Synthesis of 2-Cyclopentenones by Gold(I)-Catalyzed Rautenstrauch Rearrangement

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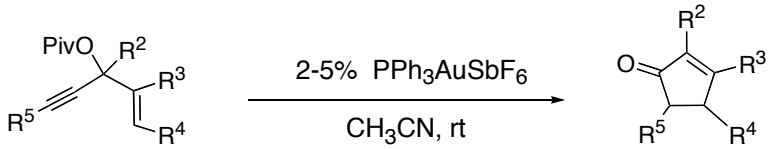
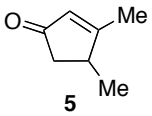
Supporting Information

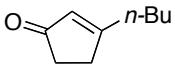
General Information. Unless otherwise noted all commercial materials were purchased from Aldrich Chemical Company and used without further purification. Reactions were carried out in two dram vials fitted with threaded caps. ACS grade solvents were obtained from EM science and used without purification. TLC analysis of reaction mixtures was preformed on Merck silica gel 60 F_{254} TLC plates. Chromatography was carried out on Merck 60 silica gel (32-63 μm). ^{1}H and ^{13}C NMR spectra were recorded with Bruker AV-300, AVB-400 and AVQ-400 spectrometers and referenced to $CDCl_3$ unless otherwise noted. Mass spectral were obtained from the Micro-Mass/Analytical Facility operated by the College of Chemistry, University of California, Berkeley. High resolution mass spectra (HRMS) were obtained on VG ProSpec Mass Spectrometer using electron impact (EI) at 70 eV unless otherwise noted. Analytical chiral HPLC was performed with a Shimadzu VP Series Chiral HPLC with detection at 210, 254, and 230 nm using Chiralcel AD and OD columns. Analytical GC was carried out with a Hewlett Packard HP 6850 GC equipped with an Agilent DB-WAX (30.0 m x 0.25 mm) column for achiral separation and a Chiraldex G-TA (30.0 m x 0.25 mm) column for chiral separation. The products were purified and confirmed by NMR spectra before enantioselectivities were measured. The peaks of two enantiomers were located based on the retention times derived from racemic mixture.



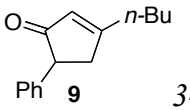
General procedure for intramolecular cyclization reactions catalyzed by PPh_3Au^+ SbF_6^-: A 2-dram vial containing a magnetic stir bar was charged with a solution of 1-ethynyl-2-propenyl pivalates (100 mg, 1 eq) in acetonitrile (0.1 M in substrate). To the resulting solutions was added freshly generated 0.05M solution of PPh_3AuSbF_6 (2 mol%) prepared by mixing stoichiometric amounts of PPh_3AuCl and $AgSbF_6$ in dichloromethane followed by filtration through a celite plug to remove precipitated AgCl. The reaction mixture was then stirred at room temperature and monitored periodically by TLC. Upon completion, the reaction mixture was loaded directly on to a silica gel column and chromatographed with the appropriate mixture of hexanes and EtOAc to give the cyclopentenone products described below.



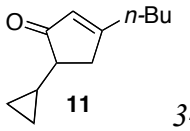
5 *3,4-Dimethyl-cyclopent-2-enone* (**5**)**:** Reaction was complete after 8h (2% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (85%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.89 (s, 1H), 2.84-2.80 (m, 1H), 2.65 (dd, 1H, J = 18.5, 6.6 Hz), 2.09 (s, 3H), 2.01 (dd, 1H, J = 18.5, 2.0 Hz), 1.20 (d, 3H, J = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 209.0, 182.7, 130.3, 44.3, 38.9, 18.8, 17.1 ppm. The ^{1}H- and ^{13}C-NMR data was consistent with literature[1] data**.**



