Chiral Ligand-Controlled Asymmetric Conjugate Addition of α-Trimethylsilanylacetate to Acyclic and Cyclic Enones

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The reaction of lithium ester enolate with enones provides a challenge for chemoselectivity, that is, discrimination between a conjugate addition and a 1,2-addition. Asymmetric conjugate addition of a lithium enolate of α-trimethylsilanylacetate to acyclic and cyclic α,β-unsaturated ketones was mediated by an external chiral ligand to give the corresponding 1,4-adducts in good enantioselectivity of 74% and good chemoselectivity.

Key words lithium enolate; chiral ligand; trimethylsilanylacetate; ketone

We describe herein our approach to the chiral ligand-controlled asymmetric conjugate addition of α-trimethylsilanylacetate *via* its lithium enolate to acyclic and cyclic enones, giving the corresponding β,β-disubstituted ketones in a good chemo- and enantioselectivity. Since the conjugate addition reaction is one of the powerful methodologies in forming a carbon–carbon bond,[1] the mediator-controlled asymmetric conjugate addition of carbonucleophiles to α,β-unsaturated carbonyl compounds has been an area of active investigations.[2—9] However, albeit of its versatility a lithium enolate of an acetate itself has been one of the scarcely investigated nucleophiles in an asymmetric conjugate addition reaction with enones and enoates probably because of its difficulty in the achievement of the chemo-selective reaction. In fact, the reported approach to the conjugate addition of an acetate *via* its lithium enolate to even enoates has been limited only to the reaction studied by Yamaguchi.[10,11] This situation is very contrasted to the many brilliant successes in the Lewis acid-mediated addition reaction of the silylketene acetal of an acetate.[12—15] It is also interesting to note that lithium enolates of ketones have been reported as nucleophiles in asymmetric conjugate addition reactions,[16,17] while little effort has been devoted to lithium ester enolates.[18,19]

We have been engaged in the chiral ligand-controlled[20] asymmetric conjugate addition reactions of various types of carbon-, nitrogen-, oxygen-, and sulfur-nucleophiles such as organolithiums,[21—23] organocoppers,[24,25] organoboranes,[26] lithium amides[27] lithium peroxides[28,29] and arylthiols.[30—33] We turned our project to a lithium ester-enolate as the next carbonucleophile in the conjugate addition to enones. Combined with the characteristic nature of the Michael donor[34—36] and high ability in enantiofacial differentiation in an enantioselective Peterson reaction under control of a chiral aminodiether (Chart 1),[37] we selected α-trimethylsilanylacetate **1**[37] as a precursor for a lithium enolate. The challenge is the methodology extension from discrimination of the either face of the enolate **2** to the enantiofacial differentiation of the carbon–carbon double bond of an enone as well as the chemoselective reaction at the olefin double bond not at the carbonyl carbon.

We began our studies with the addition of **1** *via* **2**, generated by treatment with lithium diisopropylamide (LDA) in THF, to chalcone **7** in THF at −78 °C and found the formation of the expected adduct **9** in 37% yield together with Peterson product **13** in 49% yield and reduction product **15**[38] in 8% yield (Chart 2; Table 1, entry 1). Encouraged by the for-

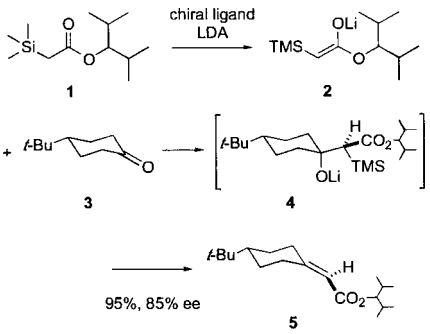

Chart 1. Asymmetric Peterson Olefination of **1** *via* Enolate **2** with **3**

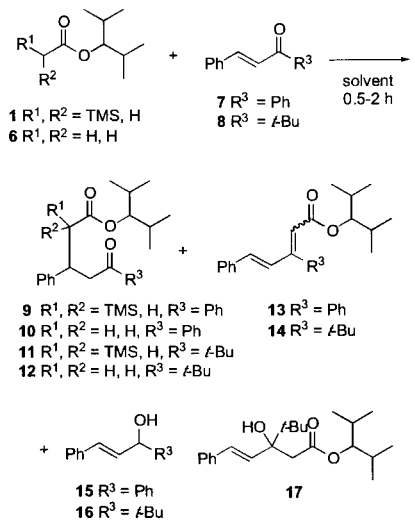

Chart 2. Reaction of Acetates **1** and **6** with Acyclic Enones **7** and **8**

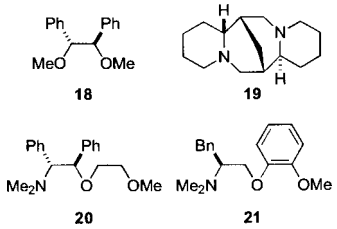

Fig. 1. Chiral Ligands **18**—**21** Used in This Study

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Table 1. Chiral Ligand-Controlled Asymmetric Reaction of Lithium Enolates of **1** and **6** with Acyclic Enones **7** and **8**

