A Practical Synthesis of Optically Active α-Substituted Ketones in High Enantiomeric Excess

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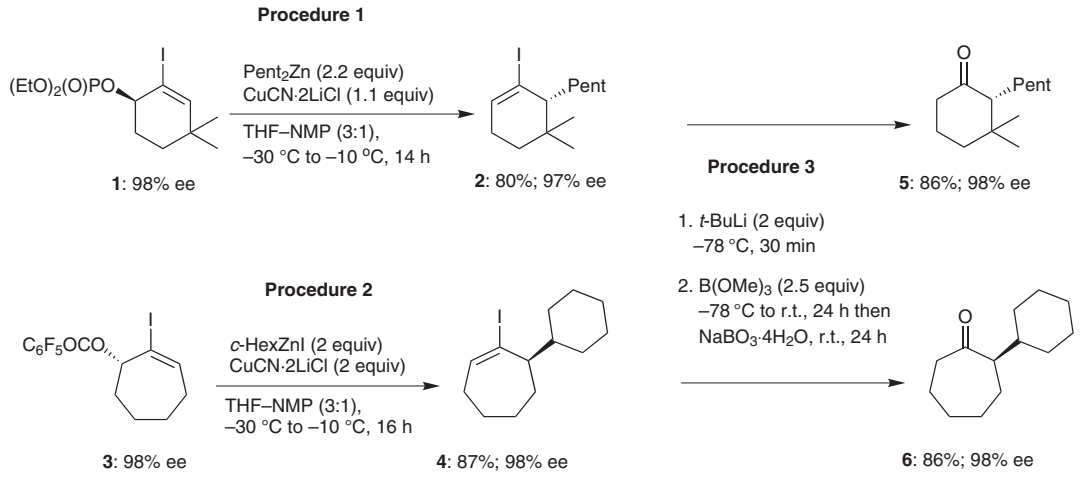
Abstract: A highly enantioselective synthesis of optically active α-substituted ketones can be achieved by using a reaction sequence involving a stereoselective *anti*-S_N2'-allylic substitution in the presence of CuCN·2LiCl, followed by the oxidation of the intermediate cycloalkenyllithium species using $B(MeO)_3/NaBO_3·4H_2O$. The substitution reaction proceeds with a perfect transfer of chirality.

Key words: allylic substitution, organozinc, organocopper, chiral α-substituted ketones



Scheme 1

Optically active α-substituted ketones are versatile building blocks for the synthesis of natural products.[1] A number of methods for the synthesis of this class of compounds have been reported, for example stereoselective α-alkylation[2] and enantioselective protonation of enolates and enols.[3] For the performance of alkylation reactions of ketone enolates, the regio- and stereoselectivity of enolate formation is essential for the overall selectivity of the reaction. The regioselectivity of ketone deprotonation was extensively investigated.[4]

Here, we describe a highly regio- and enantioselective synthesis of optically active α-substituted ketones using a reaction sequence involving a stereoselective *anti*-S_N2'-allylic substitution of 2-iodocycloallylic benzoates or phosphates[5] in the presence of CuCN·2LiCl followed by the oxidation of an intermediate cycloalkenyllithium species using $B(MeO)_3/NaBO_3·4H_2O$. A high enantiomeric purity of α-substituted ketones could be obtained via these highly stereoselective *anti*-S_N2'-allylic substitutions.

Thus, the *anti*-S_N2'-allylic substitution reaction between the chiral allylic phosphate **1** (98% ee) and dipentylzinc (**Procedure 1**)[6] in the presence of CuCN·2LiCl provided the chiral cyclohexenyl iodide **2** in 80% yield with 97% ee (Scheme 1). Similarly, treatment of the chiral allylic pentafluorobenzoate **3** (98% ee) with cyclohexylzinc iodide gave the desired *anti*-S_N2' product cycloheptenyl iodide **4** in 87% yield and 98% ee (**Procedure 2**).[7] Cycloalkenyl iodides **2** and **4** were converted into ketones **5** and **6**, respectively, using a one-pot oxidation reaction (**Procedure 3**).[7] Thus, treatment of the cycloalkenyl iodides **2** and **4** with *t*-BuLi (2 equiv) at –78 °C followed by reaction with $B(OMe)_3$ and further oxidation using $NaBO_3·4H_2O$ provided both ketones **5** and **6** in 86% yield and 98% ee (Scheme 1).