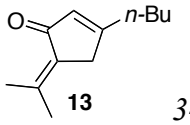
7 *3-Butyl-cyclopent-2-enone* (**7**): Reaction was complete in 8h (2% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (80%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.92 (t, 1H, J = 1.4 Hz), 2.57-2.54 (m, 2H), 2.41-2.36 (m, 4H), 1.61-1.49 (m, 2H), 1.41-1.29 (m, 2H), 0.91 (t, 3H, J = 7.3 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 210.6, 183.7, 129.7, 35.6, 33.5, 31.8, 29.4, 27.4, 22.7, 14.1 ppm. The ^{1}H- and ^{13}C-NMR data was consistent with literature[2] data**.**



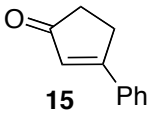
9 *3-Butyl-5-phenyl-cyclopent-2-enone* (**9**): Reaction was complete after 20h (5% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as colorless oil (73%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.38-7.17 (m, 5H), 6.07 (s, lH), 3.65 (dd, *J* = 2.8, 7.2 Hz, lH), 3.15 (dd, *J* = 7.5, 18.8 Hz, lH), 2.73 (br d, *J* = 18.8 Hz, lH), 2.53 (t, *J* = 7.5 Hz, 2H), 1.68 (quintet, *J* = 7.5 Hz, 2H), 1.47 (sextet, *J* = 7.3 Hz, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 209.1, 182.4, 139.9, 128.8, 128.5, 127.6, 126.9, 52.3, 41.4, 33.3, 29.2, 22.5, 13.8 ppm. The ^{1}H- and ^{13}C-NMR data was consistent with literature[3] data**.**



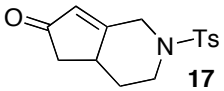
11 *3-Butyl-5-cyclopropyl-cyclopent-2-enone* (**11**): Reaction was complete after 20h (5% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (85%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.92 (s, lH), 2.72 (dd, *J* = 6.9, 18.5 Hz, lH), 2.41 (t, *J* = 7.5 Hz, 2H), 2.28 (d, J = 8.7 Hz, 1H), 2.08 (dt, J = 2.3, 7.6 Hz, 1H), 1.58 (quintet, *J* = 7.5 Hz, 2H), 1.39 (sextet, *J* = 7.3 Hz, 2H), 0,92 (t, *J* = 7.3 Hz, 3H), 0.90 (m, 1H), 0.58 (m, 1H), 0.43 (m, 2H), 0.19 (m, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 211.3, 181.6, 128.7, 48.9, 37.5, 33.2, 29.1, 27.0, 13.8, 12.7, 3.1, 1.3 ppm. HRMS (EI) calc'd for $[C_{12}H_{18}O]^{+}$: *m/z* 178.1358, found 178.1358.



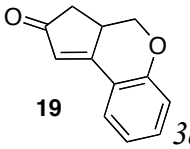
13 *3-Butyl-5-isopropylidene-cyclopent-2-enone* (**13**): Reaction was complete after 20h (5% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (81%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.75 (s 1H), 2.96 (s, 2H), 2.15 (t, 2H, J = 7.2 Hz), 1.92 (s, 3H), 1.90 (s, 3H), 1.49-1.44 (m, 2H), 1.38-1.33 (m, 2H), 0.94 (t, 3H, J = 7.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 206.8, 152.4, 141.2, 135.0, 130.0, 38.8, 35.9, 29.9, 22.6, 17.4, 14.0, 10.4 ppm. HRMS (EI) calc.'d for $[C_{12}H_{18}O]^+$: *m/z* 178.1358, found 178.1357.