Entry	**1**/**6**	**7**/**8**	Solvent	Lithium amide	Equiv.	**18**—**21**	Temp (°C)	**9**/**11** (%)	Ee (%)	**13**/**14** (%)	**15**/**16** (%)
1	**1**	**7**	THF	LDA	1.1	None	−78	37		49	8
2	**1**	**7**	Toluene	LDA	1.1	**18**	−78	5	1	61	9
3	**1**	**8**	THF	LDA	1.1	None	−78 to −20	72		0	7
4	**1**	**8**	Toluene	LDA	1.0	**18**	−78 to −20	69	20	0	0
5	**1**	**8**	Toluene	LDA	1.0	**19**	−78 to −20	99	21	0	0
6	**1**	**8**	Toluene	LDA	1.0	**20**	−78 to −20	99	15	0	0
7	**1**	**8**	Toluene	LDA	1.0	**21**	−78 to −20	99	*ent*-15	0	0
8	**1**	**8**	Toluene	LDA	2.1	**18**	−78 to −20	24	54	0	32
9	**1**	**8**	Toluene	LICA	2.1	**18**	−78 to −20	0		0	67
10	**1**	**8**	Toluene	LDCA	2.1	**18**	−78 to −20	39	30	0	6
11	**1**	**8**	Toluene	LiTMP	2.1	**18**	−78 to −20	41	13	0	0
12	**1**	**8**	Toluene	LiHMDS	2.1	**18**	−78 to −20	47	31	0	0
13	**1**	**8**	Toluene	LiNTrTMS	2.1	**18**	−78 to −20	35	22	0	0
14	**1**	**8**	Toluene	LTBTA	2.1	**18**	−78 to −20	50	26	0	0
15	**6**	**8**	Toluene	LDA	1.1	**18**	−78	0		quant[a]	0

a) The product was **17**.

mation of **9**, we examined an asymmetric reaction in the presence of a chiral ligand **18**[39] in toluene (Table 1, entry 2). Unfortunately, Peterson product **13** was obtained as a 1 : 1.2 *E*/*Z*-mixture in 61% yield together with a 1.3 : 1 diastereomeric mixture **9** in only 5% yield. The ee of **9** was determined as low as 1% by a chiral stationary phase HPLC of protodesilylated **10**. The chemoselectivity[40] of the reaction of **1** in THF was satisfactorily improved by changing a phenyl group (R^3) of **7** to a bulky *tert*-butyl group (**8**[41]), giving a 4.4 : 1 diastereomeric mixture **11** in 72% yield and **16**[42] in 7% yield without formation of Peterson product **14** (entry 3). The ligand **18**-controlled asymmetric reaction of **1** with **8** in toluene was carried out at the temperature starting from −78 °C to −20 °C for 2 h to give a 1.8 : 1 diastereomeric mixture **11** in 69% yield without formation of detectable amounts of **14** and **16** (entry 4). The diastereomeric mixture **11** was then treated with cesium fluoride in aqueous acetonitrile[34] at room temperature (rt) for 24 h to afford protodesilylated (−)-**12** in 94% yield. The ee was determined to be 20% by HPLC. Improvement in enantioselectivity was attempted by using several types of chiral ligands **19**, **20**,[37,43—45] and **21**[46—48] to give **11** quantitatively but in 15—21% enantioselectivities (entries 5—7).

The three-component reagent[49—52] of a lithium enolate, **2**-**18**-LDA, in toluene was found to give **11** in the highest 54% enantioselectivity but in 24% yield together with **16** in 32% yield. Screening of lithium amide components, lithium cyclohexylisopropylamide (LICA), lithium dicyclohexylamide (LDCA), lithium 2,2,6,6-tetramethylpiperidide (LiTMP), lithium hexamethyldisilazide (LiHMDS), lithium trimethylsilyltritylamide (LiNTrTMS),[53] and lithium *tert*-butyltritylamide (LTBTA),[54] gave **11** in 13—31% enantioselectivities and 35—50% yields (entries 8—14). Successful conjugate addition of α-trimethylsilanylacetate was apparent by the reaction of an acetate **6** giving quantitatively **17** without any formation of **12** (entry 15). Thus we found that **1** was an excellent equivalent to an acetate **6**, giving chemoselective and enantioselective conjugate addition product **11**.

We then examined the reaction of acetates with cycloalkenones. The reaction of **1** *via* its enolate **2** with cyclopentenone **23** at −78 °C for 0.5 h in THF gave a 6.1 : 1 mixture of 1,4-adducts **26** in 42% and the Peterson product

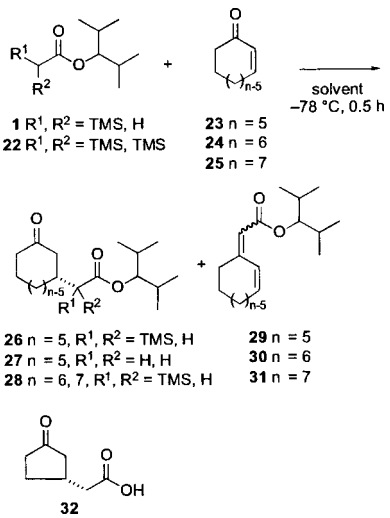

Chart 3. Reaction of Acetates with Cycloalkenones

29 in 41% (Table 2, entry 1). The ligand **18**-controlled reaction of **2** with **23** in toluene at −78 °C for 0.5 h gave a 10 : 1 diastereomeric mixture **26** in 47% and **29** in 22% (Table 2, entry 2). After protodesilylation of **26** to **27** with cesium fluoride in aqueous acetonitrile, the enantiomeric excess of (+)-**27** was determined to be 74% by ^{13}C-NMR analysis of the two peaks appeared at 30.7 and 31.1 ppm of the corresponding diastereomeric aminals prepared with (*R*,*R*)-1,2-diphenylethane-1,2-diamine[55] in deuteriochloroform. The absolute configuration of (+)-**27** was determined to be *R* by hydrolysis with conc. hydrochloric acid in refluxing aqueous dioxane to the corresponding carboxylic acid *R*-(+)-**32** of the established absolute configuration.[56]

Other chiral ligand, sparteine **19**, was not satisfactory to give **26** in 2% ee. (Table 2, entry 3). The tridentate amino diether **20** gave **26** in the best yield 73% but in 7% ee, and **21** gave **26** in 26% ee (entries 4, 5). Unfortunately improvement in enantioselectivity was not achieved by the three-component reagent of a lithium enolate, **2**-**18**-LDA in toluene to give **26** in 11% and marginal enantioselectivity (entry 6).

