Highly Practical and Enantioselective Cu-Catalyzed Conjugate Addition of Alkylzinc Reagents to Cyclic Enones at Ambient Temperature

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Supporting Information

General Information. All reactions were carried out under an atmosphere of nitrogen in flame- or oven-dried glassware with magnetic stirring unless otherwise indicated. All reaction solvents were purified by degassing with argon and passage through an activated alumina column. Copper (II) triflate, diphenylphosphine, (S)-*tert*-leucinol, and triflic anhydride and enones were obtained from Aldrich and used without further purification. Triethylamine was distilled from CaH_2 prior to use. Diethylzinc was obtained from Strem, and diisopropylzinc and dibutylzinc were made by known methods.¹ ^1H NMR spectra were recorded on a Bruker DPX-300 (300 MHz) or a DPX-500 (500 MHz) spectrometer and are reported in ppm from CDCl_3 internal standard (7.26 ppm). Data are reported as follows: (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, dt = doublet of triplets, dd = doublet of doublets, ddd = doublet of doublet of doublets; coupling constant(s) in Hz; integration; assignment). Proton decoupled ^{13}C NMR spectra were recorded on a Bruker DPX-300 (75 MHz) and are reported in ppm from CDCl_3 internal standard (77.0 ppm). ^{31}P NMR spectra were reported on a Bruker DPX-300 (121.6 MHz) and are reported in ppm from H_3PO_4 (85% in H_2O) external standard (0.0 ppm). ^{19}F NMR spectra were recorded on a Bruker DPX-300 (282 MHz) and are reported in ppm from CF_3Cl internal standard (0.0 ppm). Infrared spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR spectrometer. Gas chromatographic analyses were performed on a Hewlett-Packard 6890 Series Gas Chromatograph equipped with a capillary split-splitless inlet and flame ionization detector with electronic pneumatics control using either a Supelco β -Dex 120 (30 m x 0.25 mm) capillary GLC column or an Astec Chiraldex

(1) Knochel, P.; Singer, R. *Chem. Rev.* **1993**, 93, 2117-2188 and references cited therein.

G-TA (30 m x 0.25 mm x 0.125 μ m) capillary GLC column with Astec Retention Gap Guard Column (5m x 0.25mm). Optical rotations were recorded on a JASCO DIP-1000 digital polarimeter and the concentration c is reported in g/100 mL. Low resolution mass spectra were obtained on a JEOL HX110 mass spectrometer in the Columbia University Mass Spectrometry Laboratory.

Preparation of ligand 2e: To a cooled (-78 °C) solution of (*S*)-*tert*-leucinol (591 mg, 5.04 mmol) and triethylamine (1.40 mL, 10.1 mmol) in CH₂Cl₂ (20 mL) was added triflic anhydride (1.87mL, 11.1 mmol) in 0.1 mL portions every three minutes (over 1 hour). After the addition was complete the solution was stirred for 1 h, and then allowed to warm to -50 °C. After 14 h (**Note:** If the reaction is allowed to stir for prolonged periods at temperatures above -50 °C, an impurity develops. Careful control of the reaction temperature is necessary to avoid this) the mixture was then poured into a separatory funnel containing 20 mL of chilled (0 °C) 0.1 M HCl. The mixture was shaken and separated, and the organic phase was washed with an additional 20 mL of chilled 0.1 M HCl. The organic phase was then washed with 2 x 20 mL of chilled (0 °C) saturated aqueous sodium carbonate. The organic phase was then dried over MgSO₄, filtered and concentrated. The residue (991 mg of aziridine **1e**) was found to be >95% pure as judged by ¹H NMR analysis, and was used directly in the next step.

To a cooled (-78 °C) solution of diphenylphosphine (708 μ L, 4.07 mmol) in THF (20 mL) was added *n*-BuLi (2.5M in Hexanes, 1.64 mL, 4.07 mmol). The solution was permitted to warm to 0 °C and was then recooled to -78 °C. The aziridine **1e** (991 mg, 4.29 mmol) was added by cannula, with 3 x 3 mL THF rinse. After 15 min the solution was allowed slowly to warm to room temperature over the course of 2 h. After addition of glacial acetic acid (245 μ L, 4.29 mmol), the mixture was concentrated. The residue was treated with CH₂Cl₂ and the resulting mixture was filtered through a plug of silica gel. The filtrate was concentrated and the residue was recrystallized from hexanes (after hot filtration to remove insoluble material) to afford 1.17g (56% overall) of ligand **2e** as a crystalline white solid. [α]_D = +81.2° (c 1.93, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃), δ 7.52-7.42 (m, 2H, ArH), 7.41-7.27 (m, 8H, ArH), 4.80 (br d, J = 10.0 Hz, 1H, NH), 3.36 (m, 1H, *t*-Bu-CH), 2.56 (m, 1H, one of PCH₂), 2.08 (m, 1H, one of P-CH₂), 0.93 (s, 9H, C(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ 138.4, 138.3, 137.1, 136.9, 133.7, 133.4, 132.4, 132.1, 129.3, 128.7, 128.6, 128.5, 128.5, 121.5, 117.2, 63.0 (d, J_{PC} = 14.5 Hz), 35.8 (d, J_{PC} = 4.2 Hz), 32.6 (d, J_{PC}