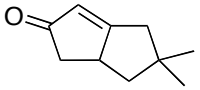
15 *3-Phenyl-cyclopent-2-enone* (**15**): Reaction was complete after 8h (2% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as colorless oil (68%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.64-7.62 (m, 2H), 7.48-7.30 (m, 3H), 6.58 (t, 1H, J = 1.7 Hz), 3.06 (m, 2H), 2.60 (m, 2H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 209.7, 174.3, 134.3, 131.5, 129.2, 127.8, 127.1, 35.6, 28.9 ppm. ^{1}H- and ^{13}C-NMR data was consistent with literature[4] data**.**



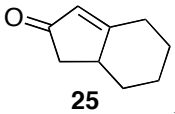
17 *N-(Tosyl)-1,2,3,4,4a,5-hexahydro-[2]pyrindin-6-one* (**17**)*:* Reaction finished in 14 hours (5% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow solid (45%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, 2H, J = 8.3Hz), 7.33 (d, 2H, J = 8.3Hz), 5.99 (s, 1H), 4.72, (d, 1H, J = 13.3Hz), 3.93 (m, 1H), 3.18 (d, 1H, J = 13.3Hz), 2.62-2.38 (m, 3H), 2.43 (s, 3H), 2.12 (m, 1H), 1.99 (dd, 1H, J = 20.3, 4.3Hz), 1.45 (ddd, 1H, J = 20.3, 12.5, 4.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 207.5, 172.5, 144.4, 133.2, 130.2, 129.4, 128.0, 127.3, 47.7, 46.0, 41.6, 39.5, 32.3, 21.8. . HRMS (EI) Calcd. for $[C_{15}H_{17}NO_3S]^+$ (M^+) is 291.092915, Found 291.092849.



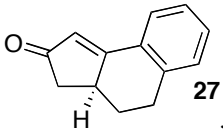
19 *3a,4-Dihydro-3H-cyclopenta[c]chromen-2-one* (**19**): Reaction was complete after 10h (5% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (48%): ^{1}H NMR (C_6D_6, 400 MHz) δ 7.16 (dd, 1 H, J = 1.5, 7.5 Hz), 7.02 (m, 1 H), 6.9 (dd, 1 H, J = 0.5, 8.0 Hz), 6.68 (m, 1 H), 6.18 (dd, 1H, J = 1.0, 2.0 Hz), 3.81 (dd, 1 H, J = 6.0, 10.5 Hz), 3.11 (dd, 1 H, J = 10.5, 13.5 Hz), 2.54 (m, 1 H), 2.13 (dd, 1 H, J = 7.0, 18 Hz), 1.45 (dd, 1H, J = 4.5, 18 Hz). ^{13}C NMR (C_6D_6, 100 MHz) δ 203.6, 201.2, 166.7, 156.2, 132.6, 127.1, 121.9, 121.0, 117.7, 69.7, 37.3, 35.8. Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.14; H, 5.59.



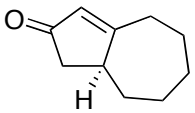
23 *5,5-Dimethyl-4,5,6,6a-tetrahydro-1H-pentalen-2-one* (**23**): Reaction was complete after 8 hours (2% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (78%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.81 (d, 1H, J = 2.2 Hz), 3.16 (m, 1H), 2.58 (dd, 1H, J = 17.8, 6.3 Hz), 2.41 (d, 2H, J = 6.0 Hz), 2.04 (dd, 1H, J = 17.8, 3.0 Hz), 1.91 (dd, 1H, J = 12.4, 8.0 Hz), 1.22 (s, 3H), 1.11 (s, 3H), 1.09 (d, 1H, J = 12 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 211.2, 191.3, 125.1, 46.4, 45.5, 42.9, 42.7, 41.2, 31.1, 30.9 ppm. ^{1}H- and ^{13}C-NMR data was consistent with literature[6] data**.**



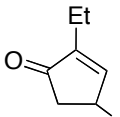
25 *1,4,5,6,7,7a-Hexahydro-inden-2-one* (**25**): Reaction was complete after 8h (2% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (82%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.83 (s, 1H), 2.82 (d, 1H, J = 13.7), 2.70-2.40 (m, 2H), 2.40-1.00 (m, 8H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 209.2, 184.9, 126.7, 42.4, 41.8, 35.0, 31.0, 27.0, 25.2 ppm. ^{1}H- and ^{13}C-NMR data was consistent with literature[5] data**.**