The lithium enolate of 2,2-bis(trimethylsilanyl)acetate[57] **22** was not a good nucleophile for the reaction with **23** in

Table 2. Chiral Ligand-Controlled Asymmetric Reaction of Lithium Enolates **2** of **1** with Cycloalkenones **23**—**25**

Entry	**23**—**25**	LDA	Solvent	**18**—**21**	**26**—**28** (%)	Ee (%)	**29**—**31** (%)
1	**23**	1.1	THF	None	42		41
2	**23**	1.1	Toluene	**18**	47	*R*-74	22
3	**23**	1.1	Toluene	**19**	50	S-2	19
4	**23**	1.1	Toluene	**20**	73	*R*-7	18
5	**23**	1.1	Toluene	**21**	46	*R*-26	29
6	**23**	2.0	Toluene	**18**	11	*S*-3	0
7	**24**	1.0	THF	None	6		84
8	**24**	1.1	Toluene	**18**	4		60
9	**25**	1.0	THF	None	0		74
10	**25**	1.0	Toluene	**18**	0		64

both THF and toluene to give the 1,4-adducts in only 0.5% and 4% yields, respectively.[58] The major and unidentified products were those arising from the dimerization of **23**.The reaction of **1** with cyclohexenone **24** in both THF and toluene gave Peterson product **30** in 84% and 60% yields, respectively, together with the 1,4-adduct **28** in only 6% and 4% yields (entries 7, 8). The reaction with cycloheptenone **25** in both THF and toluene also afforded **31** in 74% and 64% yields as a sole product (entries 9, 10).

In conclusion, the chiral ligand-controlled asymmetric conjugate addition of α-trimethylsilanylacetate *via* its lithium enolate to enones was found to give the desired adducts in fairly good chemo- and enantioselectivity. These promising results would become a basis for development of a new conjugate addition technology of an acetate.

Experimental[59]

