7.57 (dt, *J* = 1.2, 7.4, 1H), 7.73 (d, *J* = 7.6, 1H). ¹³C NMR (CDCl₃) δ = 17.5, 21.1, 28.4, 29.3, 53.3, 123.9, 126.7, 127.5, 134.8, 137.9, 154.5, 209.1. FTIR (NaCl) 2959, 2931, 2872, 1709, 1608, 1589, 1465, 1387, 1370, 1285, 752 cm⁻¹. MS (ES-) 205 [M+MeOH-H]⁻.

2-Cyclohexyl-1-indanone (Table 2, entry 6): Alkylzinc halide: (*c*-C₆H₁₁)MgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: Et₂O. Chromatography on silica gel (5% Et₂O in petroleum ether) provided 338 mg (79% yield) of a pink oil. ¹H NMR (CDCl₃) δ = 0.98-1.42 (m, 6H), 1.60-1.80 (m, 4H), 1.98-2.12 (m, 1H), 2.64 (td, *J* = 4.0, 8.0, 1H), 2.96 (dd, *J* = 4.0, 17.4, 1H), 3.14 (dd, *J* = 8.0, 17.4, 1H), 7.34 (tt, *J* = 0.9, 3.4, 1H), 7.45 (dt, *J* = 0.6, 7.7, 1H), 7.56 (t, *J* = 7.4, 1H), 7.72 (dt, *J* = 0.6, 7.6, 1H). ¹³C NMR (CDCl₃) δ = 26.4, 26.5, 26.8, 27.9, 29.4, 31.4, 39.7, 53.1, 123.7, 126.7, 127.4, 134.7, 137.9, 154.5, 209.3. FTIR (NaCl) 2924, 2851, 1709, 1609, 751 cm⁻¹. MS (ES+) 215 [M+H]⁺.

2-Cyclopentyl-1-indanone (Table 2, entry 7): Alkylzinc halide: (*c*-C₅H₉)MgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: Et₂O. Chromatography on silica gel (3% Et₂O in petroleum ether) provided 284 mg (71% yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 1.04-1.16 (m, 1H), 1.36-1.70 (M, 6H), 1.90-1.98 (m, 1H), 2.28-2.40 (m, 1H), 2.76 (dt, *J* = 3.8, 7.0, 1H), 2.87 (dd, *J* = 3.7, 17.3, 1H), 3.22 (dd, *J* = 7.9, 17.2, 1H), 7.34 (t, *J* = 7.4, 1H), 7.44 (dd, *J* = 0.8, 7.7, 1H), 7.56 (t, *J* = 7.4, 1H)

7.73 (d, $J = 7.5$, 1H). ^{13}C NMR (CDCl_3) $\delta = 25.4, 25.5, 28.7, 30.6, 31.0, 41.4, 51.0, 124.0, 126.7, 127.5, 134.7, 137.6, 154.2, 209.0$. FTIR (NaCl) 2949, 2866, 1710, 1609, 752 cm^{-1} . MS (ES+) 201 $[\text{M}+\text{H}]^+$.

2-Isopropyl-Cycloheptanone⁵ (Table 2, entry 8): Alkylzinc halide: *i*-PrMgCl + ZnBr₂ (2.0 equiv). Reaction cosolvent: Et₂O. Chromatography on silica gel (2:1 hexanes:CH₂Cl₂) provided 229 mg (75% yield) of a colorless oil. ^1H NMR (CDCl_3) $\delta = 0.85$ (d, $J = 6.7$, 3H), 0.89 (d, $J = 6.8$, 3H), 1.18-1.40 (m, 3H), 1.42-1.58 (m, 1H), 1.80-1.96 (m, 5H), 2.10-2.20 (m, 1H), 2.30-2.39 (m, 1H), 2.44-2.56 (m, 1H). ^{13}C NMR (CDCl_3) $\delta = 19.7, 21.2, 25.6, 27.9, 28.3, 30.2, 20.7, 43.0, 59.9, 217.3$.

2-Cyclohexyl-cycloheptanone (Table 2, entry 9): Alkylzinc halide: (*c*-C₆H₁₁)MgCl + ZnCl₂ (2.0 equiv). Reaction cosolvent: THF. Chromatography on silica gel (3% Et₂O in petroleum ether) provided 327 mg (84% yield) of a colorless oil. ^1H NMR (CDCl_3) $\delta = 0.90$ -1.40 (m, 8H), 1.40-1.74 (m, 7H), 1.78-1.96 (m, 4H), 2.17 (ddd, $J = 4.8, 6.9, 11.2$, 1H), 2.30 (dddd, $J = 1.2, 3.3, 5.9, 12.3$, 1H), 2.50 (dt, $J = 3.3, 12.2$, 1H). ^{13}C NMR (CDCl_3) $\delta = 25.9, 26.57, 26.60, 27.9, 28.1, 30.1, 30.3, 31.5, 40.8, 42.9, 59.4, 217.4$. FTIR (NaCl) 2920, 2852, 1702, 1450 cm^{-1} . MS (ES+) 195 $[\text{M}+\text{H}]^+$, 227 $[\text{M}+\text{MeOH}+\text{H}]^+$.

2-Cyclopentyl-cycloheptanone (Table 2, entry 10): Alkylzinc halide: (*c*-C₅H₉)MgCl + ZnBr₂ (2.0 equiv). Reaction cosolvent: Et₂O. Chromatography on silica gel (2% acetone in petroleum ether) provided 270 mg (75% yield) of a colorless oil. ^1H NMR (CDCl_3) $\delta = 1.00$ -1.19 (m, 2H), 1.22-1.36 (m, 3H), 1.42-1.72 (m, 6H), 1.72-2.04 (m, 6H), 2.24-2.38 (m, 2H), 2.51 (ddd, $J = 3.9, 11.9, 13.2$, 1H). ^{13}C NMR (CDCl_3) $\delta = 25.20, 25.22, 28.4, 29.8, 30.3, 30.6, 31.2, 42.5, 42.7, 58.7, 216.9$. FTIR (NaCl) 2934, 2860, 1703, 1453 cm^{-1} . MS (ES+) 181 $[\text{M}+\text{H}]^+$, 222 $[\text{M}+\text{CH}_3\text{CN}+\text{H}]^+$.