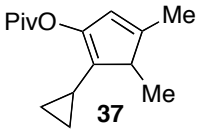
27 *3,3a,4,5-Tetrahydro-cyclopenta[a]naphthalen-2-one* (**27**): Reaction was complete after 10h (5% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (78%): ^{1}H NMR (C_6D_6, 400 MHz) δ 7.35 (m, 1 H), 7.08 (m, 1H), 6.95, (m, 1H), 6.88 (d, 1H, J = 7.6 Hz), 6.38 (d, 1H, J = 1.6 Hz), 2.3-2.6 (m, 4 H), 1.90 (dd, 1 H, J = 4.5, 18.0 Hz), 1.58 (m, 1H), 1.10 (m, 1H). ^{13}C NMR (C_6D_6, 100 MHz) δ 205.4, 173.3, 153.8, 138.9, 130.3, 129.3, 126.7, 126.3, 123.8, 42.4, 39.3, 29.6, 29.3. Anal. Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.39; H, 6.60



29 *4,5,6,7,8,8a-Hexahydro-1H-azulen-2-one* (**29**): Reaction was complete after 8h (2.5% catalyst loading). Product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (73%): ^{1}H NMR (C_6D_6, 400 MHz) δ ^{1}H NMR (C_6D_6, 400 MHz) δ 5.79 (s, 1H), 2.47 (dd, 1 H, J = 6.8, 18 Hz), 2.3 (m, 1 H), 2.18 (m, 2 H), 1.82 (dd, 1 H, J = 18, 2.8 Hz), 1.4-1.6 (m, 3 H), 1.25 (m, 2 H), 0.9-1.1 (3 H); ^{13}C NMR (C_6D_6, 100 MHz) δ 206.0, 184.6, 129.9, 44.2, 43.7, 34.0, 32.0, 30.0, 28.3, 26.1. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 79.70; H, 9.76.

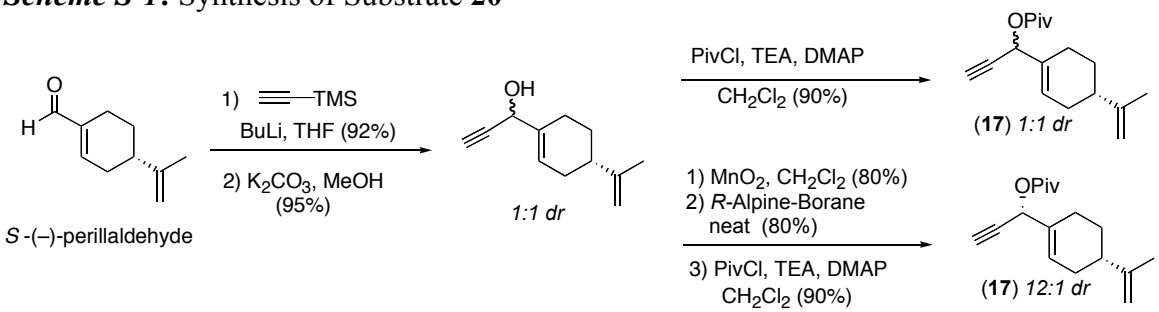


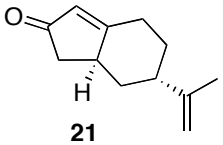
35 *2-Ethyl-4-methyl-cyclopent-2-enone* (**35**): Reaction carried out with **34** as a mixture of alkene isomers (Z:E = 1:2). Reaction was complete after 20 hours (5% catalyst loading). The reaction was purified by chromatography on silica gel (10:1 hexanes/EtOAc) to afford **35** as light yellow oil (52%, 78% based on starting *E*-isomer of **34**) and recovered *Z*-**34** (28%, 85% based on starting *Z*-isomer of **34**). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.99 (s, lH), 2.87 (m, lH), 2.62 (dd, *J* = 6.3, 18.7 Hz, 1H), 2.16 (qt, J = 7.3, 1.5 Hz, 2H), 1.98 (dd, J = 18.7, 1.8 Hz, 1H), 1.15 (d, *J* = 7.1 Hz, 3H), 1.07 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 209.8, 161.9, 146.9, 43.5, 33.3, 20.4, 17.9, 12.0 ppm; HRMS (EI) calc'd for $[C_8H_{12}O]^+$: *m/z* 124.0888, found 124.0882.



37 *2,2-Dimethyl-propionic acid 2-cyclopropyl-3,4-dimethyl-cyclopenta-1,4-dienyl ester* (**37**)**:** The cyclization product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (66%): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.86 (s, lH), 2.73 (dd, J = 7.6 Hz, 1H), 1.93 (d, J = 1.4 Hz, 3H), 1.33 (s, 9H), 1.19 (d, J = 7.7 Hz, 3H), 0.52-0.19 (m, 4H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 176.4, 146.4, 145.1, 1131.6, 123.1 (CH), 48.6 (CH), 38.9, 27.2 (CH_3), 14.4 (CH_3), 14.2 (CH_3), 7.13 (CH), 4.8 (CH_2), 4.7 (CH_2) ppm; HRMS (EI) calc'd $[C_{15}H_{22}O_2]^+$ (M^+): *m/z* 234.1620, found 234.1618.

***Scheme S-1*:** Synthesis of Substrate **20**





21 *6-Isopropenyl-1,4,5,6,7,7a-hexahydro-inden-2-one* (**21**)**:** The product was purified by chromatography on silica gel (10:1 hexanes/EtOAc) as light yellow oil (82%). The diastereomeric ratio of **21** was determined by ^{1}H-NMR and GC (retention times 14.50 min. (major), 14.23 min. (minor)): ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 5.87 (s, lH), 5.06 (s, 1H), 4.98 (s, 1H), 2.89 (m, lH), 2.70-2.41 (m, 5H), 2.39-2.30 (m, 1H), 2.00 (d, *J* = 18.0 Hz, 1H), 1.97 (s, 3H), 1.41 (dt, J = 2.4, 6.8 Hz, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 209.1, 185.5, 145.0, 126.5, 111.4, 42.4, 38.5, 37.1, 36.5, 28.6, 26.9, 22.5 ppm; HRMS (EI) calc'd for $[C_{12}H_{16}O]^+$: *m/z* 176.1201, found 176.1197.

Table S1. Effect of Anion and Temperature on the Chirality Transfer

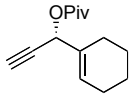
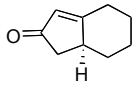
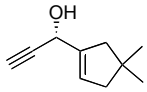
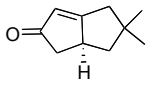
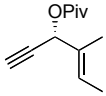
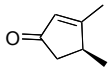
Entry	Substrate	Conditions	Product	Product ee (%)	Percentage Chirality Transfer (%)
1	 93% ee	2% PPh_3AuOTf, r. t. 8 h.		68	73
2		2% PPh_3AuSbF_6, r. t. 8h		77	83
3		5% PPh_3AuSbF_6, -20 °C 12 h.		91	98
4	 79% ee	2% PPh_3AuSbF_6, r. t. 8h		65	82
5		5% PPh_3AuSbF_6, -20 °C 12 h.		77	97
6	 88% ee	2% PPh_3AuSbF_6, r. t. 8h		71	81
7		5% PPh_3AuSbF_6, -20 °C 12 h.		82	93