2,4-Dimethylpent-3-yl 2-(trimethylsilanyl)-5-oxo-3,5-diphenylpentanoate (9), 2,4-Dimethylpentan-3-yl 3,5-diphenylpenta-2,4-dienoate (13) and (15) (Table 1, entry 2) A solution of 2,4-dimethyl-3-pentyl α-trimethylsilanylacetate **1** (0.39 ml, 1.5 mmol) and a chiral ligand **18** (508 mg, 2.1 mmol) in toluene (5 ml) was added to a solution of LDA (1.6 mmol) in toluene (7 ml) at −78 °C dropwise over 5 min. After the mixture was stirred at −20 °C for 1 h, a solution of **7** (208 mg, 1 mmol) in toluene (3 ml) was added to the mixture dropwise over 2 min at −78 °C. The whole was stirred at −78 °C for 0.5 h. Concentration and chromatography (hexane/EtOAc=50 : 1—0 : 1) gave an inseparable 1.3 : 1 diastereomeric mixture of **9** (20 mg, 5%) as a colorless oil, a separable 1 : 1.2 *E*/*Z*-mixture of **13** (210 mg, 61%) as a colorless oil, and **15** (18 mg, 9%) as a colorless oil. *E*- and *Z*-**13** were assigned based on nOe experiments in which irradiation of the α-vinyl proton gave a nOe with the γ-proton for the *Z*-**13**, which was not observed in *E*-**13**. **9**: IR (neat): 1580, 1600, 1690, 1710, 1740 cm^{-1}. EI-MS *m*/*z*: 438 (M^+), 423 (M^+-CH_3), 323 ($M^+-OCH(iPr)_2$). *Anal.* Calcd for $C_{27}H_{38}O_3Si$: C, 73.92; H, 8.73. Found: C, 74.01; H, 8.79. major-**9**: ^{1}H-NMR: 0.17 (9H, s), 0.63 (3H, d, *J*=6.7 Hz), 0.65 (3H, d, *J*=6.7 Hz), 0.66 (3H, d, *J*=6.7 Hz), 0.76 (3H, d, *J*=6.7 Hz), 1.69 (2H, dqq, *J*=6.1, 6.7, 6.7 Hz), 2.80 (1H, d, *J*=9.5 Hz), 3.40 (1H, dd, *J*=8.8, 16.5 Hz), 3.46 (1H, dd, *J*=5.1, 16.5 Hz), 3.87—3.91 (1H, m), 4.40 (1H, dd, *J*=6.1, 6.1 Hz), 7.07—7.88 (10H, m). ^{13}C-NMR: −0.59, 17.1, 18.4, 19.4, 19.6, 29.2, 29.62, 40.5, 43.1, 44.7, 82.9, 126.4, 127.8, 128.0, 128.3, 128.7, 132.74, 137.1, 143.7, 174.0, 198.5. minor-**9**: ^{1}H-NMR: −0.06 (9H, s), 0.81 (3H, d, *J*=6.7 Hz), 0.83 (3H, d, *J*=6.7 Hz), 0.92 (6H, d, *J*=6.7 Hz), 1.90 (2H, dqq, *J*=6.1, 6.7, 6.7 Hz), 2.57 (1H, d, *J*=9.5 Hz), 3.36 (1H, dd, *J*=2.8, 16.5 Hz), 3.76 (1H, dd, *J*=11.0, 16.5 Hz), 3.87—3.91 (1H, m), 4.60 (1H, dd, *J*=6.1, 6.1 Hz), 7.07—7.88 (10H, m). ^{13}C-NMR: −1.44, 17.9, 18.1, 19.68, 19.72, 29.4, 29.65, 40.3, 44.7, 45.0, 83.2, 126.6, 127.9, 128.2, 128.4, 132.71, 137.0, 142.8, 174.6, 198.3. less polar *E*-**13**: ^{1}H-NMR: 0.92 (6H, d, *J*=6.7 Hz), 0.94 (6H, d, *J*=6.7 Hz), 1.96 (2H, dqq, *J*=6.1, 6.7, 6.7 Hz), 4.73 (1H, dd, *J*=6.1, 6.1 Hz), 5.85 (1H, s), 6.62 (1H, d, *J*=16.5 Hz), 7.25—7.49 (10H, m), 8.56 (1H, d, *J*=16.5 Hz). ^{13}C-NMR: 17.3, 19.6, 29.5, 82.1, 118.2, 126.0, 127.4, 128.2, 128.4, 128.6, 128.7, 129.0, 136.6, 139.4, 140.1, 155.9, 166.5. IR (neat): 1570, 1590, 1620, 1700 cm^{-1}. EI-MS *m*/*z*: 348 (M^+), 250 ($M^+-CH(iPr)_2$), 233 ($M^+-OCH(iPr)_2$), 205. *Anal.* Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.46; H, 8.26. more polar *Z*-**13**: ^{1}H-NMR: 0.70 (6H, d, *J*=6.7 Hz), 0.78 (6H, d, *J*=6.7 Hz), 1.70 (2H, dqq, *J*=6.1, 6.7, 6.7 Hz), 4.51 (1H, dd, *J*=6.1, 6.1 Hz), 6.12 (1H, s), 6.31 (1H, d, *J*=15.9 Hz), 7.06 (1H, d, *J*=15.9 Hz), 7.19—7.41 (10H, m). ^{13}C-NMR: 17.2, 19.3, 29.2, 82.2, 120.7, 127.0, 127.5, 127.8, 128.4, 128.56, 128.59, 131.8, 136.2, 137.0, 138.0, 154.2, 166.0. IR (neat): 1570, 1590, 1610, 1690, 1710, 1720 cm^{-1}. EI-MS *m*/*z*: 348 (M^+), 250 ($M^+-CH(iPr)_2$), 233 ($M^+-OCH(iPr)_2$), 205. *Anal.* Calcd for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 82.42; H, 8.22. 1538): ^{1}H-NMR: 2.13 (1H, br s), 5.39 (1H, d, *J*=6.7 Hz), 6.39 (1H, dd, *J*=6.7, 15.9 Hz), 6.69 (1H, d, *J*=15.9 Hz), 7.22—7.44 (10H, m). IR (neat): 1600, 3400 cm^{-1}. EI-MS *m*/*z*: 210 (M^+).

2,4-Dimethylpent-3-yl 5-oxo-3,5-diphenylpentanoate (10) A solution of a diastereomeric mixture of **9** (20 mg, 0.05 mmol, Table 1, entry 2) and CsF (21 mg, 0.14 mmol) in 0.1 ml of 9 : 1 mixture of acetonitrile and water was stirred at rt for 12 h. After addition of satd. sodium bicarbonate, the mixture was extracted with ether. Concentration and chromatography (hexane/Et_2O=9/1) gave **10** (17 mg, 99%) as a colorless oil of $[\alpha]_D^{25}$ −0.82° (*c*=0.85, $CHCl_3$). The ee was determined to be 1% by HPLC (DAICEL Chiralcel AD-H, propan-2-ol/hexane=1/100, 1 ml/min, 254 nm, major: 24.2 min, minor: 34.9 min). ^{1}H-NMR: 0.69 (3H, d, *J*=7.0 Hz), 0.71 (3H, d, *J*=7.0 Hz), 0.73 (3H, d, *J*=7.0 Hz), 0.76 (3H, d, *J*=7.0 Hz), 1.79 (2H, dqq, *J*=6.1, 7.0, 7.0 Hz), 2.75 (1H, dd, *J*=8.6, 15.9 Hz), 2.86 (1H, dd, *J*=6.7, 15.9 Hz), 3.33 (1H, dd, *J*=7.2, 17.1 Hz), 3.37 (1H, dd, *J*=6.9, 17.1 Hz), 3.90 (1H, dddd, *J*=6.7, 6.9, 7.2, 8.6 Hz), 4.51 (1H, dd, *J*=6.1, 6.1 Hz), 7.15—7.54 (8H, m), 7.90—7.91 (2H, m). ^{13}C-NMR: 17.0, 17.1, 19.3, 19.4, 29.15, 29.22, 37.5, 40.5, 44.9, 82.8, 126.7, 127.4, 128.0, 128.49, 128.51, 133.0, 136.9, 143.2, 171.8, 198.2. IR (neat): 1680, 1720 cm^{-1}. EI-MS *m*/*z*: 366 (M^+), 268 ($M^+-CH(iPr)_2$), 252 ($M^+-OCH(iPr)_2$), 191. *Anal.* Calcd for $C_{24}H_{30}O_3$: C, 78.65; H, 8.25. Found: C, 78.57; H, 8.25.

2,4-Dimethylpent-3-yl 6,6-dimethyl-2-(trimethylsilanyl)-5-oxo-3-phenylheptanoate (11) and 4,4-Dimethyl-1-phenylpent-1-en-3-ol (16). Reaction of the Three-Component Reagent with 8 (Table 1, entry 8) A solution of **1** (0.34 ml, 1.3 mmol) and **18** (411 mg, 1.7 mmol) in toluene (3 ml) was added to a solution of LDA (2.6 mmol) in toluene (5 ml) at −78 °C dropwise over 5 min. The mixture was stirred at −20 °C for 1 h. A solution of **8** (188 mg, 1 mmol) in toluene (3 ml) was then added to the mixture at −78 °C dropwise over 2 min, and the whole was allowed to warm up to −20 °C over 2 h. Concentration and chromatography (hexane/benzene=1 : 1) gave an inseparable 1.7 : 1 diastereomeric mixture of **11** (99 mg, 24%, 54% ee: determined by HPLC of **12**) as a colorless oil of $[\alpha]_D^{25}$ −22.4° (*c*=0.99, $CHCl_3$) and **16** (60 mg, 32%) as a colorless oil. **11**: IR (neat): 1710, 1720 cm^{-1}. EI-MS *m*/*z*: 418 (M^+), 303 ($M^+-OCH(iPr)_2$), 246 ($M^+-OCH(iPr)_2-t$Bu). *Anal.* Calcd for $C_{25}H_{42}O_3Si$: C, 71.72; H, 10.11. Found: C, 71.65; H, 9.93. major **11**: ^{1}H-NMR: −0.10 (9H, s), 0.82 (3H, d, *J*=6.7 Hz), 0.84 (3H, d, *J*=6.7 Hz), 0.90 (9H, s), 0.92 (6H, d, *J*=6.7 Hz), 1.90 (2H, dqq, *J*=6.1, 6.7, 6.7 Hz), 2.47 (1H, d, *J*=9.8 Hz), 2.67 (1H, dd, *J*=2.5, 16.8 Hz), 3.39 (1H, dd, *J*=11.0, 16.8 Hz), 3.72—3.76 (1H, m), 4.57 (1H, dd, *J*=6.1, 6.1 Hz), 7.09—7.31 (5H, m). ^{13}C-NMR: −1.50, 18.1, 19.7, 25.8, 29.5, 29.7, 39.6, 43.2, 43.8, 44.6, 83.2, 126.6, 128.2, 128.5, 143.4, 174.7, 213.3. minor **11**: ^{1}H-NMR: 0.15 (9H, s), 0.60 (3H, d, *J*=6.7 Hz), 0.68 (3H, d, *J*=6.7 Hz), 0.70 (3H, d, *J*=6.7 Hz), 0.73 (3H, d, *J*=6.7 Hz), 0.87 (9H, s), 1.60—1.75 (2H, m), 2.67 (1H, d, *J*=15.0 Hz), 2.74 (1H, dd, *J*=4.0, 16.8 Hz), 3.02 (1H, dd, *J*=10.8, 16.8 Hz), 3.72—3.76 (1H, m), 4.38 (1H, dd, *J*=6.1, 6.1 Hz), 7.09—7.31 (5H, m). ^{13}C-NMR: −0.78, 17.0, 17.2, 19.2, 19.5, 25.5, 29.3, 29.6, 40.0, 43.0, 43.2, 43.8, 82.8, 126.3, 127.9, 128.6, 144.0, 173.9, 213.3. **16**[42]: ^{1}H-NMR: 0.97 (9H, s), 1.55 (1H, s), 3.93 (1H, d, *J*=7.0 Hz), 6.29 (1H, dd, *J*=7.0, 15.9 Hz), 6.58 (1H, d, *J*=15.9 Hz), 7.23—7.40 (5H, m). ^{13}C-NMR: 25.7, 35.3, 81.0, 126.5, 127.6, 128.6, 129.6, 131.9, 136.9. IR (neat): 1600, 3400 cm^{-1}, EI-MS *m*/*z*: 190 (M^+), 133 (M^+-tBu).

2,4-Dimethylpent-3-yl 6,6-dimethyl-5-oxo-3-phenylheptanoate (12) Protodesilylation of **11** (Table 1, entry 8) with CsF in aq. acetonitrile gave **12** as a colorless oil of $[\alpha]_D^{25}$ −19.3° (*c*=0.82, benzene) in 93% yield. The ee was determined to be 54% by HPLC (DAICEL Chiralcel AD-H, propan-2-ol/hexane=1/100, 0.5 ml/min, 254 nm, major: 16.0 min, minor: 13.3 min). ^{1}H-NMR: 0.71 (9H, d, *J*=6.8 Hz), 0.74 (3H, d, *J*=6.8 Hz), 1.02 (9H, s), 1.79 (2H, dqq, *J*=6.1, 6.8, 6.8 Hz), 2.67 (1H, dd, *J*=8.9, 15.6 Hz), 2.76 (1H, dd, *J*=6.7, 15.6 Hz), 2.80 (1H, dd, *J*=6.4, 17.4 Hz), 2.89 (1H, dd, *J*=7.3, 17.4 Hz), 3.75 (1H, dddd, *J*=6.4, 6.7, 7.3, 8.9 Hz), 4.49 (1H, dd, *J*=6.1, 6.1 Hz), 7.15—7.27 (5H, m). ^{13}C-NMR: 16.9, 17.1, 26.0, 29.1, 37.0, 40.2, 43.1, 44.0, 82.7, 126.6, 127.5, 128.4, 143.6, 171.9, 213.6. IR (neat): 1700, 1730 cm^{-1}, EI-MS *m*/*z*: 346 (M^+), 248 ($M^+-CH(iPr)_2$), 231 ($M^+-OCH(iPr)_2$), 191. *Anal.* Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.98; H, 9.82.

