Asymmetric Synthesis of Silylated α-Amino Acid Esters through Dynamic Kinetic Resolution

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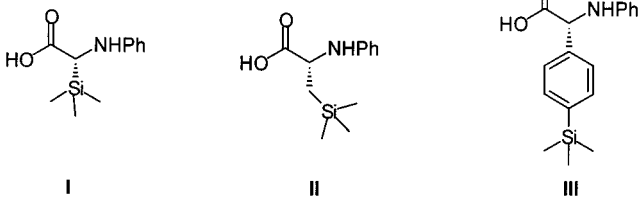
Abstract: Esters of three types of silylated α-amino acids have been prepared from appropriate zirconaaziridines. Slow addition (syringe pump) of the (*R*,*R*) carbonate of *trans*-stilbene gave metallacycles with the maximum possible diastereomeric excess (as determined by the diastereomeric excess produced by the Hoffmann test—the same reaction but with racemic carbonate). Methanolysis gave esters $(RO_2C)CH(R')(NHPh)$ (R′ = Me_3Si, Me_3SiCH_2, and *p*-$Me_3SiC_6H_4$) with the same optical purity at the α carbon.

Silylated amino acids can be used to make unconventional biological substrates that are unknown in nature and not easily metabolized. Such amino acids are thus gaining increasing importance in chemistry and the life sciences.[1] The three major types that have been reported are I−III.

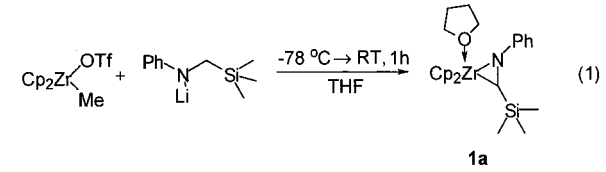


I II III

The first α-silylated amino acid (type I) was reported recently,[2] but there has been no asymmetric synthesis of such a compound. Optically active type II compounds have been synthesized by the Schöllkopf method,[3] using enantiomerically pure dihydropyrazine derivatives made from L-valine.[4] The most recent synthesis of the optically active type III amino acids involved an enzymatic process.[1a]

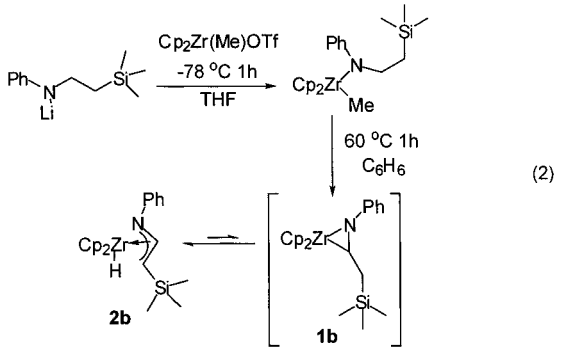
We have shown that α-amino acid esters can be prepared asymmetrically by the dynamic kinetic resolution[5] of appropriate zirconaaziridines, using a C_2-symmetric cyclic carbonate as an optical active CO_2 equivalent.[6,7] Slow addition of the optically active carbonate allows the zirconaaziridine enantiomers to interconvert rapidly as insertion proceeds, significantly improving the diastereoselectivity of insertion and leading to the formation of α-amino acid esters in good ee. We have now applied this method to the synthesis of esters of all the three types of silylated α-amino acids.

One required zirconaaziridine **1a** is available by a reported method (eq 1).[8] Attempts to prepare its homologue **1b** appear to give instead the azaallyl hydride **2b** (eq 2), but we have found that such azaallyl hydrides react like zirconaaziridines with electrophilic reagents;[6c,9] presumably a small amount of **1b** is present in equilibrium with **2b**. The *p*-silylphenyl zirconaaziridine **1c** is easily prepared in a one-pot process from the appropriate imine and (by way of the Negishi reagent[10]) Cp_2ZrCl_2 (eq 3).[11]



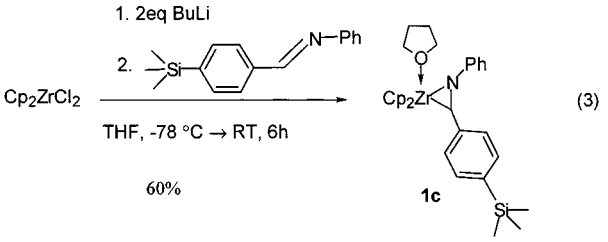
(1)