Table S2. Methods for the Determination of Enantiomeric Excess

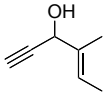
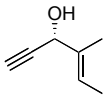
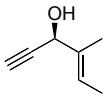
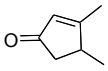
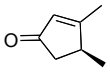
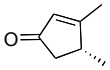
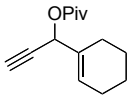
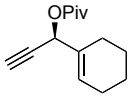
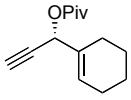
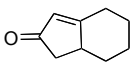
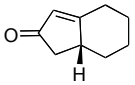
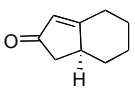
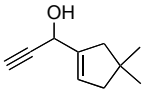
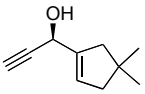
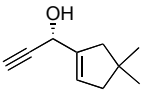
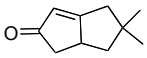
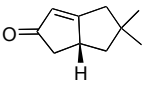
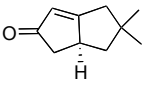
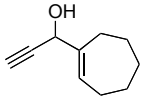
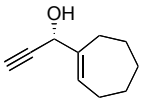
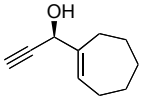
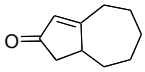
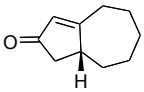
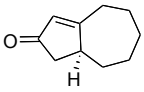
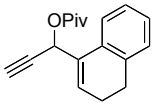
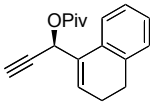
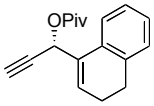
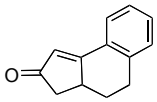
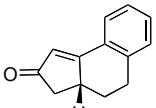
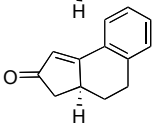
Entry	Substrate	Method	Conditions	Retention Time (min)	
1		GC Chiraldex G-TA	40 °C, 0 min 1 °C/min to 90 °C, 10 min		41.91 major (R)
					43.14 minor (S)
2		GC Chiraldex G-TA	90 °C, 0 min 10 °C/min to 140 °C, 20 min		5.22 major (S)
					5.69 minor (R)
3		HPLC Chiralcel OD	0.5% iPrOH/Hexane 0.5 mL/min		8.42 minor (S)
					8.77 major (R)
4		HPLC Chiralcel OD	1% iPrOH/Hexane 0.5 mL/min		44.30 minor (R)
					46.39 major (S)

Table S2. Methods for the Determination of Enantiomeric Excess (…cont.)

Entry	Substrate	Method	Conditions	Retention Time (min)	
5		GC Chiraldex G-TA	TFAA, 40°C, 0 min 2.5 °C/min to 60 °C, 50 min	 	35.42 minor (S) 38.17 major (R)
6		HPLC Chiralcel AD	0.5% iPrOH/Hexane 0.5 mL/min	 	41.91minor (R) 43.14 major (S)
7		GC Chiraldex G-TA	TFAA, 40 °C, 0 min 2.5 °C/min to 60 °C, 50 min	 	16.13 major (R) 15.89 minor (S)
8		GC Chiraldex G-TA	90 °C, 0 min 10 °C/min to 140 °C, 20 min	 	17.93 minor (R) 16.88 major (S)
9		HPLC Chiralcel AD	1% iPrOH/Hexane 1.0 mL/min	 	38.22 minor (S) 36.40 major (R)
10		HPLC Chiralcel AD	10% iPrOH/Hexane 1.0 mL/min	 	9.95 minor (R) 11.27 major (S)

References

(1) Plenio, H.; Diodone, R. *J. Org. Chem.* **1993**, *58*, 8650.
(2) Doris, E.; Dechoux, L.; Mioskowski, C. *J. Am. Chem. Soc.* **1995**, *117*, 12700.
(3) Hermanson, J. R.; Hershberger, J. W.; Pinhas, A. R. *Organometallics* **1995**, *14*, 5426.
(4) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727.
(5) Polo, E.; Bellabarba, R. M.; Prini, G.; Traverso, O.; Green, M. L. H. *J. Oranomet. Chem.* **1999**, *577*, 211.
(6) Jeong, N.; Hwang, S. H.; Lee, Y. *J. Am. Chem. Soc.* **1994**, *116*, 3159.