2,4-Dimethylpent-3-yl 3-*tert*-butyl-3-hydroxy-5-phenylpent-4-enoate

(17) (Table 1, entry 15) A solution of 2,4-dimethyl-3-pentyl acetate **6** (0.54 ml, 3 mmol) and **18** (1.02 g, 4.2 mmol) in toluene (7 ml) was added to a solution of LDA (3 mmol) in toluene (23 ml) at −78 °C dropwise over 5 min. The mixture was stirred at −20 °C for 1 h. A solution of **8** (188 mg, 1 mmol) in toluene (6 ml) was then added to the mixture dropwise over 2 min at −78 °C, and the whole was stirred for 0.5 h. Concentration and chromatography (hexane/EtOAc=20 : 1—3 : 1) gave **17** (344 mg, 99%) as a colorless oil of $[\alpha]_D^{25}$ +0.45° (c=1.12, $CHCl_3$). ^{1}H-NMR: 0.71 (6H, d, J=6.7 Hz), 0.83 (3H, d, J=6.7 Hz), 0.84 (3H, d, J=6.7 Hz), 1.01 (9H, s), 1.79 (1H, dqq, J=6.1, 6.7, 6.7 Hz), 1.86 (1H, dqq, J=6.1, 6.7, 6.7 Hz), 2.74 (2H, s), 4.54 (1H, s), 4.56 (1H, dd, J=6.1, 6.1 Hz), 6.30 (1H, d, J=15.9 Hz), 6.65 (1H, d, J=15.9 Hz), 7.17—7.33 (5H, m). ^{13}C-NMR: 17.1, 17.3, 19.3, 19.4, 25.2, 29.1, 29.2, 38.1, 39.0, 77.4, 83.5, 126.5, 127.2, 128.4, 130.5, 132.0, 136.9, 174.1. IR (neat): 1600, 1710, 3450 cm^{-1}. EI-MS m/z: 289 (M^+-tBu), 191. HR-FAB-MS m/z: $[M-H]^-$ Calcd for $C_{22}H_{33}O_3$, 345.2430; Found, 345.2417.

2,4-Dimethylpent-3-yl 2-(trimethylsilanyl)-2-(3-oxocyclopentyl)acetate (26) and 2,4-Dimethylpentan-3-yl 2-(cyclopent-2-enylidene)acetate (29) (Table 2, entry 2) A solution of **1** (0.39 ml, 1.5 mmol) and **18** (508 mg, 2.1 mmol) in toluene (5 ml) was added to a solution of LDA (1.6 mmol) in toluene (7 ml) at −78 °C dropwise over 5 min. The mixture was stirred at −20 °C for 1 h. A solution of cyclopentenone **23** (0.08 ml, 1 mmol) in toluene (3 ml) was then added to the mixture at −78 °C dropwise over 2 min, and the whole was stirred for 0.5 h at the same temperature. Concentration and chromatography (hexane/Et_2O=9/1) gave an inseparable 10 : 1 diastereomeric mixture of **26** (140 mg, 47%) as a colorless oil of $[\alpha]_D^{25}$ +40.1° (c=1.00, $CHCl_3$) and an inseparable 6.5 : 1 E/Z-mixture of **29** (22%). **26**: The NMR peaks of major isomer were presented. ^{1}H-NMR: 0.18 (9H, s), 0.88 (3H, d, J=6.8 Hz), 0.89 (3H, d, J=6.8 Hz), 0.90 (3H, d, J=6.8 Hz), 0.91 (3H, d, J=6.8 Hz), 1.68—2.59 (10H, m), 4.59 (1H, dd, J=5.8, 5.8 Hz). ^{13}C-NMR: −1.11, 17.7, 18.0, 19.7, 19.9, 29.4, 29.5, 29.6, 36.5, 38.9, 42.0, 44.5, 82.8, 174.3, 218.7. IR (nujol): 1710, 1750 cm^{-1}. EI-MS m/z: 312 (M^+), 214, 197 ($M^+-OCH(i\mathrm{Pr})_2$). *Anal.* Calcd for $C_{17}H_{32}O_3Si$: C, 65.33; H, 10.32. Found: C, 65.32; H, 10.04. **29**: IR (neat) 1630, 1690 cm^{-1}. EI-MS m/z: 222 (M^+), 124, 107 ($M^+-OCH(i\mathrm{Pr})_2$). HR-MS m/z: Calcd for $C_{14}H_{22}O_2$, 222.1620; Found, 222.1612. major E-**29**: Irradiation of the α-vinyl proton gave a nOe with the γ-proton, allowing assignment as the E-isomer. ^{1}H-NMR: 0.88 (6H, d, J=6.4 Hz), 0.90 (6H, d, J=6.4 Hz), 1.92 (2H, dqq, J=6.1, 6.4, 6.4 Hz), 2.61—2.63 (2H, m), 3.01—3.03 (2H, m), 4.65 (1H, dd, J=6.1, 6.1 Hz), 5.80 (1H, s), 6.31 (1H, d, J=5.5 Hz), 6.59—6.61 (1H, m). ^{13}C-NMR: 17.3, 19.5, 29.5, 29.8, 33.3, 81.4, 109.2, 134.8, 147.6, 167.2, 168.0. minor Z-**29**: ^{1}H-NMR: 0.88 (6H, d, J=6.4 Hz), 0.90 (6H, d, J=6.4 Hz), 1.92 (2H, dqq, J=6.1, 6.4, 6.4 Hz), 2.53—2.54 (2H, m), 2.68—2.69 (2H, m), 4.65 (1H, dd, J=6.1, 6.1 Hz), 5.66 (1H, s), 6.63 (1H, m), 7.38 (1H, d, J=5.5 Hz). ^{13}C-NMR: 17.3, 19.5, 29.5, 31.0, 31.2, 81.4, 107.5, 132.3, 148.4, 165.6, 167.1.