3-Methyl-1-phenylbutan-1-one⁶ (Table 2, entry 11): Alkylzinc halide: *i*-PrMgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: THF. Chromatography on silica gel (3% Et₂O in petroleum ether) provided 290 mg (90% yield) of a colorless oil. ^1H NMR (CDCl_3) $\delta = 0.99$ (d, 7.0, 6H), 2.30 (nonet, $J = 6.7$, 1H), 2.83 (d, $J = 6.8$, 2H), 7.41-7.48 (m, 2H), 7.51-7.58 (m, 1H), 7.92-7.98 (m, 2H). ^{13}C NMR (CDCl_3) $\delta = 23.0, 25.4, 47.7, 128.3, 138.8, 133.1, 137.6, 200.5$.

(Benzoylmethyl)cyclohexane⁷ (Table 2, entry 12): Alkylzinc halide: (*c*-C₆H₁₁)MgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: THF.

Chromatography on silica gel (3% Et₂O in petroleum ether) provided 364 mg (90% yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 0.94-1.36 (m, 5H), 1.58-1.80 (m, 5H), 1.90-2.04 (m, 1H), 2.82 (d, *J* = 6.7, 2H), 7.42-7.48 (m, 2H), 7.55 (tt, *J* = 1.7, 7.4, 1H), 7.95 (dt, *J* = 1.4, 7.1, 2H). ¹³C NMR (CDCl₃) δ = 26.38, 26.49, 33.7, 34.8, 46.5, 128.4, 128.8, 133.1, 137.7, 200.5. MS (ES+) 203 [M+H]⁺.

(Benzoylmethyl)cyclopentane (Table 2, entry 13): Alkylzinc halide: (*c*-C₅H₉)MgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: THF.

Chromatography on silica gel (3% Et₂O in petroleum ether) provided 313 mg (83% yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 1.10-1.26 (m, 2H), 1.50-1.70 (m, 4H), 1.82-1.94 (m, 2H), 2.39 (sept, *J* = 7.9, 1H), 2.98 (d, *J* = 7.4, 2H), 7.45 (tt, *J* = 1.6, 6.7, 2H), 7.55 (tt, *J* = 1.9, 7.4, 1H), 7.93-7.98 (m, 2H). ¹³C NMR (CDCl₃) δ = 25.2, 33.0, 36.3, 45.1, 128.3, 128.8, 133.1, 137.5, 200.7. FTIR (NaCl) 2951, 2868, 1686, 1448, 1210, 752, 691 cm⁻¹. MS (APCI+) 189 [M+H]⁺, 221 [M+MeOH+H]⁺.

2-isopropyl-1-phenylbutan-1-one (Table 2, entry 14): Alkylzinc halide: *i*-PrMgCl + ZnBr₂ (2.0 equiv). Reaction cosolvent: Et₂O.

Chromatography on silica gel (1.5% Et₂O in petroleum ether) provided 313 mg of a 97:3 ratio (Benzoylmethyl)cyclopentane : 2-chlorobutyrophenone (80% yield). Repeated chromatography provided an analytically pure sample as a colorless oil. ¹H NMR (CDCl₃) δ = 0.81 (t, *J* = 7.4, 3H), 0.90 (d, *J* = 6.8, 3H), 0.91 (d, *J* = 6.8, 3H), 1.55-1.64 (m, 1H), 1.76-1.87 (m, 1H), 2.03 (qd, *J* = 6.9, 13.6, 1H), 3.18, (ddd, *J* = 3.6, 7.0, 9.8, 1H), 7.42-7.48 (m, 2H), 7.51-7.57 (m, 1H), 7.93-7.97 (m, 2H). ¹³C NMR (CDCl₃) δ = 12.3, 19.8, 21.6, 22.1, 30.6, 54.3, 128.4, 128.8, 132.9, 138.9, 205.0. FTIR (NaCl) 2964, 1680, 1597, 1580, 1461, 1447, 1387, 1370, 1214, 702 cm⁻¹. MS (ES+) 191 [M+H]⁺.

3,4-Dihydro-2-isopropynaphthalen-1(2H)-one⁸ (Table 2, entry 15):

Alkylzinc halide: *i*-PrMgCl + ZnCl₂ (1.5 equiv). Reaction cosolvent: THF.

Chromatography on silica gel (3% Et₂O in petroleum ether) provided 333 mg (89% yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 0.90 (d, *J* = 6.7, 3H), 1.01 (d, *J* = 7.1, 3H), 1.88-2.02 (m, 1H), 2.10-2.22 (m, 1H), 2.32 (td, *J* = 4.5, 11.3, 1H), 2.54 (dsep, *J* = 4.9, 6.7, 1H), 2.88-3.09 (m, 2H), 7.22 (d, *J* = 7.3, 1H), 7.29 (dt, *J* = 0.6, 7.3, 1H), 7.44, (dt, *J* = 1.5, 7.5,

1H), 8.02 (dd, $J = 1.4, 7.8$, 1H). ^{13}C NMR (CDCl_3) $\delta = 18.7, 20.9, 23.7, 26.4, 28.8, 54.0, 126.7, 127.7, 128.8, 133.2, 144.2, 200.1$. MS (ES-) 219 $[\text{M}+\text{MeOH}-\text{H}]^-$.

