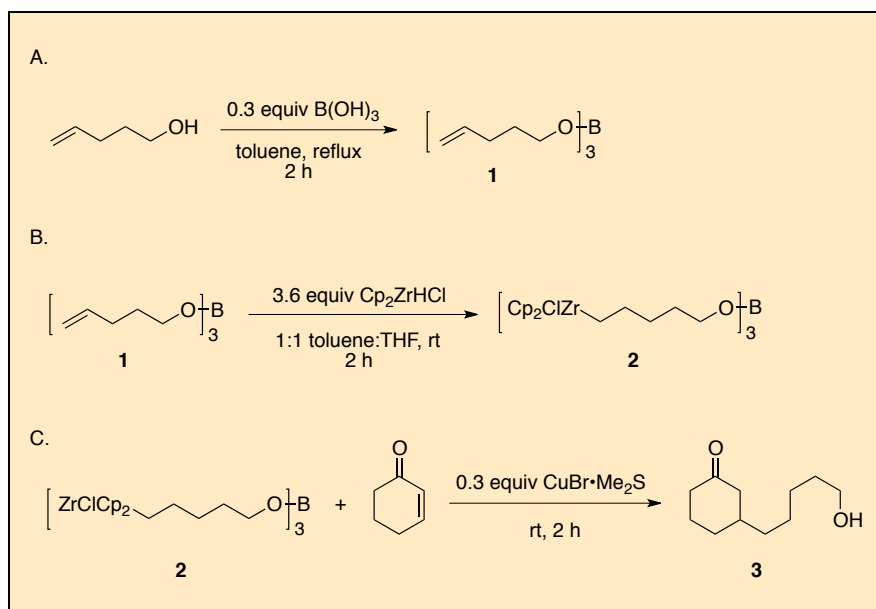


## One-pot Hydrozirconation/Copper-catalyzed Conjugate Addition of Alkylzirconocenes to Enones

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### Procedure

A. *Tripent-4-enyl borate (1)*. A 300-mL, three-necked, flame-dried, round-bottomed flask equipped with a Teflon-coated stir bar (3 cm), two septa (Necks 1 and 3) and a Dean-Stark trap (20 mL, Neck 2) wrapped in aluminum foil and fitted with a reflux condenser (20 cm), and a nitrogen gas inlet adaptor (Note 1) is charged with boric acid (886 mg, 14.3 mmol, 1.0 equiv) (Note 2), toluene (70 mL) (Note 3), and 4-penten-1-ol (4.48 mL,

43.4 mmol, 3.0 equiv) (Note 2) at room temperature (Figure 1). The resulting suspension is slowly heated in an oil bath (135–136 °C) to reflux over 30 min and heating is continued at reflux for 1.5 h (Note 4). The reaction mixture turns homogeneous after 50 min of heating.



Figure 1. Apparatus Assembly for Step A

After heating at reflux for 1.5 h, the flask is removed from the oil bath and stirred at room temperature for 10 min before the septum (Neck 1) is replaced with a thermometer adaptor/thermometer (Note 5) and the Dean-Stark trap/reflux condenser (Neck 2) is replaced with a dry reflux condenser (20 cm) equipped with a nitrogen gas inlet adaptor (Figure 2). The resulting apparatus is further cooled for 20 min with the aid of an ice/water bath (Note 4) to 23–24 °C (internal temperature). The cooling bath



is removed and the *in situ* generated tripent-4-enyl borate used directly for the next step (Note 6).



Figure 2. Apparatus Assembly for Step B

B. *Tris[5-(bis(cyclopentadienyl)zirconium(IV)chloride)pentyl] borate (2)*. To the clear tripent-4-enyl borate solution is quickly added THF (50 mL) by syringe (Note 3), followed by  $\text{Cp}_2\text{ZrHCl}$  (14.7 g, 57.0 mmol, 4.0 equiv) (Note 7) in one portion via a powder funnel (Neck 3) at 24 °C (internal temperature) (Note 8). The resulting white suspension (Figure 3) bubbles gently for approximately 5 s, turns yellow/orange in color (Figure 4), and then clear (Figure 5) after approximately 15 min (Note 9). The hydrozirconation reaction is complete after 2 h (Note 10), and the solution of the alkyl zirconocene product formed is used without purification for the next step.