2,4-Dimethylpent-3-yl 2-(3-oxocyclopentyl)acetate (27) Protodesilylation of **26** (Table 2, entry 2) with CsF in aq. acetonitrile gave **27** as a colorless oil of $[\alpha]_D^{25}$ +58.1° (c=0.73, $CHCl_3$) in 39% yield. ^{1}H-NMR: 0.86 (6H, d, J=6.7 Hz), 0.88 (6H, d, J=6.7 Hz), 1.58—2.67 (11H, m), 4.62 (1H, dd, J=6.1, 6.1 Hz). ^{13}C-NMR: 17.3, 19.6, 29.3, 33.5, 38.3, 40.0, 44.7, 82.9, 172.1, 218.4. IR (neat): 1730, 1740 cm^{-1}. EI-MS m/z: 240 (M^+), 197 ($M^+-CH(CH_3)_2$), 141 ($M^+-CH(i\mathrm{Pr})_2$), 125 ($M^+-OCH(i\mathrm{Pr})_2$). *Anal.* Calcd for $C_{14}H_{24}O_3$: C, 69.96; H, 10.07. Found: C, 70.10; H, 9.77. The ee was determined to be 74% by ^{13}C-NMR of the aminals (major: 30.7, minor: 31.1 ppm) obtained by treating **27** (2.9 mg, 0.01 mmol) with (*R*,*R*)-1,2-diphenylethane-1,2-diamine (3 mg, 0.015 mmol) in $CDCl_3$ in the presence of molecular sieves 4A at rt for 12 h.

Determination of the Absolute Configuration of 27 by Converting to *R*-(+)-2-(3-Oxocyclopentyl)acetic acid (32) A mixture of (+)-**27** (23 mg, 0.09 mmol) and conc. HCl (0.2 ml) in 1 : 1 mixture of dioxane and water (0.4 ml) was stirred under reflux for 19 h. After the mixture was basified with satd aq. sodium bicarbonate (20 ml), the aqueous layer was separated, which was then acidified with 10% HCl and extracted with ethyl acetate. Concentration and chromatography gave *R*-(+)-**32**[56] (8 mg, 63%) as a colorless oil of $[\alpha]_D^{23}$ +88.1° (c=0.79, $CHCl_3$). ^{1}H-NMR: 1.62 (1H, m), 1.92 (1H, dd, J=10.1, 18.2 Hz), 2.18—2.37 (3H, m), 2.48—2.66 (4H, m). ^{13}C-NMR: 29.2, 33.1, 38.3, 39.3, 44.5, 177.6, 218.2. IR (neat): 1720, 1740, 3200 cm^{-1}. EI-MS m/z: 142 (M^+).

2,4-Dimethylpent-3-yl 2,2-bis(trimethylsilanyl)acetate (22) A solution of **1** (26.2 ml, 0.1 mol) in THF (50 ml) was added to a solution of LDA (0.15 mol) in THF (350 ml) at −78 °C dropwise over 10 min. After stirring for 2 h at −78 °C a solution of trimethylsilyl chloride (127 ml, 1 mol) in THF (200 ml) was added to the mixture at −78 °C dropwise over 10 min. The whole was allowed to warm up to rt and diluted with ethyl acetate. The organic layers were washed with brine and dried over potassium carbonate. Concentration and distillation (180—190 °C/7 mmHg) gave **22** as colorless needles (13.9 g, 46%) of mp 36—40 °C. ^{1}H-NMR: 0.15 (18H, s), 0.89 (6H, d, J=6.7 Hz), 0.90 (6H, d, J=6.7 Hz), 1.70 (1H, s), 1.88 (2H, dqq, J=5.8, 6.7, 6.7 Hz), 4.51 (1H, dd, J=5.8, 5.8 Hz). ^{13}C-NMR: 0.29, 17.9, 19.9, 29.5, 30.5, 82.5, 174.3. IR (nujol): 1690 cm^{-1}. EI-MS m/z: 287 (M^+-Me), 187 ($M^+-OCH(i\mathrm{Pr})_2$). *Anal.* Calcd for $C_{15}H_{34}O_2Si_2$: C, 59.54; H, 11.33. Found: C, 59.37; H, 11.28.