3,4-Dihydro-2-butyl-1-naphthalen-1(2H)-one⁹ (Table 2, entry 16):

Alkylzinc halide: ($n\text{-C}_4\text{H}_9$)MgCl + ZnBr_2 (2.0 equiv). Reaction cosolvent: Et_2O . Chromatography on silica gel (3% Et_2O in petroleum ether) provided 376 mg (93% yield) of a colorless oil. ^1H NMR

(CDCl_3) $\delta = 0.92$ (t, $J = 7.1$, 3H), 1.30-1.55 (m, 5H), 1.84-2.00 (m, 2H), 2.24 (ddd, $J = 4.8, 9.9$, 13.3, 1H), 2.42-2.50 (m, 1H), 2.91-3.05 (m, 2H), 7.22 (d, $J = 7.5$, 1H), 7.29 (t, $J = 7.5$, 1H), 7.44 (dt, $J = 1.5, 7.6$, 1H), 8.02 (dd, $J = 1.1, 7.7$, 1H). ^{13}C NMR (CDCl_3) $\delta = 14.2, 23.0, 28.3, 28.4, 29.2, 29.4, 47.6, 126.6, 127.6, 128.8, 132.7, 133.2, 144.1, 200.6$. MS (ES+) 203 $[\text{M}+\text{H}]^+$, 235 $[\text{M}+\text{MeOH}+\text{H}]^+$.

3,4-Dihydro-2-ethyl-1-naphthalen-1(2H)-one⁸ (Table 2, entry 17):

Alkylzinc halide: ($n\text{-C}_2\text{H}_5$)MgBr + ZnBr_2 (1.5 equiv). Reaction cosolvent: Et_2O . Chromatography on silica gel (3% Et_2O in petroleum ether) provided

270 mg (78% yield) of a colorless oil. ^1H NMR (CDCl_3) $\delta = 1.00$ (t, $J = 7.5$, 3H), 1.50-1.64 (m, 1H), 1.82-2.05 (m, 2H), 2.24 (qd, $J = 4.6, 13.3$, 1H), 2.36-2.46 (m, 1H), 2.96-3.06 (m, 2H), 7.22 (d, $J = 7.6$, 1H), 7.29 (dt, $J = 0.6, 7.4$, 1H), 7.45 (dt, $J = 1.4, 7.5$, 1H), 8.03 (dd, $J = 1.4, 7.7$, 1H). ^{13}C NMR (CDCl_3) $\delta = 11.7, 22.6, 27.9, 28.6, 49.1, 126.8, 127.7, 128.9, 132.8, 133.3, 144.2, 200.6$. MS (ES+) 175 $[\text{M}+\text{H}]^+$.

3,4-Dihydro-2-cyclohexyl-1-naphthalen-1(2H)-one (Table 2, entry 18):

Alkylzinc halide: ($c\text{-C}_6\text{H}_{11}$)MgCl + ZnCl_2 (1.5 equiv). Reaction cosolvent: Et_2O . Chromatography on silica gel (3% Et_2O in petroleum ether) provided

398 mg (87% yield) of a colorless oil. ^1H NMR (CDCl_3) $\delta = 0.96$ -1.40 (m, 5H), 1.50-1.80 (m, 5H), 1.92-2.04 (m, 1H), 2.06-2.20 (m, 2H), 2.30 (td, $J = 5.0, 10.8$, 1H), 2.9 (ddd, $J = 4.6, 9.5, 16.5$, 1H), 3.02 (td, $J = 5.2, 16.8$, 1H), 7.20-7.32 (m, 2H), 7.14 (dt, $J = 1.4, 7.3$, 1H), 8.01 (dd, $J = 1.5, 7.6$, 1H). ^{13}C NMR (CDCl_3) $\delta = 24.5, 26.68, 26.75, 26.88, 28.6, 29.4, 31.4, 36.4, 53.5, 126.7, 127.7, 128.8, 133.2, 144.2, 200.2$. FTIR (NaCl) 2925, 2851, 1683, 1600, 1451, 1296, 1222, 743 cm^{-1} . MS (ES-) 259 $[\text{M}+\text{MeOH}-\text{H}]^-$.

3,4-Dihydro-2-cyclopentyl-1-naphthalen-1(2H)-one (Table 2, entry 19):

Alkylzinc halide: ($c\text{-C}_5\text{H}_9$)MgCl + ZnCl_2 (1.5 equiv). Reaction cosolvent:

Et₂O. Chromatography on silica gel (3% Et₂O in hexanes provided 364 mg (85% yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 1.18-1.28 (m, 1H), 1.20-1.41 (m, 1H), 1.48-1.69 (m, 4H), 1.74-1.88 (m, 2H), 1.96-2.05 (m, 1H), 2.18-2.36 (m, 2H), 2.42 (dt, *J* = 4.0, 8.2, 1H), 2.92 (ddd, *J* = 4.9, 7.9, 17.0, 1H), 3.07 (ddd, *J* = 4.7, 7.5, 17.0, 1H), 7.22 (d, *J* = 7.7, 1H), 7.28 (dt, *J* = 0.5, 7.6, 1H), 7.44 (dt, *J* = 1.4, 7.5, 1H), 8.10 (dd, *J* = 1.1, 7.9, 1H). ¹³C NMR (CDCl₃) δ = 25.38, 25.44, 26.5, 27.8, 30.3, 31.0, 38.9, 52.4, 126.7, 127.6, 128.9, 133.0, 133.2, 144.0, 200.8. FTIR (NaCl) 2949, 2866, 1682, 1600, 1454, 1288, 1223, 743 cm⁻¹. MS (APCI+) 215 [M+H]⁺, 247 [M+MeOH+H]⁺.