Figure 3. Initial white solution formed in Step B



Figure 4. Yellow suspension formed in Step B



**Figure 5.** Clear solution formed in Step B

C. *3-(5-Hydroxypentyl)cyclohexan-1-one* (**3**). To the crude tris[5-(bis(cyclopentadienyl)zirconium(IV)chloride)pentyl] borate solution is added 2-cyclohexen-1-one (4.58 mL, 47.3 mmol, 3.3 equiv) by syringe (Notes 8 and 11) followed by  $\text{CuBr}\cdot\text{Me}_2\text{S}$  (884 mg, 4.30 mmol, 0.3 equiv) (Note 8) via a powder funnel (Neck 3) in one portion at 24 °C. A strongly exothermic reaction ensues upon addition of  $\text{CuBr}\cdot\text{Me}_2\text{S}$ , with the reaction temperature rising from 24 °C to 38 °C within 10 min (Note 12). The heterogeneous reaction mixture turns black (Figure 6) (Note 13) and the conjugate addition reaction is found to be complete after 2 h (Note 14).



**Figure 6.** Black solution formed in Step C

The reaction is quenched by pouring the reaction mixture into a 500-mL Erlenmeyer flask that contains a concentrated  $\text{NH}_4\text{OH}$  solution (150 mL) (Note 3) and a Teflon-coated stir bar (5.0 cm). The remaining residue in the three-necked, round-bottomed flask is transferred to the Erlenmeyer flask with an ether wash (100 mL) (Note 3) and the resulting heterogeneous, biphasic, grey mixture is vigorously stirred at room temperature for 2 h.

After 2 h, the mixture turns light blue in color (Figure 7) and is suction filtered (37 mmHg) through a 350-mL glass filter (porosity: 40-60  $\mu\text{m}$ ) into a 1000-mL filtration flask. The resulting pale blue solids and the 500-mL Erlenmeyer flask are washed with deionized water (3 x 40 mL) followed by ether (3 x 40 mL), and the filtrate is transferred to a 500-mL separatory funnel (Figure 8).



**Figure 7.** Light blue solution formed in Step C

The dark yellow ether layer is removed and the dark blue aqueous layer is extracted with ether (2 x 100 mL). The ether extracts are combined in a 1000-mL Erlenmeyer flask, dried over  $\text{Na}_2\text{SO}_4$  (20.3 g, 15 min) (Note 15) and filtered (slight over pressure of air) through a plug of  $\text{SiO}_2$  (25.0 g, height = 10.0 cm, diameter = 2.5 cm) into a 1000-mL round-bottomed flask with excess ether (100 mL), which is also used to rinse the Erlenmeyer flask. The yellow filtrate is concentrated by rotary evaporation (20 to 50 °C/50 mmHg) and the resulting oil (Note 16) is loaded with a 1:1 hexanes:EtOAc solution (10.0 mL) onto a 4.5-cm diameter flash column, dry packed (pre-flushed with 1:1 hexanes:EtOAc solution until uniformly solvated) with  $\text{SiO}_2$  (162 g) (Note 17). Following the sample addition, the column is eluted with a 1:1 hexanes:EtOAc solution (1.6 L total volume, 33 mL/min. average flow rate) and the first 325 mL of eluent are collected as one fraction. At this time, a