The method has a broad scope for the preparation of a variety of chiral α-substituted cyclohexanones and cycloheptanones in high enantiomeric purity.[8] Furthermore, this procedure can be applied to five-membered rings as well. Thus, the stereoselective *anti*-S_N2' substitution of

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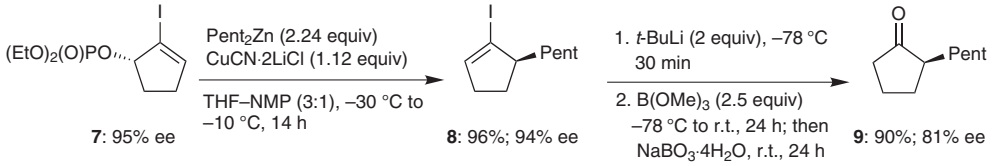


Scheme 2

the allylic phosphate **7** with dipentylzinc gave the chiral cyclopentenyl iodide **8** in 96% yield with 94% ee (Scheme 2). Using a one-pot oxidation reaction, the cyclopentanone (*S*)-**9** was obtained in 86% overall yield with 81% ee starting from the allylic phosphate **7**. This optically pure cyclopentanone and its enantiomer are useful perfumes with a jasmine-like odor. They are also valuable precursors for the synthesis of tetrahydro-6-pentyl-2*H*-pyran-2-one.[9]

Interestingly, this method also allows a practical regioselective synthesis of ketones bearing a quaternary center at the α-position to the carbonyl group with high enantioselectivity (Scheme 3). Thus, the reaction of the pentafluorobenzoate **10** with dipentylzinc (2.4 equiv) and CuCN·2LiCl (1.2 equiv) in THF for four hours at 25 °C provided the *anti*-S_N2' substitution product **11** in 93% yield and 95% ee. Transmetalation of the resulting cycloalkenyllithium species with $B(OMe)_3$ and further oxidation using $NaBO_3·4H_2O$ afforded the chiral ketone **12** in 70% yield and 95% ee.[7]

In summary, we have developed a short, highly enantioselective synthetic sequence allowing the preparation of various chiral ketones with an α-stereogenic center.

(6*R*)-1-Iodo-5,5-dimethyl-6-pentylcyclohex-1-ene (2);[6] Typical Procedure 1

A flame-dried round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 0.56 mL, 0.56 mmol, 1.12 equiv) and NMP (1.30 mL) and the mixture was cooled to –30 °C. Dipentylzinc (4.80 M in THF, 0.23 mL, 1.12 mmol, 2.24 equiv) was added dropwise and the mixture was stirred at –30 °C for 30 min. Then diethyl (1*R*)-2-iodo-4,4-dimethylcyclohex-2-en-1-yl phosphate (**1**; 194 mg, 0.50 mmol, 1.0 equiv) was added dropwise as a solution in THF (0.8 mL). The mixture was stirred at –30 to –10 °C for 14 h. A sat. aq NH_4Cl solution (20 mL) was added followed by 25% aq NH_3 solution (1 mL). The mixture was stirred at 25 °C until the copper salts had dissolved, then extracted with Et_2O (3 × 20 mL). The combined organic phases were washed with brine (10 mL) and dried (Na_2SO_4). Purification by column chromatography (silica gel, pentane) afforded the product (*R*)-**2** as a colorless oil; yield: 122 mg (80%); 97% ee; $[\alpha]_D^{20}$ +60.2 (*c* = 1.25, CH_2Cl_2).

GC (Chiraldex B-PH, 30 mm × 0.25 mm); conditions: 125 °C constant: t_R (min) = 19.079 (minor), 19.965 (major).