3,4-Dihydro-2-isopropyl-6-

(trifluoromethylsulfonato)naphthalen-1(2H)-one (Table 2,

entry 20): Reaction carried out as described in the general

procedure, but on a 1 mmol scale. Alkylzinc halide: *i*-PrMgCl +

ZnCl₂ (1.5 equiv). Reaction cosolvent: THF. Chromatography on silica gel (5% Et₂O in petroleum ether) provided 292 mg (87% yield) of an amorphous white solid. ¹H NMR (CDCl₃) δ = 0.91 (d, *J* = 7.0, 3H), 1.01 (d, *J* = 7.0, 3H), 1.91-2.05 (m, 1H), 2.19 (qd, *J* = 4.6, 13.5, 1H), 2.35 (td, *J* = 4.6, 11.5, 1H), 2.45-2.56 (m, 1H), 2.93-3.12 (m, 2H), 7.14-7.21 (m, 2H), 8.12 (d, 8.2, 1H). ¹³C NMR (CDCl₃) δ = 18.6, 20.8, 23.4, 26.4, 28.9, 53.8, 118.9 (*J*_{C-F} = 322), 119.8, 121.4, 130.5, 133.0, 146.8, 152.4, 198.3. FTIR (NaCl) 2970, 1675, 1604, 1420, 1208, 1144 cm⁻¹. MS (ES-) 335 [M-H]⁻.

3,4-Dihydro-2-isopropyl-6-cyano-naphthalen-1(2H)-one (Table 2,

entry 21): Reaction carried out as described in the general procedure,

but on a 1 mmol scale. Alkylzinc halide: *i*-PrMgCl + ZnCl₂ (1.5

equiv). Reaction cosolvent: THF. Chromatography on silica gel

(10% Et₂O in hexanes) provided 174 mg (82% yield) of a white solid. ¹H NMR (CDCl₃) δ = 0.91 (d, *J* = 6.8, 3H), 1.01 (d, *J* = 7.0, 3H), 1.91-2.04 (m, 1H), 2.20 (qd, *J* = 4.6, 13.6, 1H), 2.38 (td, *J* = 4.6, 7.0, 1H), 2.49 (dsex, *J* = 2.0, 6.9, 1H), 2.92-3.12 (m, 2H), 7.45-7.59 (m, 2H), 8.08-8.12 (m, 1H). ¹³C NMR (CDCl₃) δ = 18.6, 20.8, 23.3, 26.4, 28.4, 54.0, 116.3, 118.4, 128.3, 130.1, 132.9, 136.0, 144.6, 198.7. FTIR (NaCl) 2963, 2231, 1686, 1430, 1412, 1370 cm⁻¹. MS (EI) 213 [M]⁺.

5-Isopropyl-3-methyl-2-cyclohexeneone (piperitone)¹⁰ (Table 2, entry 22): Alkylzinc halide: *i*-PrMgCl + ZnBr₂ (2.0 equiv). Reaction cosolvent: Et₂O. Chromatography on silica gel (10% Et₂O in petroleum ether) provided 138 mg (45% yield) of a colorless oil. ¹H NMR (CDCl₃) δ = 0.84 (d, *J* = 6.8, 3H), 0.93 (d, *J* = 7.0, 3H), 1.72-1.86 (m, 1H), 1.91 (d, *J* = 0.9, 3H), 1.93-2.04 (m, 2H), 2.22-2.40 (m, 3H), 5.83-5.83 (m, 1H). ¹³C NMR (CDCl₃) δ = 18.8, 20.9, 23.1, 24.3, 26.0, 30.6, 51.8, 127.0, 161.3, 201.5. MS (EI) 152 [M]⁺.

2-Chloro-1-isopropyl-1-cyclohexanol (**5**)

To a mixture of Mg turnings (0.59g, 24.5 mmol) in THF (100 mL) was added 2-bromopropene (2.84 mL, 20.7 mmol). The reaction mixture was heated to reflux with a heat gun, and then allowed to stir at 25 °C for 2h. A solution of 2-chlorocyclohexanone (2.48 g, 18.8 mmol) in THF (10 mL) was added to the Grignard reagent at 0 °C via cannula. After stirring at 25 °C for 30 min, water (1 mL) was added, reaction mixture was diluted with Et₂O (200 mL) and extracted with 1M HCl (100 mL). The organic layer was separated, dried over MgSO₄, concentrated and purified chromatographically over silica gel (10% Et₂O in petroleum ether). To a solution of the olefin in EtOAc (32 mL) was added Pd/C (50 mg of 10 wt%). The reaction vessel was purged with N₂ and then exposed to H₂ (1 atm). After 20 h, the reaction vessel was purged with N₂. The reaction mixture was diluted with EtOAc (50 mL) and filtered through Celite®. Concentration of the filtrate under reduced pressure provided **5** as a colorless oil (1.39 g, 42 % yield). ¹H NMR (CDCl₃) δ = 0.89 (d, *J* = 7.0, 3H), 0.94 (d, *J* = 7.0, 3H), 1.18-1.33 (m, 2H), 1.42-1.83 (m, 5H), 1.91-2.15 (m, 3H), 4.17 (dd, *J* = 5.1, 11.2, 1H). ¹H NMR (CDCl₃) δ = 16.2, 17.6, 20.6, 26.2,

28.6, 33.1, 35.5, 67.8, 75.3. Relative stereochemistry was assigned on the basis of the coupling constants of H₁ (one axial-axial coupling, one axial-equatorial coupling) and a 5% NOE observed between H₁ and one of the isopropyl CH₃'s.

Exposure of 5 to the cross-coupling reaction conditions (eq 1):

To a solution of alcohol **5** (36 mg, 0.2 mmol), dodecane (2 μL , internal standard) and either $\text{Cu}(\text{acac})_2$ (2.6 mg, 0.01 mmol, 5 mol%) and THF (0.4 mL) or just THF (0.4 mL) was added a solution of $i\text{-PrZnCl}\cdot\text{MgCl}_2$ (1.5 mL of 0.2 M suspension in Et_2O , 0.3 mmol). The reaction mixture was stirred for 16 h at 25 $^\circ\text{C}$ then diluted with EtOAc and extracted with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$. The organic layer was separated and dried over Na_2SO_4 . GC analysis showed <5% 2-isopropylcyclohexanone and >90% recovered **5**. Under more forcing reaction conditions (in toluene at 55 $^\circ\text{C}$ for 4 h), chlorohydrin **5** was converted to a mixture of **1aa** (17%) and cyclopentyl-isopropyl-ketone (**I**) (26%, structure confirmed by comparison to an authentic sample prepared as described below). Unreacted **5** (38%) was also recovered.

1-Cyclopentyl-2-methyl-propan-1-one¹¹ (I**).**

To a solution of isobutyraldehyde (0.45 mL, 5 mmol) in Et_2O (30 mL) under an N_2 atmosphere at 0 $^\circ\text{C}$, ($c\text{-C}_5\text{H}_9$) MgCl (2.5 mL 2.0 M in Et_2O , 5 mmol) was added and the reaction mixture stirred for 30 min. The reaction was quenched with H_2O (10 mL), diluted with Et_2O (50 mL) and extracted with 1 M HCl (30 mL). The organic layer was separated, dried over MgSO_4 and concentrated under reduced pressure. To a solution of the crude material in CH_2Cl_2 (50 mL), Celite[®] (1.6 g) and pyridinium chlorochromate (1.62 g, 7.5 mmol) were added. The reaction mixture was stirred at 25 $^\circ\text{C}$ for 2 h. The reaction mixture was filtered through a pad of silica gel, which was then washed with Et_2O (2 x 75 mL). The solvent was evaporated under reduced pressure and the crude mixture was purified by chromatography on silica gel (gradient elution; 1% to 3% Et_2O in petroleum ether). The volatile ketone (**I**) was recovered as pale yellow oil (0.150 g, 22% yield). ^1H NMR (CDCl_3) δ = 1.1 (d, J = 7.0, 6H), 1.51-1.84 (m, 8H), 2.72 (sep, J

= 6.9, 1H), 2.98-3.06 (m, 1H). ^{13}C NMR (CDCl_3) δ = 14.2, 18.6, 22.5, 26.3, 29.7, 34.3, 40.3, 49.5, 217.7.

Control experiment to confirm zinc alkoxide does not interfere with cross coupling: In order to confirm that the experimental conditions of eq 1 are identical to the cross-coupling reactions, the cross coupling of 2-chlorotetralone with *i*-PrZnCl•MgCl₂ was performed in the presence of catalytic amounts of halohydrin **5** (eq S1).

To a mixture of halohydrin **5** (3.5 mg, 0.02 mmol), chloroketone **2f** (36 mg, 0.2 mmol), Cu(acac)₂ (2.6 mg, 0.01 mmol), and dodecane (2 μL , internal standard) in THF (400 μL) was added a solution of *i*-PrZnCl•MgCl₂ (1.5 mL of 0.2 M suspension in Et₂O, 0.3 mmol). The reaction mixture was stirred for 3 h at 25 °C then diluted with EtOAc (30 mL) and extracted with sat. NH₄Cl_(aq) (30mL). The organic layer was separated and dried over Na₂SO₄. GC analysis of the crude reaction mixture indicated quantitative conversion of **2f** to 2-isopropyl tetralone (**1fa**). Halohydrin **5** was recovered unchanged; <1% **1aa** was detected.

Control experiment to confirm the formation of zinc alkoxide: In order to confirm the formation of a zinc alkoxide (the presumptive intermediate in path a, Scheme 2) under the conditions of eq 1, the following experiments were performed (eq S2, S3).

In one experiment (eq S2), $i\text{-PrZnCl}\cdot\text{MgCl}_2$ (0.25 mmol, 1.25 mL of 0.2 M solution in Et_2O) was added to THF (0.4 mL) and stirred for 1 h at 25 °C. The reaction mixture was transferred via cannula to a mixture of chlorotetralone **2f** (36 mg, 0.2 mmol), dodecane (2 μL , internal standard), $\text{Cu}(\text{acac})_2$ (2.6 mg, 0.01 mmol, 5 mol%) and THF (0.2 mL). The reaction mixture was stirred for 1 h, diluted with EtOAc and extracted with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$. The organic layer was separated and dried over Na_2SO_4 . GC analysis indicated complete conversion of **2f** to isopropyltetralone **1fa**. In a second experiment (eq S3) $i\text{-PrZnCl}\cdot\text{MgCl}_2$ (0.25 mmol, 1.25 mL of 0.2 M solution in Et_2O) was added a solution of chlorohydrin **5** (35 mg, 0.2 mmol) in THF (0.4 mL) and stirred for 1 h at 25 °C. The reaction mixture was transferred via cannula to a mixture of chlorotetralone **2f** (36 mg, 0.2 mmol), dodecane (2 μL , internal standard), $\text{Cu}(\text{acac})_2$ (2.6 mg, 0.01 mmol, 5 mol%) and THF (0.2 mL). The reaction mixture was stirred for 1 h, diluted with EtOAc and extracted with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$. The organic layer was separated and dried over Na_2SO_4 . GC analysis indicated 65% conversion of **2f** to chlorotetralone **1fa**. Therefore, 0.11 mmol $i\text{-PrZnCl}\cdot\text{MgCl}_2$ was consumed by **5**, corresponding to >50% conversion of **5** to its zinc (or magnesium) alkoxide under the reaction conditions of eq 1 and eq S3. No formation of **1aa** was observed under the conditions of eq S3.

1. *i*-PrMgCl
 2. ZnCl₂
 3. Cu(acac)₂

5 **5** **1aa** **I** (S4)
 95% recovery ~2% ~2%

(S)-(+)-2,3-dimethyl-1-phenyl-butan-1-one (1ja, eq 2)

S14

FTIR (NaCl) 3064, 2964, 2874, 1682, 1597, 1579, 1463, 1448, 1368, 1218, 969 cm^{-1} . $[\alpha]^{23}_{\text{D}}$ +56.7 ($c=0.39$, CH_2Cl_2).

Absolute stereochemistry was assigned by comparison to an authentic sample prepared following Myers' method:¹²

LiCl (2.91 g, 68.53 mmol) was heated under vacuum at $150\text{ }^\circ\text{C}$ for 24 h then cooled to room temperature. THF (3.5 mL) and diisopropylamine (0.94 mL, 6.71 mmol) were added, the mixture was cooled to $-78\text{ }^\circ\text{C}$ and *n*-butyl lithium (3.9 mL 1.6 M in hexane, 6.20 mmol) was slowly added. The reaction was warmed to $0\text{ }^\circ\text{C}$ for 5 min and then cooled back down to $-78\text{ }^\circ\text{C}$. A solution of the known¹² carbamate (S,S)-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*,3-dimethyl butanamide (0.85 g, 2.98 mmol) in THF (10 mL) was slowly added by cannula. The reaction was stirred for 1 h at $-78\text{ }^\circ\text{C}$, $0\text{ }^\circ\text{C}$ for 15 min, and $25\text{ }^\circ\text{C}$ for 5 min successively. The reaction mixture was cooled to $0\text{ }^\circ\text{C}$ and iodomethane (0.74 mL, 11.92 mmol) was slowly added. The mixture was stirred for 1 h at $0\text{ }^\circ\text{C}$. The reaction was quenched by adding sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (1 mL) and then diluted with EtOAc (15 mL) and extracted with sat. $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL). The organic layer was separated and dried over MgSO_4 . The solvent was evaporated under reduced pressure and the crude mixture was purified by chromatography on silica gel (gradient elution; 40% to 50% EtOAc in hexanes) to provide 410 mg (47% yield) a pale yellow oil, (S,S,S)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,3-trimethyl butanamide. ^1H NMR (3:1 rotamer ratio, * denotes minor rotamer peaks, CDCl_3) δ = 0.87 (d, J = 6.7, 3H), 0.88* (d, J = 6.7, 3H), 0.92 (d, J = 6.7, 3H), 0.93* (d, J = 6.7, 3H), 1.00 (d, J = 6.7, 3H), 1.04* (d, J = 6.7, 3H), 1.07* (d, J = 6.7, 3H), 1.22 (d, J = 6.7, 3H), 1.78-1.96 (m, 1H) 2.30 (qd, J = 6.8, 7.6, 1H), 2.51-2.61* (m, 1H), 2.80 (s, 1H), 2.91* (s, 1H), 3.61* (d, J = 3.0, 1H), 4.09-4.20* (m, 1H), 4.30-4.35 (m, 1H), 4.58* (dd, J = 2.7, 8.3, 1H), 4.64 (t, (d, J = 7.0, 1H), 5.16 (s, 1H), 7.21-7.40 (m, 5H). ^{13}C NMR (3:1 rotamer ratio, * denotes minor rotamer peaks, CDCl_3) δ = 14.4, 14.9, 15.6*, 19.3, 19.4*, 21.5, 21.6*, 27.2*, 31.1, 31.5*, 34.2*, 34.4, 42.5*, 43.4, 58.1, 60.0*, 75.4*, 76.3, 126.2, 126.9*, 127.4, 128.1*, 128.2, 128.6*, 142.0*, 142.8, 177.9*, 179.0. FTIR (NaCl) 3370, 3087, 3063, 3030, 2966, 2873, 1614, 1453, 1374 cm^{-1} . $[\alpha]^{23}_{\text{D}}$ +133 ($c=0.87$, CH_2Cl_2).

A mixture of (S,S,S)-*N*-(2-Hydroxy-1-methyl-2-phenylethyl)-*N*,2,3-trimethyl butanamide (150 mg, 0.502 mmol) and toluene (3.0 mL) was heated to 70 °C until a homogeneous solution was obtained. The solution was cooled to 25 °C and the toluene removed under reduced pressure. The flask was flushed with N₂ and THF (6 mL) was added. The mixture was cooled to -78 °C. Phenyl lithium (0.67 mL 1.8 M in 70% cyclohexane in Et₂O, 1.21 mmol) was added slowly to the reaction mixture. The mixture was warmed to 0 °C and stirred for 10 min. Diisopropylamine (71 μL, 0.502 mmol) was added and the mixture stirred for 15 min. A 10% (v/v) solution of acetic acid in Et₂O (6.0 mL) was then added to the mixture. The mixture was then diluted with EtOAc (15 mL) and extracted with sat. NaHCO₃ (aq) (2 x 10 mL). The organic layer was separated and dried over MgSO₄. The solvent was evaporated under reduced pressure and the crude mixture was purified by chromatography on silica gel (gradient elution; 1% to 4% EtOAc in hexanes) to provide 40 mg (45% yield) of a pale yellow oil, (+)-2,3-dimethyl-1-phenyl-butan-1-one [(S)-**1ja**] in 94% ee. The product thus obtained was found to be the same enantiomer (chiral HPLC, optical rotation) as **1ja** formed from (S)-**2j**, as described above.