= 16.9 Hz), 26.5; ^{31}P NMR (121.6 MHz, CDCl_3) δ -23.8 (q, $J_{\text{PF}} = 15.2$ Hz); ^{19}F NMR (282 MHz, CDCl_3) δ 75.0 (d, $J_{\text{PF}} = 15.0$ Hz); IR (thin film) 3830 (br), 3053, 2967, 1480, 1436, 1367, 1195, 1141, 739, 697, 612 cm^{-1} ; LRMS (FAB+) calc'd 417.114, found 417.116.

Procedure for the reaction shown in Scheme 2: To a suspension of 38 mg (.104 mmol) of $\text{Cu}(\text{OTf})_2$ and 109 mg (.260 mmol) of ligand **2e** in 150 mL of CH_2Cl_2 was added dropwise 13.1 mL (15.4 g, 125 mmol) of Et_2Zn . The suspension was stirred for 10 min, and the reaction vessel was then immersed in an ambient temperature ($\sim 23^\circ\text{C}$) water bath. 2-cyclohexen-1-one (10.1 mL, 10.0 g, 104 mmol) was added dropwise over approximately 2 min (NOTE: if the enone is added too rapidly, a mild exotherm ensues; we have found that the rate of addition and extent of exotherm have little effect on the yield and enantioselectivity of the reaction). As monitored by GC (Chiraldex G-TA column) the reaction was complete within 1.5 h. The reaction mixture was cooled with an ice bath and the reaction was quenched by the *dropwise at first* addition of 1 M HCl (aq) (**CAUTION!** this quenching of excess Et_2Zn must be carried out slowly to avoid a vigorous exotherm). After 300 mL of 1 M HCl had been added, the mixture was poured into a separatory funnel. The mixture was shaken, the layers were then separated and the aqueous phase was extracted with an additional 3 x 300 mL CH_2Cl_2 . The combined organic extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified by flash column chromatography on silica gel (19:1 Pentane: Et_2O), to afford 11.3 grams (86% yield, 97% *ee*) of (*S*)-3-ethylcyclohexanone as a colorless oil.

General Procedure for Conjugate Addition: A 25 mL roundbottom flask is charged with $\text{Cu}(\text{OTf})_2$ (7.2 mg, .020 mmol), ligand **2e** (20.8 mg, .050 mmol) and 5 mL CH_2Cl_2 . The resulting suspension is stirred for 20 min, after which time neat R_2Zn (3.0 mmol) and enone (1.0 mmol) are added, 10 minutes apart (see Table 2 for order of addition). After the reaction is complete as monitored by TLC, 1M HCl (5 mL) is added (*dropwise at first!*) and the mixture is extracted with 3 x 10 mL of ether. The combined organics are dried over MgSO_4 , filtered and concentrated. The residue is purified by flash chromatography (19:1 ether:pentane) to give the products in the yields and enantioselectivities indicated in Table 2.

Preparation of (1*S*,5*S*,7*R*)-5-Ethyl-8,8-dimethyl-bicyclo[5.1.0]octan-3-one (Scheme 3): The general procedure was employed (see above). $[\alpha]_D = +107^\circ$ (c 1.24, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) δ 2.79 (1H, dd, $J = 11.5, 5.0$ Hz, one of $\text{C}(2)\text{H}_2\text{CO}$), 2.53 (1H, ddd, $J = 14.3, 7.0, 1.6$ Hz, one of $\text{COC}(4)\text{H}_2$), 2.13 (1H, dd, $J = 14.3, 10.2$ Hz, one of $\text{COC}(4)\text{H}_2$), 2.07 (1H, dd, $J = 11.5, 8.6$ Hz, one of $\text{C}(2)\text{H}_2\text{CO}$), 2.04-1.95 (1H, m, one of $\text{C}(6)\text{H}_2$), 1.80-1.72 (1H, m, one of $\text{C}(6)\text{H}_2$), 1.33 (2H, apparent quint, $J = 7.2$ Hz, $\text{C}(5)\text{HCH}_2\text{CH}_3$), 1.08 (3H, s, one of $(\text{CH}_3)_2\text{C}(8)$), 1.06 (3H, s, one of $(\text{CH}_3)_2\text{C}(8)$), 1.0-0.89 (4H, m, $\text{C}(5)\text{H}$ and $\text{C}(5)\text{HCH}_2\text{CH}_3$), 0.80-0.65 (2H, m, $\text{C}(7)\text{H}$ and $\text{C}(1)\text{H}$); ^{13}C NMR (75 MHz, CDCl_3) δ 212.5, 50.3, 39.6, 39.5, 30.0, 28.9, 26.8, 21.7, 20.5, 15.5, 12.0; IR (neat) 2957, 2928, 2875, 1703, 1459, 1378, 1288, 1165, 796 cm^{-1} ; LRMS (APCI, $\text{M}+\text{H}$) calc'd 181.30, found 181.06.