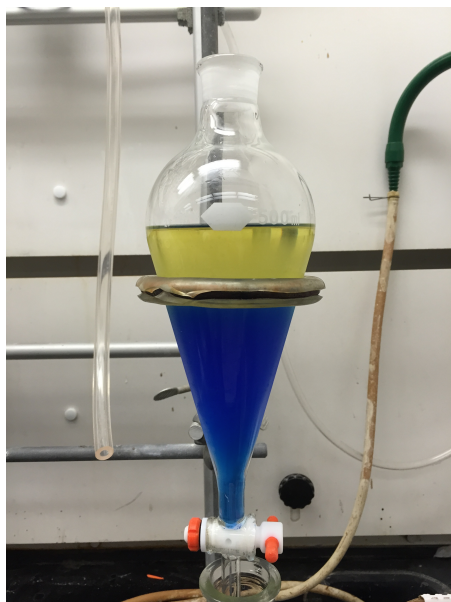


Figure 8. Biphasic solution in separatory funnel

yellow band (Note 18) begins to elute from the column and fractions 60 mL in volume are collected. The desired product elutes over fractions 13-52 and a sample of the desired product enriched with the regioisomeric byproduct 3-(5-hydroxypentan-2-yl)cyclohexanone (**4**) is isolated over fractions 53-60 (Notes 19 and 20). Fractions 13-52 are combined (each test tube is rinsed with ether (2 mL)), concentrated by rotary evaporation (20 to 40 °C/50 mmHg), transferred to a pre-weighed 50-mL round-bottomed flask with ether (10 mL), re-concentrated by rotary evaporation (20 to 40 °C/50 mmHg) and dried under high vacuum (14 mmHg, 12 h) to afford 3-(5-hydroxypentyl)cyclohexan-1-one (**3**) as a pale yellow oil (5.20 g, 66%) (Notes 21 and 22).

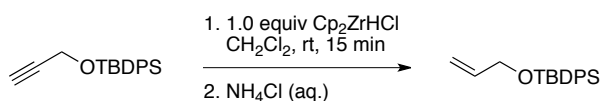
## Notes

1. All glassware contained 24/40 joints and was either flame-dried or oven-dried (110 °C) overnight prior to use, if not otherwise noted. All reaction steps and reagents were performed under a partial positive



- nitrogen gas atmosphere using a nitrogen gas line connected to an external mineral oil bubbler.
2. Copper(I)bromide dimethylsulfide (99%, Acros Organics), 4-penten-1-ol (99%, Acros Organics), and boric acid (>95%, Fisher Scientific, Reagent grade) were used as received. 2-Cyclohexene-1-one (>95%, Sigma-Aldrich) was freshly distilled (76 °C, 37 mmHg) prior to use. The submitters mentioned boric acid was either used as received or recrystallized two times from boiling deionized water and dried under high vacuum.<sup>2</sup> No appreciable difference in overall yield or reactivity was observed by the checkers using recrystallized *vs.* non-recrystallized boric acid.
  3. Toluene and tetrahydrofuran were dried using a solvent purification system manufactured by SG Water U.S.A., LLC. Column chromatography solvents EtOAc and hexanes were used as received. Diethyl ether (ACS grade) and NH<sub>4</sub>OH (ACS grade) were used as received.
  4. A Pyrex® crystallization dish with a diameter of 15.0 cm and a height of 7.0 cm was used.
  5. A mercury thermometer with a range of -20 to 110 °C was used.
  6. The submitter followed the reaction progress by removing an aliquot (0.15 mL) of the reaction mixture after cooling to 22–23 °C and directly transferring it to an NMR tube for <sup>1</sup>H NMR analysis. The analysis showed ~85% conversion of the reagents to a single borate species: <sup>1</sup>H NMR (300 MHz, dry CDCl<sub>3</sub>) δ: 1.77–1.84 (m, 2 H), 2.26–2.29 (m, 2 H), 3.94–3.99 (m, 2 H), 5.11–5.22 (m, 2 H), 5.92–6.06 (m, 1 H). This reaction has been performed under the same reaction conditions on a 1.0-mmol scale in both benzene and toluene at reflux furnishing the crude tripent-4-enyl borate, after removal of the reaction solvent via distillation and high vacuum, with 95–98% mass recoveries and in nearly identical purity to that of this reaction as analyzed by <sup>1</sup>H NMR.
  7. Cp<sub>2</sub>ZrHCl was prepared employing a method reported by Buchwald and co-workers.<sup>3</sup> The activity of this reagent was measured by a convenient <sup>1</sup>H NMR assay: To a suspension of Cp<sub>2</sub>ZrHCl (0.05 mmol, 12.9 mg, 1.0 equiv) in dry CH<sub>2</sub>Cl<sub>2</sub> (0.50 mL) was immediately added *tert*-butyldiphenyl(prop-2-ynyloxy)silane (0.05 mmol, 14.7 mg, 1.0 equiv). The resulting homogeneous pale yellow reaction mixture was stirred at room temperature for 15 min, quenched by the addition of saturated NH<sub>4</sub>Cl solution (0.50 mL), and stirred for 5 min. The organic solvent