Cis-4-*tert*-butyl-2-isopropyl-cyclohexanone (1ka**) (eq S5).**

To a mixture of trans- α -chloroketone **2k** (38mg, 0.2 mmol), Cu(acac)₂ (2.6 mg, 0.01 mmol), and dodecane (2 μL, internal standard) in Et₂O (400 μL) was added a solution of *i*-PrZnCl·MgCl₂ (1.5 mL of 0.2 M suspension in Et₂O, 0.3 mmol). The reaction mixture was stirred for 2.5 h at 25 °C then diluted with EtOAc (30 mL) and extracted with sat. NH₄Cl (aq) (30mL). The organic layer was separated and dried over Na₂SO₄. GC analysis of the starting material showed a 38:1 ratio of **2k**:**2l**. GC analysis of the crude reaction mixture indicated cis-ketone **1ka** was formed in 80% yield as a 16:1 ratio of diastereomers (major diastereomer shown). An analytically pure sample of **1ka** was obtained as a pale yellow oil after chromatography on silica gel (gradient

elution; 20% to 35% CH₂Cl₂ in hexanes). ¹H NMR (CDCl₃) δ = 0.85 (d, *J* = 6.6, 3H), 0.90-0.92 (m, 12H), 1.1-1.2 (m, 1H), 1.41 (dq, *J* = 4.6, 12.4, 1H), 1.53 (tt, *J* = 2.8, 11.9, 1H), 2.01-2.2 (m, 4H), 2.27 (dt, *J* = 5.5, 13.3, 1H), 2.35 (ddd, *J* = 3.0, 4.8, 13.7, 1H). ¹³C NMR (CDCl₃) δ = 18.8, 21.2, 26.4, 27.9, 28.6, 29.8, 32.8, 42.2, 47.3, 55.7, 213.2. FTIR (NaCl) 2957, 2871, 1713, 1366 cm⁻¹.

Reduction of ketone **1ka** (LiAlH₄ in Et₂O, eq S6) provided 2 diastereomeric alcohols (4:1) in quantitative yield. The major diastereomer (**II**) was determined to have an all-equatorial conformation on the basis of two axial-axial and one axial-equatorial coupling constants for the proton on the carbinol carbon: *J*_{H1} = 4.5, 10.5, 10.5.

Under otherwise identical conditions, but in the absence of copper, ketone **1ka** was formed in ~10 % yield (GC) as a ≥ 10:1 ratio of diastereomers.

Trans-4-tert-butyl-2-chloro-cyclohexanone (1la**) (eq S7).**

To a mixture of cis-α-chloroketone **2l** (38mg, 0.2 mmol), Cu(acac)₂ (2.6 mg, 0.01 mmol), and dodecane (2 μL, internal standard) in Et₂O (400 μL) was added a solution of *i*-PrZnCl•MgCl₂ (1.5 mL of 0.2 M suspension in Et₂O, 0.3 mmol). The reaction mixture was stirred for 14 h at 25 °C then diluted with EtOAc (30 mL) and extracted with sat. NH₄Cl_(aq) (30mL). The organic layer was separated and dried over Na₂SO₄. GC analysis of the starting material showed a 40:1

ratio of **2l:2k**. GC analysis of the crude reaction mixture indicated trans-ketone **1la** was formed in 80% yield as a 32:1 ratio of diastereomers (major diastereomer shown). An analytically pure sample of **1la** was obtained as a pale yellow oil after chromatography on silica gel (first column: gradient elution; 20% to 35% CH₂Cl₂ in hexanes; second column: gradient elution; 2% to 6% Et₂O in hexanes). FTIR (NaCl) 2961, 2871, 1713, 1367 cm⁻¹.

Table S1. NMR data for *trans*-4-*tert*-butyl-2-chloro-cyclohexanone (**1la**).^{a,b}

¹ H NMR data	¹³ C NMR data	¹ H- ¹ H Coupling (J) ^{c,d}
(H ₁₁) 0.71 (s, 9H)	(C ₈) 20.6	H_{2e}-H_{3a} (5.0)
(H ₈) 0.73 (d, 3H)	(C ₉) 21.7	H _{3a} -H _{3e} (12.7)
(H ₉) 0.81 (d, 3H)	(C ₁₁) 28.0	H _{3a} -H _{4a} (12.3)
(H _{5a}) 1.08 (dq, 1H)	(C ₇) 28.2	H _{3e} -H _{4a} (2.9)
(H _{3a}) 1.16 (dt, 1H)	(C ₅) 28.4	H _{4a} -H _{5a} (12.5)
(H _{4a}) 1.21 (tt, 1H)	(C ₃) 30.3	H _{4a} -H _{5e} (2.9)
(H _{5e}) 1.55-1.58 (m, 1H)	(C ₁₀) 32.7	H _{5a} -H _{5e} (12.8)
(H _{3e} , H ₇) 1.66-1.73 (m, 2H)	(C ₆) 39.4	H _{5a} -H _{6a} (13.4)
(H _{2e}) 1.89-1.91 (m, 1H)	(C ₄) 41.7	H _{5a} -H _{6e} (4.4)
(H _{6a}) 2.0 (dt, 1H)	(C ₂) 57.9	H _{5e} -H _{6e} (6.5)
(H _{6e}) 2.14-2.16 (m, 1H)	(C ₁) 213.0	H _{6a} -H _{6e} (13.8)
		H ₇ -H ₈ (6.8)

		H ₇ -H ₉ (6.8)
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^aa = axial, e = equatorial. ^bIn benzene-*d*₆. ^cIn Hz. ^dDetermined from 1D ¹H NMR (800 MHz) or dqCOSY (500 MHz).