1a



(2)

2b **1b**



(3)

1c

If a racemic zirconaaziridine is treated with an optically active carbonate, the maximum possible diastereoselectivity is given by the selectivity factor *s*, the ratio of

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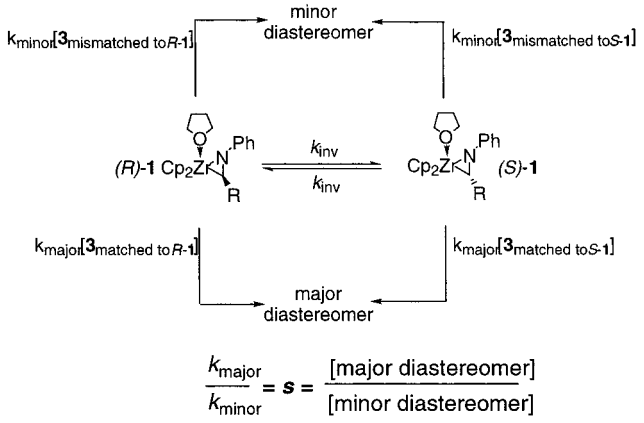
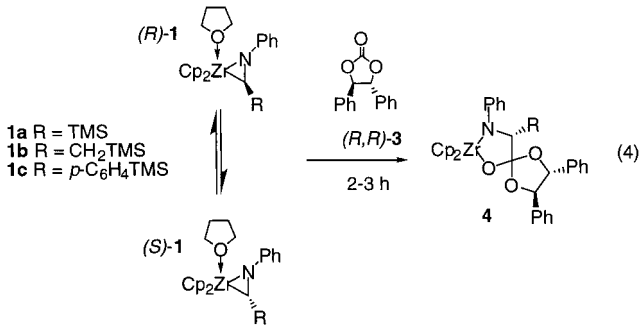
Scheme 1



the two rate constants k_{major}/k_{minor} in Scheme 1. This ratio is easily determined by treating the racemic zirconaaziridine **1** with the racemic carbonate **3**, the "Hoffmann test".[12] (Note that $[\mathbf{3}]_{total} = [\mathbf{3}_{matched\ to\ R}] + [\mathbf{3}_{matched\ to\ S}] = [\mathbf{3}_{mismatched\ to\ R}] + [\mathbf{3}_{mismatched\ to\ S}]$.) For the trimethylsilyl-substituted zirconaaziridine **1a**, *s* proved to be 49 (corresposponding to a de of 96%); for the trimethylsilylmethyl zirconaaziridine **1b**, *s* proved to be 6.7 (a de of 74%); for the *p*-trimethylsilylphenyl zirconaaziridine **1c**, *s* proved to be 14.4 (a de of 87%).

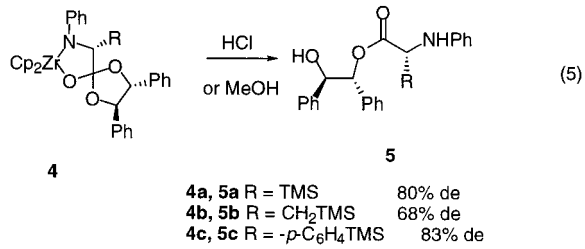
When a solution of the *R*,*R* carbonate **3** was added to the solution of **1a**, **1b**, or **1c** with a syringe pump over a time period of 2−3 h, the insertion products **4a**−**c** were formed in substantial diastereomeric excess: 80% for **4a**, 68% for **4b**, 83% for **4c** (eq 4). In all three cases,



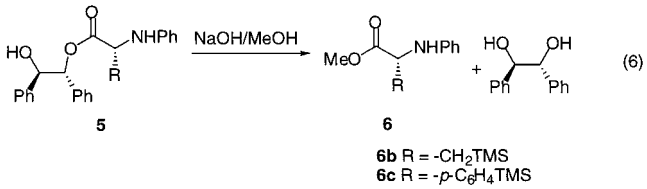
particularly **2b** → **4b** and **2c** → **4c**, the observed diastereoselectivity was close to the maximum indicated by the Hoffmann test. As the (*R*,*R*) carbonate **3** has produced insertion product with an (*R*,*R*,*R*) configuration when R = phenyl or benzyl,[6c,13] it seems certain that **4c** has the configuration shown in eq 4 (which for **4c** is (*R*,*R*,*R*)), and likely that **4a** and **4b** do also (this configuration is (*R*,*R*,*R*) for **4a** and (*S*,*R*,*R*) for **4b**).

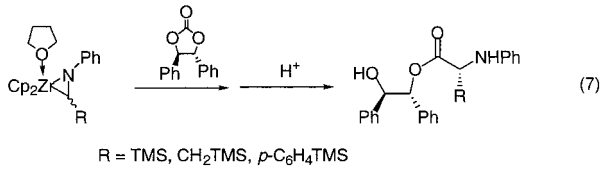
Removal of the zirconium from **4a**−**c** with MeOH gave the 2-hydroxyethyl esters **5a**−**c** in 64−80% isolated yield (eq 5). The diastereomers of **5b** and **5c** were separated by HPLC; separation was not attempted with **5a** because of our inability (see below) to remove the optically active diol.

Compound **5a** proved too base-sensitive (^{1}H NMR showed loss of the silyl substituent) to be converted into the methyl ester. However, compounds **5b** and **5c** readily



underwent base-catalyzed transesterification, giving the methyl esters **6b** and **6c** in quantitative yield (eq 6).





Thus the zirconaaziridine route is, as shown in eq 7 (the combination of eqs 4 and 5), effective for the asymmetric preparation of silicon-containing amino acid esters.

Experimental Section

Materials. Unless otherwise noted, all manipulations of air-sensitive compounds were performed under a N_2 atmosphere, using standard Schlenk techniques or in a glovebox (<1 ppm O_2).[14] Ether, THF, and benzene were dried and deoxygenated by distillation under nitrogen from sodium−benzophenone ketyl. Amines were degassed by three freeze/pump/thaw cycles or by purging with nitrogen, then distilled from sodium under vacuum. (*R*,*R*)-(+)-1,2-Diphenyl-1,2-ethanediol was prepared on a 100 g scale by the method of Sharpless;[15] racemic *trans*-1,2-diphenyl-1,2-ethanediol was prepared by epoxidation of *trans*-stilbene followed by ring opening.[16] Both were converted to the cyclic carbonate using phosgene/pyridine.[17] Cp_2ZrCl_2 was generously supplied by Boulder Scientific, and converted to $Cp_2Zr(Me)OTf$ by an established procedure.[18]

Chiral stationary phase HPLC analyses were obtained at Merck[19] on a Bakerbond OD chiralcel column,with detection at 215 or 254 nm.

$Cp_2Zr(PhNCHSiM_3)THF$ (1a). To a solution of 179 mg (1.0 mmol) of *N*-phenylaminomethyltrimethylsilane[20] in 5 mL of Et_2O at 0 °C was added 0.63 mL of 1.6 M BuLi/hexane solution. After being stirred 10 min, the Et_2O was removed and the residue was dissolved in THF (5 mL). A solution of 385 mg of $Cp_2ZrMeOTf$ (1.0 mmol) in THF (5 mL) was added at −35 °C. The resulting solution was warmed to room temperature and stirred for 10 min before the solvent was removed. Benzene (10 mL) was added, and the solution was filtered. The filtrate was concen-

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(19) We are grateful to Dr. D. R. Sidler, Merck, for these analyses.

trated to about 3 mL, and then hexane (30 mL) was added to afford a precipitate of the orange product. After collection and drying under vacuum, the yield was 294 mg (63%). ^{1}H NMR (300 MHz, C_6D_6) δ 0.32 (s, 9 H), 1.17 (m, 4 H), 1.38 (s, 1 H), 3.27 (m, 4 H), 5.54 (br s, 5 H), 5.92 (br s, 5 H), 6.71 (m, 2 H), 6.81 (m, 1 H), 7.40 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ 3.1, 26.1, 45.0, 72.1, 109.4, 111.8, 114.1, 117.7, 129.6, 161.1.