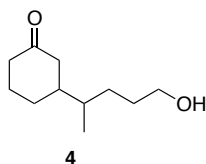
layer was separated, filtered through a 1" plug of Celite contained in a disposable 5  $\frac{3}{4}$ " Pasteur pipette, washed with additional  $\text{CH}_2\text{Cl}_2$  (1.5 mL) and concentrated by rotary evaporation (40 °C). The resulting white solids were dried under high vacuum for 30 min. This procedure was repeated three times on three different samples for each new batch of  $\text{Cp}_2\text{ZrHCl}$ . The percent conversion for each reaction was then determined via a  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) analysis by comparison of the integrated areas for the alkyne  $\text{CH}_2\text{O}$  peak at  $\delta$  4.32 (d,  $J = 2.4$  Hz, 2 H) to the alkene  $\text{CH}_2\text{O}$  peak at  $\delta$  4.22 (dt,  $J = 4.5, 2.0$  Hz, 2 H). Typical values for the average % conversion among the three experiments were found to be 73-83%. The numerical value for the average % conversion for a particular batch of  $\text{Cp}_2\text{ZrHCl}$  was used to calculate the number of equivalents of  $\text{Cp}_2\text{ZrHCl}$  (by mass) used in these hydrozirconations, ensuring that only a slight excess of  $\text{Cp}_2\text{ZrHCl}$  (3.1 equiv) was used in each experiment. Sample calculation: average % conversion = 78%; 3.1 active equiv of  $\text{Cp}_2\text{ZrHCl} = (X \text{ equiv of } \text{Cp}_2\text{ZrHCl}) \times 0.78 \Rightarrow X = 4.0 \text{ equiv of } \text{Cp}_2\text{ZrHCl}$ .



- The septum in Neck 3 was removed with the apparatus under a positive pressure of nitrogen gas atmosphere and then immediately replaced after the addition of reagent.
- No exotherm was noted upon the addition of  $\text{Cp}_2\text{ZrHCl}$  to **1**. The submitter mentioned that this observation stands in contrast to the reaction of 4-penten-1-ol (2.07 mL, 20.0 mmol, 1.0 equiv) with  $\text{Cp}_2\text{ZrHCl}$  (11.1 g, 43.0 mmol, 2.15 equiv) in THF (50 mL) at 25 °C (internal temperature) which was found to be exothermic (reaction temperature increasing to 34 °C) and accompanied by a vigorous ( $\text{H}_2$ ) gas release, which persisted for 2 min, as a result of the deprotonation of 4-penten-1-ol with  $\text{Cp}_2\text{ZrHCl}$ .
- The submitter followed the reaction progress by  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) analysis of aliquots (0.10 mL) of the reaction mixture. An approximate % conversion for the hydrozirconation reaction can be obtained by comparing the integrated areas for the tripten-4-enyl borate olefin proton resonance  $\delta$  4.97–5.10 (m,  $\text{CH}_2$ ) vs. the newly formed tris[5-(biscyclopentadienyl)zirconium(IV)chloride]penty] borate methylene