NMR data is reported in **Table S1**. The proton and carbon assignments were based on data from a 500 MHz dqCOSY and a 600 MHz HSQC. The relative stereochemistry of **1la** was assigned on the basis of the coupling constant for H_{2e}-H_{3a} ($J = 5.0$ Hz) which is consistent with an axial-equatorial coupling and inconsistent with an axial-axial coupling. The stereochemical assignment is further supported by the following experiment: NaOMe (1.52 mg, 0.082 mmol) was added to separate solutions of **1ka** (4.6 mg, 0.0235 mmol) in MeOH (23.5 μ L) and **1la** (4.6 mg, 0.0235 mmol) in MeOH (23.5 μ L). The reaction solutions were stirred at 50 °C for 25 min. GC analysis showed that both **1ka** and **1la** had isomerized to a 2.7:1 ratio of **1ka:1la**, thus demonstrating that **1ka** is the thermodynamically more stable product, which is to be expected if both alkyl groups occupy equatorial positions. The equilibrium ratio of diastereomers is consistent with previous reports.¹³

Unambiguous proof of the relative stereochemistry for **1la** was provided by an X-ray crystal structure of the *p*-toluenesulfonyl hydrazone derivative (Figure S5). Under otherwise identical conditions, but in the absence of copper, ketone **1la** was formed in ~7 % yield (GC) as a $\geq 10:1$ ratio of diastereomers.

Uncatalyzed reaction of 2a with *i*-PrZnCl•MgCl₂ (Table 1, entry 8).

To a mixture of 2-chlorocyclohexanone (**2a**, 27 mg, 0.2 mmol) and dodecane (2 μ L, internal standard) in THF (400 μ L) was added a solution of *i*-PrZnCl•MgCl₂ (1.5 mL of 0.2 M suspension in Et₂O, 0.3 mmol). The reaction mixture was stirred for 18 h at 25 °C then diluted with EtOAc (30 mL) and extracted with sat. NH₄Cl_(aq) (30 mL). The organic layer was separated and dried over Na₂SO₄. GC analysis of the crude reaction mixture indicated 2-isopropylcyclohexanone was formed in 21% yield. Results were similar using *i*-PrZnCl•MgCl₂ derived from 97% pure ZnCl₂ (Fischer Scientific) and 99.999% pure ZnCl₂ (Aldrich) ruling out the possibility that trace impurities in ZnCl₂ were acting as a catalyst.

Figure S1

File : c:\class-vp\cmi147a
 Method : c:\class-vp\methods\cfm.met
 Sample ID : cfmi147
 Acquired : Jul 04, 2004 18:18:42
 Printed : Jul 16, 2004 09:17:08
 User : System

Channel A Results -- PDA Channel 3, 230 nm, 8 nm Band

Peak	Time	Area	Area %
1	4.68	14138421	48.602
2	5.28	14951862	51.398
Totals :		29090284	100.000

Chiralcel OD-H 1 mL/ min
 Mobile phase = 10% isopropanol in hexanes.

Figure S2

File : c:\class-vp\cmi151a
 Method : c:\class-vp\methods\cfm.met
 Sample ID : cfm151
 Acquired : Jul 04, 2004 17:09:23
 Printed : Jul 15, 2004 11:46:05
 User : System

Channel A Results -- PDA Channel 3, 230 nm, 8 nm Band

Peak	Time	Area	Area %
1	4.73	457803	2.375
2	5.30	18819490	97.625

Totals :
 19277292 100.000

Chiralcel OD-H 1 mL/min
 Mobile phase = 10% isopropanol in hexanes.

Figure S3

File : c:\class-vp\cmi1482i
 Method : c:\class-vp\methods\cfm.met
 Sample ID : cfmi148-2
 Acquired : Jul 15, 2004 16:11:28
 Printed : Jul 15, 2004 16:35:41
 User : System

Channel A Results -- PDA Channel 3, 230 nm, 8 nm Band

Peak	Time	Area	Area %
1	10.20	7403990	47.268
2	10.77	8259956	52.732

Totals :
 15663946 100.000

Chiralcel OD-H 1 mL/ min
 Column was pre-equilibrated at 0.1% isopropanol in
 hexanes for 20 minutes prior to injection.
 Mobile phase = 100% hexanes.

Figure S4

File : c:\class-vp\cmi1541b
 Method : c:\class-vp\methods\cfm.met
 Sample ID : cfmi154-1
 Acquired : Jul 15, 2004 15:35:29
 Printed : Jul 15, 2004 15:58:20
 User : System

Channel A Results -- PDA Channel 3, 230 nm, 8 nm Band

Peak	Time	Area	Area %
1	10.40	269258	2.403
2	10.92	10936987	97.597

Totals :
 11206245 100.000

Chiralcel OD-H 1 mL/min
 Column was pre-equilibrated at 0.1% isopropanol in
 hexanes for 20 minutes prior to injection.
 Mobile phase = 100% hexanes.

Figure S5. X-ray crystal structure of *anti*-2-isopropyl-4-*tert*-butyl cyclohexanone tosyl hyrazone.¹⁴

Mo Ka radiation

room temperature

Monoclinic Space group Ca

$a = 12.5107(12)\text{\AA}$ $\alpha = 90.0^\circ$

$b = 14.3179(14)\text{\AA}$ $\beta = 114.824(4)^\circ$

$c = 12.8516(16)\text{\AA}$ $\gamma = 90.0^\circ$

$V = 2089.4\text{\AA}^3$

$Z = 4$

$D_{\text{calc}} = 1.14\text{g/cc}$

Data Collection

Bruker KappaCCD diffractometer

1272 independent reflection

$R_{\text{int}} = 0.061$

$h = 0$ to 8

$k = 0$ to 12

$l = -10$ to 9

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