$Cp_2Zr(N(Ph)CH_2CH_2SiMe_3)CH_3$. To a solution of 193 mg (1.0 mmol) 1-anilino-2-(trimethylsilyl)ethane[21] in 5 mL of Et_2O at 0 °C was added 0.63 mL of 1.6 M BuLi/hexane solution. After 10 min stirring the Et_2O was removed and the residue dissolved in THF (5 mL). A solution of 385 mg of $Cp_2ZrMeOTf$ (1.0 mmol) in THF (5 mL) was added at −78 °C, and the mixture was warmed to room temperature and stirred for 30 min before the solvent was removed. The product was taken up in benzene (10 mL), and the solution was filtered and used in the next reaction. ^{1}H NMR (300 MHz, C_6D_6) δ −0.04 (s, 9 H), 0.33 (s, 3 H), 0.71 (m, 2 H), 3.27 (m, 2 H), 5.69 (br. s, 10 H), 6.68 (m, 2 H), 6.91 (m, 1H), 7.22 (m, 2 H); ^{13}C NMR (75 MHz, C_6D_6) δ −1.35, 17.8, 23.6, 47.8, 110.4, 121.2, 124.5, 128.8, 158.1.

$Cp_2Zr(\eta^3$-N(SiMe$_3$)CHCHPh)H (2b). A NMR tube containing about 20 mg of the preceding amido methyl zirconocene complex in C_6D_6 was heated at 60 °C for 3.5 h. By ^{1}H NMR the resulting orange solution contained **2b** as the major product in about 70% yield. ^{1}H NMR (C_6D_6) δ 0.32 (s, 9 H), 2.64 (d, J = 14.0 Hz, 1H), 2.97 (s, 1 H), 5.45 (br. s, 10H), 5.58 (d, J = 14.0 Hz, 1H), 6.92−7.07 (m, 3 H), 7.27−7.37 (m, 2 H); ^{13}C NMR (C_6D_6) δ 1.3, 71.2, 103.0, 120.1, 129.6, 130.0, 131.2, 153.7.

$Cp_2Zr(THF)N(Ph)CH(p$-$C_6H_4SiMe_3$) (1c). To a solution of 438 mg (1.5 mmol) of Cp_2ZrCl_2 in THF (10 mL) at −78 °C was added 1.88 mL of 1.6 M BuLi/hexane solution, and the reaction was stirred at this temperature for 0.5 h. 4-Trimethylsilylbenzaldehyde was converted to its phenyl imine,[22] and 380 mg (1.5 mmol) of the latter was dissolved in THF (5 mL) and added to the "zirconocene" solution. The mixture was slowly (6 h) warmed to room temperature and stirred for another h. The solvent was evaporated, and the residue was taken up in benzene (10 mL) and the solution filtered; the filtrate was concentrated to 2−3 mL, and hexane (50 mL) was added. After standing overnight 490 mg (60%) of the product precipitated. (Further purification is possible by recrystallization from benzene/hexane.) ^{1}H NMR (300 MHz, C_6D_6) δ 0.36 (s, 9 H), 1.17 (br. s, 4 H), 3.27 (br. s, 4 H), 3.80 (br. s, 1 H), 5.45 (br. s, 5 H), 5.56 (br. s, 5 H), 5.71−5.90 (m, 4H), 7.20−7.31 (m, 3 H), 7.64−7.75 (m, 2 H).

Determination of Selectivity Factor *s* in Scheme 1. In the case of **1a** or **1c**, 0.1 mmol of the racemic compound was dissolved in C_6D_6 and 0.1 mmol of the racemic carbonate **3** added at room temperature. The racemic azaallyl hydride **2b** was generated by heating a C_6D_6 solution of its methyl amide precursor (0.1 mmol) for 1 h at 60 °C and then adding racemic **3** (0.1 mmol). The de of the insertion products was determined by integration of the ^{1}H NMR Cp or TMS resonances (major enantiomers/minor enantiomers): **4a** (96%), **4b** (74%), **4c** (87%). Similar results were obtained when the reaction was repeated.