IR (film): 2955 (s), 2929 (s), 2870 (s), 1466 (m), 1385 (w), 1365 (w), 924 (w), 828 (w), 742 cm^{-1} (w).

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.12 (t, *J* = 3.8 Hz, 1 H), 2.05–1.95 (m, 2 H), 1.92–1.86 (m, 1 H), 1.50–1.38 (m, 3 H), 1.38–1.10 (m, 7 H), 0.92 (s, 3 H), 0.88 (s, 3 H), 0.83 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.3, 106.0, 56.8, 35.5, 32.9, 32.3, 30.8, 29.6, 28.4, 28.0, 27.4, 22.9, 14.5.

MS (EI, 70 eV): *m*/*z* (%) = 306 (M^+, 29), 251 (10), 250 (98), 236 (40), 180 (22), 179 (12), 123 (22), 109 (31), 93 (33), 81 (100), 67 (79), 55 (19).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{23}I$: 306.0844; found: 306.0818.

Anal. Calcd for $C_{13}H_{23}I$ (306.22): C, 50.99; H, 7.57. Found: C, 51.19; H, 7.68.

(5*S*)-1-Iodo-5-pentylcyclopent-1-ene (8)

$[\alpha]_D^{20}$ +13 (*c* = 0.31, CH_2Cl_2).

GC (Chirasil-Dex CB, 25 mm × 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/min to 160 °C; t_R (min) = 16.296 (major), 16.446 (minor); 94% ee.

IR (film): 2956 (s), 2926 (s), 2854 (s), 1466 (m), 1378 cm^{-1} (w).

^1H NMR ($CDCl_3$, 300 MHz): δ = 6.10–6.00 (m, 1 H), 2.68–2.47 (m, 1 H), 2.35–2.10 (m, 2 H), 2.08–1.90 (m, 2 H), 1.68–1.42 (m, 3 H), 1.40–0.98 (m, 5 H), 0.92–0.75 (m, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.6, 102.6, 52.4, 34.9, 33.7, 32.4, 28.7, 26.6, 23.0, 14.5.

MS (EI, 70 eV): *m*/*z* (%) = 264 (M^+, 45), 194 (37), 193 (38), 137 (21), 95 (21), 81 (43), 67 (96), 66 (100).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{17}I$: 264.0375; found: 264.0382.

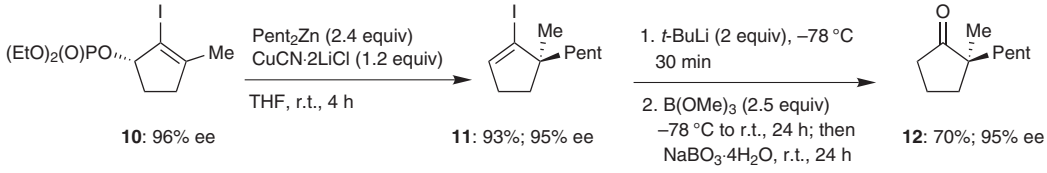
(5*S*)-1-Iodo-5-methyl-5-pentylcyclopent-1-ene (11)

$[\alpha]_D^{20}$ +6.2 (*c* = 0.26, CH_2Cl_2).

GC (Chirasil-Dex CB, 25 mm × 0.25 mm); conditions: 60 °C (1 min), ramp of 20 °C/min to 160 °C; t_R (min) = 7.057 (major), 7.151 (minor); 95% ee.

IR (film): 2954 (s), 2925 (s), 2849 (s), 1738 (m), 1455 (m), 1374 (m), 1217 cm^{-1} (m).

^1H NMR ($CDCl_3$, 300 MHz): δ = 5.95 (t, *J* = 2.54 Hz, 1 H), 2.32–2.12 (m, 2 H), 1.90–1.78 (m, 1 H), 1.66–1.54 (m, 1 H), 1.32–1.04 (m, 8 H), 0.91 (s, 3 H), 0.82 (t, *J* = 6.91 Hz, 3 H).



Scheme 3

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 138.3, 111.0, 52.5, 40.6, 33.6, 32.8, 32.3, 27.6, 24.4, 23.0, 14.5.

MS (EI, 70 eV): *m*/*z* (%) = 278 (M^+, 16), 207 (100), 192 (2), 151 (3), 91 (3), 80 (77).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{19}I$: 278.053; found: 278.0544.

(7*R*)-7-Cyclohexyl-1-iodocyclohept-1-ene (4);[7] Typical Procedure 2

A flame-dried round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with a CuCN·2LiCl solution (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) and cooled to –30 °C. Cyclohexylzinc iodide[10] (1.0 M in THF, 2.0 mL, 2.0 mmol, 2.0 equiv) was added dropwise to the resulting solution. The mixture was stirred at –30 °C for 30 min, then (1*S*)-2-iodocyclohept-2-en-1-yl pentafluorobenzoate (**3**; 432 mg, 1.0 mmol) was added dropwise as a solution in NMP (1.3 mL). The mixture was stirred at –30 to –10 °C for 16 h. A sat. aq NH_4Cl solution (20 mL) was added followed by 25% aq NH_3 solution. The mixture was stirred at 25 °C until the copper salts had dissolved, and then extracted with Et_2O (3 × 20 mL). The combined organic phase was washed with brine (10 mL) and dried (Na_2SO_4). Purification by column chromatography (silica gel, pentane) afforded the product (*R*)-**4** as a colorless oil; yield: 264 mg (87%); 98% ee; $[\alpha]_D^{20}$ –19.4 (*c* = 0.31, CH_2Cl_2).

IR (film): 2922 (s), 2850 (s), 1446 cm^{-1} (s).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.60–6.50 (m, 1 H), 2.58–2.48 (m, 1 H), 2.30–2.16 (m, 1 H), 2.10–2.00 (m, 1 H), 1.96–1.52 (m, 11 H), 1.48–1.10 (m, 5 H), 0.96–0.80 (m, 1 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 141.8, 107.4, 59.6, 39.3, 32.4, 30.7, 30.4, 27.2, 26.9 (2 C), 26.71, 26.68, 25.5.

MS (EI, 70 eV): *m*/*z* (%) = 304 (M^+, 32), 222 (44), 177 (13), 121 (6), 95 (100), 83 (47).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{21}I$: 304.0688; found: 304.0702.

(2*S*)-2-Pentylcyclopentanone (9);[7,9] Typical Procedure 3

A flame-dried round-bottomed flask equipped with a magnetic stirring bar, an argon inlet, and a rubber septum was charged with cyclopentenyl iodide (**8**; 132 mg, 0.50 mmol, 1.0 equiv) and THF (4.0 mL). The mixture was cooled to –78 °C, and then *t*-BuLi (1.60 M in pentane, 0.63 mL, 1.0 mmol, 2.0 equiv) was added dropwise. The mixture was stirred at –78 °C for 30 min, then $B(OMe)_3$ (0.14 mL, 1.25 mmol, 2.50 equiv) was added dropwise. The mixture was stirred and allowed to warm to 25 °C for 24 h, then a suspension of $NaBO_3·4H_2O$ (10 equiv, 769 mg, 5.0 mmol) in H_2O (6 mL) was added at 25 °C. After stirring at 25 °C for 24 h, the mixture was poured into H_2O and extracted with Et_2O (3 × 25 mL). The combined organic phases were washed with brine (10 mL) and dried ($MgSO_4$). The solvents were evaporated and the crude product was purified by column chromatography (silica gel, 10% Et_2O–pentane) to give the chiral ketone (*S*)-**9** as a colorless oil; yield: 69 mg (90%); 81% ee.

IR (film): 2959 (m), 2930 (m), 2858 (m), 1739 (s), 1454 (w), 1154 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.30–1.87 (m, 6 H), 1.85–1.60 (m, 2 H), 1.55–1.38 (m, 1 H), 1.35–1.10 (m, 6 H), 0.90–0.75 (m, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 221.9, 49.5, 38.5, 32.1, 30.0 (2 C), 27.6, 22.9, 21.1, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 154 (M^+, 7), 112 (1), 111 (1), 97 (13), 84 (100), 69 (4), 55 (9).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{18}O$: 154.1358; found: 154.1362.