- proton resonance  $\delta$  0.90-0.97 (m, 2H). This analysis gave 90%, 97% and 96% conversions for reactions run on 7%, 50% and 100% scales, respectively. Thin layer chromatography (Whatman®, aluminum backed, 250  $\mu$ m thickness) analysis using a 1:1 mixture of hexanes:EtOAc as the eluent and a *p*-anisaldehyde solution (2.5 mL of *p*-anisaldehyde, 2.0 mL of AcOH, and 3.5 mL of conc. H<sub>2</sub>SO<sub>4</sub> in 100 mL of 95% EtOH) for visualization showed a dark green/brown spot with an  $R_f = 0.03$  for the hydrozirconation product.
- The submitter mentioned that a mild exotherm was noted upon the addition of 2-cyclohexen-1-one to the reaction mixture with the reaction temperature rising from 23 °C to 25 °C. This exothermic reaction is quite possibly the result of the reaction of any excess Cp<sub>2</sub>ZrHCl with 2-cyclohexen-1-one, since it was found that an exothermic reaction took place upon the addition of Cp<sub>2</sub>ZrHCl (134.0 mg, 0.52 mmol, 1.0 equiv) to a solution of 2-cyclohexen-1-one (47.4  $\mu$ L, 0.52 mmol, 1.0 equiv) in THF (3.0 mL) with the reaction temperature rising from 25 °C to 32 °C. This reaction provided 2-cyclohexen-1-ol in good conversion by crude <sup>1</sup>HNMR (300 MHz, CDCl<sub>3</sub>) analysis and demonstrates the importance of using a slight excess of 2-cyclohexen-1-one in the above protocol.
  - The reaction mixture slowly re-cooled to 23 °C over 1.5 h.
  - The black color is a result of precipitation of copper(0) from the reaction mixture.
  - The submitter reported that the reaction progress was monitored by thin layer chromatography (Whatman® aluminum backed, 250  $\mu$ m thickness) using a 1:1 mixture of hexanes:EtOAc as the eluent and a *p*-anisaldehyde solution for visualization. After 2 h reaction time, the conversion of 2-cyclohexen-1-one ( $R_f = 0.72$ ) to the product 3-(5-hydroxypentyl)cyclohexan-1-one ( $R_f = 0.43$ ) ceased after near complete consumption of 2-cyclohexen-1-one.
  - Anhydrous sodium sulfate (EMD, ACS grade, granular powder) was used as received.
  - A 3.0 mg sample of the crude mixture was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (1.0 mL) and analyzed by GC (HP-5ms agilent 30 m x 0.25 mm x 0.25  $\mu$ m, helium flow 1.0 mL/min, temperature gradient 110 °C to 280 °C at 30 °C/min, FID detector). GC analysis showed a >96:4 ratio of the desired product 3-(5-hydroxypentyl)cyclohexanone (**3**) (retention time of 4.74 min) to the side product 3-(5-hydroxypentan-2-yl)cyclohexanone (**4**).
  - SiO<sub>2</sub> 40-63  $\mu$ m D (Silicycle, Quebec City, Canada) was used.

18. The submitter noted that the yellow band was found to contain a complex mixture of reaction byproducts including 2-cyclohexen-1-ol, 4-penten-1-ol and 1-pentanol as determined by  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) analysis.
19. Column chromatography conditions to completely separate 3-(5-hydroxypentyl)cyclohexan-1-one and the minor regioisomer 3-(5-hydroxypentan-2-yl)cyclohexanone have not been identified. The chromatography conditions reported above allow for a partial separation of the two reaction products in which the last fractions of 3-(5-hydroxypentyl)cyclohexan-1-one are enriched with the byproduct 3-(5-hydroxypentan-2-yl)cyclohexanone. Collection, combination and concentration of column fractions 53-60 led to an enriched sample (90 mg) containing a 94:6 mixture of 3-(5-hydroxypentyl)cyclohexan-1-one (3): 3-(5-hydroxypentan-2-yl)cyclohexanone (4), as determined by GC (conditions in Note 16) and  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) analysis. The isomer 3-(5-hydroxypentan-2-yl)cyclohexanone (4) can be identified by  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) as a result of its characteristic methyl peak at  $\delta$  0.89 (d,  $J = 6.8$  Hz, 3 H,  $-\text{CH}_3$ ).



20. The submitters reported that attempts to optimize this reaction included: (A) Reacting 4-penten-1-ol (0.269 mL, 2.58 mmol) with 2.0 equivalents of  $\text{Cp}_2\text{ZrHCl}$  (1.33 g, 5.16 mmol) at 5 °C in THF (10 mL) either by the addition of 4-penten-1-ol to a suspension of  $\text{Cp}_2\text{ZrHCl}$  (2.0 equiv) in THF at 5 °C followed by warming to 20 °C over 20 min or by sequentially reacting  $\text{Cp}_2\text{ZrHCl}$  (1.0 equiv) with 4-penten-1-ol (1.0 equiv) at 5 °C and then warming the mixture to 20 °C over 20 min before adding a second equivalent of  $\text{Cp}_2\text{ZrHCl}$ . The optimized procedure was found to give a cleaner hydrozirconation reaction product by  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ) analysis. (B) The reaction mixtures were heated to 40 °C for 15-20 min to effect the hydrozirconation reaction, followed by cooling to 25 °C. (C) To the alkyl zirconocene solutions were added 2-cyclohexen-1-one (0.255 mL, 2.58 mmol, 1.0 equiv) followed by  $\text{CuBr}\cdot\text{Me}_2\text{S}$  (53.5 mg, 0.258 mmol,

- 1.0 equiv) at 25 °C and the resulting brown mixtures were heated to 40 °C for 30 min to effect the transmetallation/conjugate addition reaction. Finally, these reactions were quenched with NH<sub>4</sub>OH (14.8 M, 50 mL). While these reaction variants successfully produced 3-(5-hydroxypentyl)cyclohexan-1-one in comparable yields (60-70%, 283–337 mg), the isolated products were found to be contaminated with ca. 8-10% of the 3-(5-hydroxypentan-2-yl)cyclohexanone byproduct (4).
21. The product isolated in fractions 13-52 was found to be 97.6% pure by GC (conditions in Note 16) and contain 0.8% of 3-(5-hydroxypentan-2-yl)cyclohexanone. The product has the following characteristic physicochemical properties: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 1.23–1.39 (m, 7 H), 1.49–1.69 (m, 3 H), 1.68–1.80 (m, 2 H), 1.81–2.08 (m, 3 H), 2.18–2.42 (m, 3 H), 3.60 (t, *J* = 6.6 Hz, 2 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 25.4, 25.9, 26.6, 31.4, 32.7, 36.6, 39.1, 41.6, 48.3, 62.9, 212.4; IR (neat) 3412, 2927, 2856, 1704, 1447, 1421, 1346, 1313, 1279, 1053 cm<sup>-1</sup>; ESI-MS *m/z* 185 (24), 207 (100); HRMS (ESI) *m/z* calcd for C<sub>11</sub>H<sub>21</sub>O<sub>2</sub> [M+H]<sup>+</sup> 185.1536, found 185.1536. A 2.0 g sample was subjected to bulb-to-bulb distillation (150–151 °C/4.0 mmHg) affording 0.957 g (48% recovery) of the product as a clear oil. Anal Calcd for C<sub>11</sub>H<sub>20</sub>O<sub>2</sub>: C, 71.70; H, 10.94; O, 17.36; Found: C, 71.53, H, 11.10.
22. A reaction checked at half-scale provided 2.69 g (68%) of the product. The submitters report that reactions run on 7% and 50% scales produced the product under identical reaction/workup conditions in 65% yield for both reactions with measured GC purities of ≥98% (conditions in Note 16).