(*R,R,R*)-PhHNCH(SiMe$_3$)CO$_2$CH(Ph)CH(Ph)OH (5a). Compound **1a** (94 mg, 0.20 mmol) was dissolved in 10 mL of C_6H_6; *(R,R)*-**3** (48 mg, 0.20 mmol) was dissolved in 3 mL of C_6H_6. The solution of **3** was drawn into a Gastight syringe equipped with a 22-gauge needle, which was placed directly in the vigorously stirred solution of **1a**; the solution of **3** was added at a rate of 1.0 mL/h with the aid of a syringe pump. During addition the color of the solution changed from orange to deep red. A small aliquot was withdrawn and its solvent removed, and C_6D_6 was added to determine the de (80%) by ^{1}H NMR. The addition of 5 mL of MeOH to the remaining solution made it colorless. After it was stirred overnight, the solvent was removed and the residue taken up in 4 mL of hexane/EtOAc (1:1); that solution was filtered with Celite and the filtrate evaporated to dryness. Recrystallization (benzene/hexanes) gave 54 mg (64%) of a white solid with a de of 85% by ^{1}H NMR. (Silica gel or Al_2O_3 chromatography resulted in decomposition.) For the major diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.12 (s, 9 H), 2.01 (d, J = 2.7 Hz, 1 H), 3.87 (d, J = 9.7 Hz, 1 H), 4.04 (d, J = 9.7 Hz, 1 H), 4.70 (dd, J = 8.6, 2.7 Hz, 1 H), 5.71 (d, J = 8.6 Hz, 1 H), 6.67−6.74 (m, 2 H), 6.76−6.83 (m, 1 H), 6.93−7.49 (m, 12 H); ^{13}C (75 MHz, $CDCl_3$) δ −2.7, 51.2, 77.3, 81.5, 113.8, 119.4, 126.5, 127.6, 128.1, 128.4, 128.6, 129.6, 130.1, 137.8, 139.7, 149.4, 173.1. In C_6D_6 the δ 5.71 methine doublet of the major diastereomer shifted to δ 6.01, while that of the minor diastereomer occurred at δ 6.07; the de was calculated from their integrated intensities. HRMS calcd m/z for $[C_{25}H_{29}NO_3Si + H]^+$ 420.1995, found for $[M + H]^+$ 420.1996.

(*S,R,R*)-PhHNCH(CH$_2$SiMe$_3$)CO$_2$CH(Ph)CH(Ph)OH (5b). Half of the benzene solution of $Cp_2Zr(N(Ph)CH_2CH_2SiMe_3)CH_3$ prepared as above (containing 0.50 mmol) was heated at 60 °C for 4 h (converting it to an equilibrium mixture of **1b** and **2b**) and then cooled to room temperature. Compound *(R,R)*-**3** (120 mg, 0.50 mmol) was dissolved in 4 mL of C_6H_6, and the solution was drawn into a Gastight syringe equipped with a 22-gauge needle. The needle was placed directly in the solution of **1b** and **2b** (which was vigorously stirred), and the solution of **3** was added at a rate of 2.0 mL/h via syringe pump. Again the color of the solution changed from orange to deep red. Aqueous HCl (5 mL, 1 M) was added and the mixture stirred for 15 min; the product was extracted with CH_2Cl_2 and purified by a silica gel flash column (CH_2Cl_2 as eluant) to give 155 mg (72%) of a white solid, 68% de by ^{1}H NMR. (Recrystallization from benzene/hexane improved the de to 77%.) For the major diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.04 (s, 9 H), 0.81−1.15 (m, 2 H), 2.04 (d, J = 3.4 Hz, 1 H), 3.87 (br s, 1 H), 4.08−4.23 (m, 1 H), 4.70−4.82 (dd, J = 8.0, 3.4 Hz, 1 H), 5.71 (d, J = 8.0 Hz, 1 H), 6.61−6.70 (m, 2 H), 6.73−6.83 (m, 1 H), 6.77−7.11 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −1.1, 21.3, 54.6, 77.2, 80.8, 113.3, 119.0, 127.2, 127.9, 128.0, 128.1, 128.2, 129.7, 136.4, 138.4, 146.9, 174.3. HRMS calcd m/z for $[C_{26}H_{31}NO_3Si + H]^+$ 434.2151, found for $[M + H]^+$ 434.2136.