2,4-Dimethylpent-3-yl 2-(trimethylsilanyl)-2-(3-oxocyclohexyl)acetate (28: n=6) and 2,4-Dimethylpentan-3-yl 2-(cyclohex-2-enylidene)acetate (30) (Table 2, entry 8) The same reaction for entry 2, Table 2 gave an inseparable 2.1 : 1 diastereomeric mixture of **28** as a colorless oil in 4% and an inseparable 1 : 3 E/Z-mixture of **30** as a colorless oil in 60% yield. **28** (n=6): ^{1}H-NMR: 0.17 (9H, s), 0.89 (3H, d, J=6.4 Hz), 0.91 (6H, d, J=6.4 Hz), 0.92 (3H, d, J=6.4 Hz), 1.57—2.13 (8H, m), 2.19 (1H, d, J=4.9 Hz), 2.23—2.36 (2H, m), 2.96 (1H, m), 4.61 (1H, dd, J=5.8, 5.8 Hz). ^{13}C-NMR: −0.96, 17.7, 17.8, 19.7, 19.8, 25.2, 29.4, 29.5, 31.6, 38.7, 40.9, 42.9, 46.3, 82.6, 174.3, 211.7. IR (nujol): 1710 cm^{-1}. EI-MS m/z: 327 (M^++1), 228, 211 ($M^+-OCH(i\mathrm{Pr})_2$). HR-MS m/z: Calcd for $C_{18}H_{34}O_3Si$, 326.2277; Found, 326.2281. **30**: The E/Z stereochemistry was assigned by analogy to **29** in which the Z-isomer possessed the lower field γ-proton. IR (neat): 1600, 1630, 1710 cm^{-1}. EI-MS m/z: 236 (M^+), 138, 121 ($M^+-OCH(i\mathrm{Pr})_2$). *Anal.* Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 75.97; H, 10.43. major Z-**30**: ^{1}H-NMR: 0.87 (6H, d, J=7.1 Hz), 0.89 (6H, d, J=7.1 Hz), 1.79 (1H, tt, J=6.5, 6.5 Hz), 1.91 (2H, dqq, J=6.4, 7.1, 7.1 Hz), 2.19—2.23 (2H, m), 2.40 (2H, dt, J=1.6, 6.5 Hz), 4.63 (1H, dd, J=6.4, 6.4 Hz), 5.52 (1H, s), 6.18—6.24 (2H, m), 7.49 (1H, d, J=10.1 Hz). ^{13}C-NMR: 17.3, 19.5, 22.6, 26.1, 29.4, 32.5, 81.5, 113.4, 125.4, 137.9, 152.2, 166.7. minor E-**30**: ^{1}H-NMR: 0.87 (6H, d, J=7.1 Hz), 0.89 (6H, d, J=7.1 Hz), 1.73 (1H, tt, J=6.5, 6.5 Hz), 1.91 (2H, dqq, J=6.4, 7.1, 7.1 Hz), 2.19—2.23 (2H, m), 2.97 (2H, dt, J=1.6, 6.5 Hz), 4.61 (1H, dd, J=6.4, 6.4 Hz), 5.61 (1H, s), 6.13 (1H, d, J=10.1 Hz), 6.18—6.24 (2H, m). ^{13}C-NMR: 17.3, 19.5, 21.8, 25.5, 29.4, 32.5, 81.5, 115.3, 130.4, 137.6, 153.6, 167.4.

2,4-Dimethylpent-3-yl 2-(cyclohept-2-enylidene)acetate (31) (Table 2, entry 10) Obtained as a separable 1 : 3.6 E/Z-mixture of **31** in 64% yield as a colorless oil under the same conditions for Table 2, entry 2. The E/Z-stereochemistry was assigned by analogy to **29** in which the Z-isomer possessed the lower field γ-proton. More polar major Z-**31**: ^{1}H-NMR: 0.87 (6H, d, J=7.0 Hz), 0.89 (6H, d, J=7.0 Hz), 1.70—1.79 (4H, m), 1.90 (2H, dqq, J=6.1, 7.0, 7.0 Hz), 2.29—2.31 (2H, m), 2.47 (2H, t, J=5.8 Hz), 4.62 (1H, dd, J=6.1, 6.1 Hz), 5.63 (1H, s), 6.13 (1H, ddd, J=6.1, 11.6, 11.6 Hz), 7.24 (1H, d, J=11.6 Hz). ^{13}C-NMR: 17.3, 19.5, 26.4, 27.1, 28.5, 29.4, 37.3, 81.6, 116.3, 119.2, 138.7, 156.9, 166.6. IR (neat): 1590, 1630, 1710 cm^{-1}. EI-MS m/z: 250 (M^+), 152, 135 ($M^+-OCH(i\mathrm{Pr})_2$). *Anal.* Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.75; H, 10.35. less polar minor E-**31**: ^{1}H-NMR: 0.87 (6H, d, J=6.8 Hz), 0.89 (6H, d, J=6.8 Hz), 1.70—1.81 (4H, m), 1.91 (2H, dqq, J=6.1, 6.8, 6.8 Hz), 2.29—2.31 (2H, m), 3.03 (2H, t, J=6.4 Hz), 4.63 (1H, dd, J=6.1, 6.1 Hz), 5.71 (1H, s), 6.04 (1H, ddd, J=5.5, 11.6, 11.6 Hz), 6.14 (1H, d, J=11.6 Hz). ^{13}C-NMR: 17.2, 19.5, 25.5, 26.8, 28.5, 29.4, 29.6, 81.6, 118.3, 133.9, 138.8, 158.0, 167.3. IR (neat): 1600, 1630, 1710 cm^{-1}. EI-MS m/z: 250 (M^+), 152, 135 ($M^+-OCH(i\mathrm{Pr})_2$). HR-MS m/z: Calcd for $C_{16}H_{26}O_2$, 250.1933; Found, 250.1941.

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