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## Discussion

The copper-catalyzed conjugate Michael reaction and related additions of alkylzirconocenes to  $\alpha,\beta$ -unsaturated carbonyl compounds have emerged as synthetically useful C-C bond forming processes.<sup>4-16</sup> Recent examples include catalytic asymmetric additions to  $\alpha,\beta$ -unsaturated lactones and enones.<sup>17,18</sup> The scope of this reaction has been previously investigated and some representative examples are shown in Table 1.<sup>9,11,12</sup> As shown, these reactions are tolerant of cyclic and acyclic alkenes, as well as silyl ether, silyl ester and acetal functionalities. A variety of enones have also been successfully employed, including cyclic, acyclic, sterically hindered and chiral substrates.

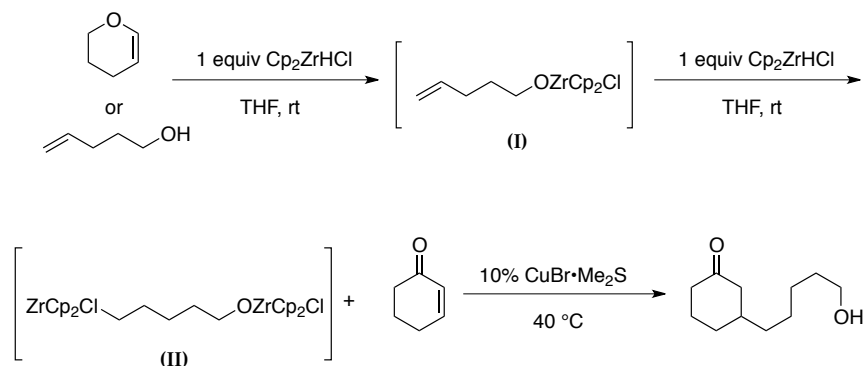


Table 1. Copper-Catalyzed Conjugate Addition Reactions of Alkylzirconocenes to Enones

| Entry | Alkene | Enone | Product | Yield <sup>a</sup>   |
|-------|--------|-------|---------|----------------------|
| 1     |        |       |         | 76% <sup>b,c</sup>   |
| 2     |        |       |         | 85% <sup>b,c,d</sup> |
| 3     |        |       |         | 78% <sup>b,c</sup>   |
| 4     |        |       |         | 78% <sup>b</sup>     |
| 5     |        |       |         | 46% <sup>b,e</sup>   |
| 6     |        |       |         | 51% <sup>b,c</sup>   |
| 7     |        |       |         | 60% <sup>e,f,g</sup> |

<sup>a</sup>Reactions were typically conducted in THF by reacting the alkene with Cp<sub>2</sub>ZrHCl for 10 min at 40 °C followed by cooling to rt, adding the enone, followed by 10% CuBr·Me<sub>2</sub>S and heating to 40 °C for 10 min. <sup>b</sup>See reference 11. <sup>c</sup>See reference 12. <sup>d</sup>Two equiv of Cp<sub>2</sub>ZrHCl were used. <sup>e</sup>One equiv of BF<sub>3</sub>·OEt<sub>2</sub> was used. <sup>f</sup>See reference 9. <sup>g</sup>90%de.