(*R,R,R*)-N(Ph)CH(*p*-C$_6$H$_4$SiMe$_3$)CO$_2$CH(Ph)CH(Ph)OH (5c) was prepared in the same way as **5a**, but on an 0.15 mmol scale with **1a** replaced by **1c**. After treatment with aqueous HCl (2 mL, 1 M), the product was extracted with CH_2Cl_2 and purified by a silica gel flash column (CH_2Cl_2 as eluant). The two diastereomers were separated, giving 55 mg (74%) of the major diastereomer, and 5 mg (6%) of the minor (a de of 83%). For the major diastereomer, ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.27 (s, 9 H), 1.97 (d, J = 3.4 Hz, 1 H), 4.78−4.84 (dd, J = 7.2, 3.4 Hz, 1 H), 4.91 (d, J = 5.6 Hz, 1 H), 5.14 (d, J = 5.6 Hz, 1 H), 5.79 (d, J = 7.2 Hz, 1 H), 6.54 (m, 2 H), 6.70 (m, 1 H), 6.91 (m, 2 H), 7.04−7.16 (m, 7 H), 7.20−7.29 (m, 3 H), 7.48−7.58 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7, 61.6, 77.2, 81.9, 113.7, 118.7, 126.9, 127.3, 127.7, 128.4, 128.5, 128.7, 128.9, 129.7, 134.6, 136.5, 138.5, 138.6, 141.5, 146.3, 171.1. HRMS, calcd m/z for $[C_{31}H_{33}O_3NSi + H]^+$ 496.2308, found for $[M + H]^+$ 496.2327.

Methyl Esters 6b,c. The 2-hydroxyethyl ester **5b** was used as a 77% de sample (prepared as above from benzene/hexane); **5c** was used as the pure major diastereomer. Either **5b** or **5c** was dissolved in enough methanol to make a 0.04 M solution; 10 mol % 0.2 M NaOH/MeOH was added and the solution stirred at room temperature for 15−20 min. For **6b** it was evaporated to dryness and the residue separated by flash column (CH_2Cl_2 as eluant) to give the product in quantitative yield. **6b**: ^{1}H (300 MHz, $CDCl_3$) δ 0.07 (s, 9 H), 1.01−1.21 (m, 2 H), 3.65 (s, 3 H), 3.88−3.98 (m, 1 H), 4.03−4.14 (m, 1 H), 6.55−6.64 (m, 2 H), 6.70−6.79 (m, 1 H), 7.12−7.21 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7, 22.2, 52.4, 54.2, 113.9, 118.8, 129.7, 147.1, 176.2. HRMS, calcd m/z for $C_{13}H_{21}NO_2Si$ 251.1342, found 251.1341. HPLC (*R,R*) Whelko; 10% IPA/hexane; 240 nm, 2.0 mL/min, t_R(maj) = 9.2, t_R(min) = 4.5; 77% ee.

For **6c** the solution was made acidic with 1 M HCl and then reduced to dryness; the product was taken up with CH_2Cl_2 and the solution washed with $NaHCO_3/H_2O$. Solvent removal gave a 1:1 mixture of **6c** and hydrobenzoin in quantitative yield. The α-amino ester was separated from the diol by either (a) extraction into hexane, or (b) a flash column with CH_2Cl_2 as eluant. **6c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.26 (s, 9 H), 3.72 (s, 3 H), 4.89−4.96 (m,1 H), 5.05−5.11 (m, 1 H), 6.53−6.60 (m, 2 H), 6.66−6.76 (m, 1 H), 7.07−7.17 (m, 2 H), 7.43−7.54 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.7, 53.2, 61.1, 113.7, 118.5, 126.9,

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129.6, 134.3, 138.4, 141.1, 146.4, 172.7. HRMS, calcd *m*/*z* for $[C_{18}H_{23}NO_2Si + H]^+$ 314.1576, found 314.1596. HPLC (*R*,*R*) Whelko; 10% IPA/hexane; 240 nm, 2.0 mL/min, t_R(maj) = 5.8, t_R(min) = 4.8; 96% ee.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for $Cp_2Zr(Me)N(Ph)CH_2CH_2SiMe_3$ and compounds **2b**, **4a**, **5a**,**b**,**c**, and **6b**,**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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