(2*R*)-3,3-Dimethyl-2-pentylcyclohexanone (5)

$[\alpha]_D^{20}$ –23 (*c* = 0.41, Et_2O).

GC (Chirasil-Dex CB, 25 mm × 0.25 mm); conditions: 60 °C (1 min), ramp of 10 °C/min to 160 °C; t_R (min) = 10.991 (minor), 11.080 (major).

IR (film): 2956 (s), 2872 (m), 1711 (s), 1460 (m), 1369 (w), 1261 (w), 1079 cm^{-1} (w).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.27–2.05 (m, 2 H), 2.00–1.90 (m, 1 H), 1.83–1.63 (m, 2 H), 1.62–1.40 (m, 3 H), 1.25–1.05 (m, 6 H), 1.04–0.83 (m, 4 H), 0.82–0.70 (m, 3 H), 0.66 (s, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 212.2, 59.6, 39.2, 37.9, 36.9, 30.4, 27.6, 27.0, 22.7, 21.5, 21.1, 20.9, 12.4.

MS (EI, 70 eV): *m*/*z* (%) = 196 (M^+, 1), 181 (12), 153 (3), 139 (4), 126 (18), 111 (100), 83 (3), 69 (7).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{24}O$: 196.1827; found: 196.1831.

(2*R*)-2-Cyclohexylcycloheptanone (6)

$[\alpha]_D^{20}$ +87 (*c* = 0.284, CH_2Cl_2).

GC (Chirasil-Dex CB, 25 mm × 0.25 mm); conditions: 60 °C (1 min), ramp of 2 °C/min to 160 °C; t_R (min) = 44.308 (minor), 44.411 (major).

IR (film): 2924 (s), 2852 (s), 1702 (s), 1450 (s), 1342 (m), 1323 (m), 1166 (m), 936 cm^{-1} (m).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.45 (dt, *J* = 2.88, 12.0 Hz, 1 H), 2.32–2.21 (m, 1 H), 2.19–2.07 (m, 1 H), 1.94–1.72 (m, 4 H), 1.71–1.38 (m, 7 H), 1.38–1.00 (m, 6 H), 1.00–0.80 (m, 2 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 217.5, 59.6, 43.1, 40.9, 31.7, 30.5, 30.3, 28.2, 28.1, 26.76 (2 C), 26.73, 26.0.

MS (EI, 70 eV): *m*/*z* (%) = 194 (M^+, 1), 151 (3), 123 (3), 112 (100), 97 (11), 84 (14), 67 (8).

HRMS (EI): *m*/*z* calcd for $C_{13}H_{22}O$: 194.1671; found: 194.1740.

(2*S*)-2-Methyl-2-pentylcyclopentanone (12)[7]

Compound **12** was prepared on a 0.78 mmol scale (217 mg) according to typical procedure 3; yield: 92 mg (70%); 95% ee; $[\alpha]_D^{20}$ +53 (*c* = 0.24, CH_2Cl_2).

GC (Chirasil-Dex CB, 25 mm × 0.25 mm); conditions: 60 °C (1 min), ramp of 5 °C/min to 160 °C; t_R (min) = 14.223 (minor), 14.336 (major).

IR (film): 2958 (s), 2931 (s), 2860 (m), 1738 (s), 1461 (m), 1161 cm^{-1} (w).

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.28–2.02 (m, 2 H), 1.72 (m, 3 H), 1.70–1.58 (m, 1 H), 1.40–1.00 (m, 8 H), 0.92 (s, 3 H), 0.80 (t, *J* = 6.97 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ = 224.3, 48.7, 38.1, 37.0, 36.0, 32.8, 24.3, 22.9, 22.2, 19.1, 14.4.

MS (EI, 70 eV): *m*/*z* (%) = 99 (5), 98 (100), 83 (5), 69 (7), 56 (26).

HRMS (EI): *m*/*z* calcd for $C_{11}H_{20}O$: 168.1514; found: 168.1516.

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