The hydrozirconation/copper-catalyzed conjugate addition reaction of 3,4-dihydro-2H-pyran (DHP) with cyclohexen-1-one was shown to produce the title compound 3-(5-hydroxypentyl)cyclohexan-1-one in 85% yield.<sup>11,12</sup> The sequence of steps for this reaction is reported to involve an initial hydrozirconation of DHP followed by  $\beta$ -elimination to form intermediate (I), and then a second hydrozirconation of (I) generating intermediate (II) which undergoes the copper-catalyzed conjugate addition reaction with 2-cyclohexen-1-one (Scheme 1). Analysis of the reaction sequence suggested that this reaction could be generalized to include the conjugate addition of unprotected alkenyl alcohols. To test this hypothesis, reaction conditions were optimized for the reaction of 4-penten-1-ol with 2 equiv of  $\text{Cp}_2\text{ZrHCl}$  in THF (Note 20). This reaction proceeds through the initial deprotonation of 4-penten-1-ol with 1 equiv of  $\text{Cp}_2\text{ZrHCl}$  at 5 °C to generate the common intermediate (I), followed by hydrozirconation of (I) at 40 °C forming (II) which undergoes the copper-catalyzed conjugate addition to 2-cyclohexen-1-one in 60-70% yield (Scheme 1). While the yields for this addition reaction are acceptable, the isolated products are contaminated with 8-10% of the regioisomeric 3-(5-hydroxypentan-2-yl)cyclohexanone.



**Scheme 1. Hydrozirconation / Copper-Catalyzed Conjugate Addition of 2-Cyclohexen-1-one to DHP / 4-Penten-1-ol**

As a result of the cost of  $\text{Cp}_2\text{ZrCl}_2$  and the high molecular weight of  $\text{Cp}_2\text{ZrHCl}$ , we were interested in developing a more cost effective and atom economical route involving the temporary protection of alkenyl-alcohol substrates to be utilized in this methodology. We found that the condensation of 4-penten-1-ol with boric acid, which changed the

temporary organometallic alcohol protecting group from the zirconate  $\text{RO-ZrCp}_2\text{Cl}$  to the boronate  $(\text{RO})_3\text{B}$ , was well tolerated in the subsequent hydrozirconation/copper-catalyzed conjugate addition reaction to 2-cyclohexen-1-one, and all steps following the formation of borate could be conducted at room temperature. Significantly, while this reaction led to comparable overall one-pot yields *vs.* the reaction performed with 2 equivalents of  $\text{Cp}_2\text{ZrHCl}$ , switching the initially produced metal alkoxide from  $\text{Cp}_2\text{ClZr-OR}$  to  $\text{B-(OR)}_3$  allowed for a relatively fast hydrozirconation/copper-catalyzed conjugate addition reaction sequence at room temperature, which reduced the 3-(5-hydroxypentan-2-yl)cyclohexanone regioisomer formation to ca.  $\leq 3.3\%$  as determined by GC analysis of the crude reaction mixtures at all scales.

The procedure reported herein further exemplifies the utility and scalability of the one-pot tandem hydrozirconation/copper-catalyzed conjugate addition of alkylzirconocenes to enones. This reaction sequence allows for the economical use of unprotected alkenyl alcohols by utilizing the relatively benign  $\text{B(OH)}_3$  as a temporary boron-based alcohol protecting group.

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### Appendix

#### Chemical Abstracts Nomenclature (Registry Number)

Boric acid: trihydroxidoboron; (10043-35-3)

4-Penten-1-ol: pent-4-en-1-ol; (821-09-0)

Cp<sub>2</sub>ZrHCl: bis(cyclopentadienyl)zirconium(IV) chloride hydride;  
(37342-97-5)

2-Cyclohexen-1-one: (930-69-7)

CuBr•Me<sub>2</sub>S: bromocopper-methylsulfanylmethane; (54678-23-8)

NH<sub>4</sub>OH: ammonium hydroxide; (1336-21-6)



David M. Arnold obtained his B.S. in Chemistry from Kings College in 2005 and graduated with a Master of Science degree from the University of Pittsburgh in 2010. Under the direction of Prof. Peter Wipf, he worked on the synthesis of biologically active heterocycles and the development of new organometallic methods.



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