Stereochemical determinations and proofs:

Proof of the *cis* relative configuration for (1*S*,5*S*,7*R*)-5-Ethyl-8,8-dimethyl-bicyclo[5.1.0]octan-3-one was provided by the illustrated nOe experiment (Figure 1).

Figure 1. Key nOe interaction observed to establish *cis* relative configuration.

3-(*S*)-(2'-Methylethyl)-cyclopentanone (Table 2, entry 1): Astec Chiraldex G-TA (30m x 0.25mm x 0.125 μm) with Astec Retention Gap Guard Column (5m x 0.25mm), 1.0 mL/min He flow, 90 $^\circ\text{C}$. This is a known compound.² The absolute configuration was assigned by analogy.

(2) Degrado, S. J.; Mizutani, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2001**, *123*, 755-756.

4-(*R*)-Ethyl-3,3-dimethylcyclopentanone (Table 2, entry 2): Astec Chiraldex G-TA (30m x 0.25mm x 0.125 μ m) with Astec Retention Gap Guard Column (5m x 0.25mm), 1.0 mL/min He flow, 100 °C. This is a known compound and it has been established that the *S* enantiomer has the shorter retention time.²

3-(*S*)-Ethylcyclohexanone (Table 2, entry 3): Astec Chiraldex G-TA (30m x 0.25mm x 0.125 μ m) with Astec Retention Gap Guard Column (5m x 0.25mm), 1.0 mL/min He flow, 100 °C. This is a known compound and it has been established that the *R* enantiomer has the shorter retention time.²

(racemic)

(Table 2, entry 3)

3-(*S*)-Butylcyclohexanone (Table 2, entry 4): Astec Chiraldex G-TA (30m x 0.25mm x 0.125 μ m) with Astec Retention Gap Guard Column (5m x 0.25mm), 3.4 mL/min He flow, 60 °C. This is a known compound.² The absolute configuration was assigned by analogy.

(racemic)

(Table 2, entry 4)

3-(*S*)-(2'-Methylethyl)-cyclopentanone (Table 2, entry 5): Astec Chiraldex G-TA (30m x 0.25mm x 0.125 μ m) with Astec Retention Gap Guard Column (5m x 0.25mm), 1.0 mL/min He flow, 100 °C. This is a known compound.² The absolute configuration was assigned by analogy.

3-(*R*)-Ethyl-4,4-dimethylcyclopentanone (Table 2, entry 6): Astec ChiralDEX G-TA (30m x 0.25mm x 0.125 μ m) with Astec Retention Gap Guard Column (5m x 0.25mm), 1.0 mL/min He flow, 100 °C. This is a known compound.³ The absolute configuration was assigned by analogy.

3-(*S*)-Ethylcycloheptanone (Table 2, entry 7): Astec ChiralDEX G-TA (30m x 0.25mm x 0.125 μ m) with Astec Retention Gap Guard Column (5m x 0.25mm), 1.0 mL/min He flow, 100 °C. This is a known compound.² The absolute configuration was established by optical rotation: $[\alpha]_D = -61.7^\circ$ (c 1.06, CHCl_3); lit.² $[\alpha]_D = +60.4^\circ$ (c 1.04, CHCl_3) for the *R* enantiomer of 98% ee.

3-(*S*)-(2'-Methylethyl)-cycloheptanone (Table 2, entry 8): Astec Chiraldex G-TA (30m x 0.25mm x 0.125 μ m) with Astec Retention Gap Guard Column (5m x 0.25mm), 1.0 mL/min He flow, 100 °C. This is a known compound.² The absolute configuration was assigned by analogy.

^1H NMR (300 MHz, CDCl_3) spectrum of ligand **2e**:

^1H NMR (300 MHz, CDCl_3) spectrum of (1*S*,5*S*,7*R*)-5-Ethyl-8,8-dimethyl-bicyclo[5.1.0]octan-3-one: