Cyclic Model for the Asymmetric Conjugate Addition of Organolithium with Enoate

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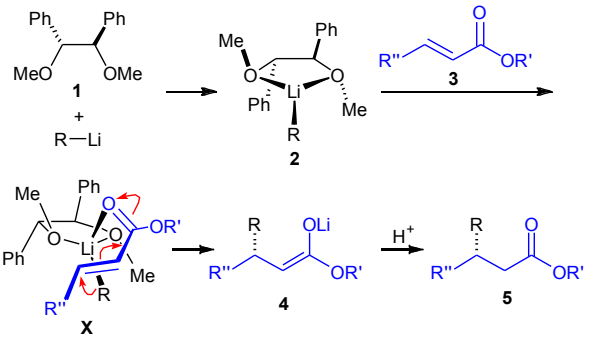
Abstract: The chiral diether ligand-controlled asymmetric conjugate addition of organolithiums to nona-2,7-dienedioate preferentially proceeded via the s-*cis* conformation with coordination of the carbonyl oxygen atom to the lithium to give *E*-lithium enolate intermediate. Subsequent intramolecular conjugate addition of the enolate also proceeded via the cyclic transition state involving the lithium and the s-*cis*-enoate, and *trans,trans*-trisubstituted cyclohexanes were obtained with high ee and yields.

Key words: chiral ligand, asymmetric synthesis, organolithiums, conjugate addition, cascade reaction

Asymmetric conjugate addition of carbonucleophile to electron-deficient olefin is one of the most attractive and powerful methods for an asymmetric construction of carbon–carbon bonds.[1] It is advantageous that an initial product of asymmetric conjugate addition of an organolithium to an α,β-unsaturated carbonyl compound is a chiral lithium enolate and thus can further react with an electrophile to form an additional bond. The conformation of the α,β-unsaturated carbonyl compound, i.e., s-*cis* or s-*trans*, is responsible to the facial selectivity of the conjugate addition and also to the *E,Z*-geometry of the resulting enolate, which should then governs the diastereoselectivity of the subsequent reaction with other electrophiles. Accordingly, the reactive conformation of carbonyl compounds in which conjugate addition occurs has been a central matter of interest.[2]

We have been engaged in an external chiral ligand controlled asymmetric conjugate addition reaction of a variety of lithiated nucleophiles such as organolithium, lithium ester enolate, lithium thiolate, and lithium amide to linear α,β-unsaturated imine,[3] enoate[4,5,6] and nitroolefin[7]. Our NMR studies revealed that chiral diether ligand **1** and a lithium reagent form C_2-symmetric-like[8] five-membered chelate complex **2** by coordination of the two ethereal oxygen atoms of **1** to the lithium atom, in which the methyl groups on the oxygen atoms are fixed to situate up and down faces of chelation **2** avoiding steric repulsion by the phenyl groups on the chiral centers.[9] The reaction of complex **2** with enoate **3** afforded conjugate addition product **5** with high enantioselectivity. On the basis of the relationship between the newly created stereogenic center in **5** and chiral chelate complex **2**, we proposed cyclic reaction model **X**, in which the lithium atom is coordinated by the carbonyl oxygen atom of s-*cis*-enoate on the olefin side. The olefin moiety is placed in the less crowded space avoiding the steric repulsion by the two methyl groups of **2** (Scheme 1).[3a,3b,5b,10] Then, R group attacks the olefin moiety from underneath to give, after protonation of the resulting *E*-enolate **4**, **5** with the observed absolute configuration.[3-7] If *s-trans*-enoate, instead of *s-cis*, were involved in the reaction, *Z*-enolate with the opposite absolute configuration would result.

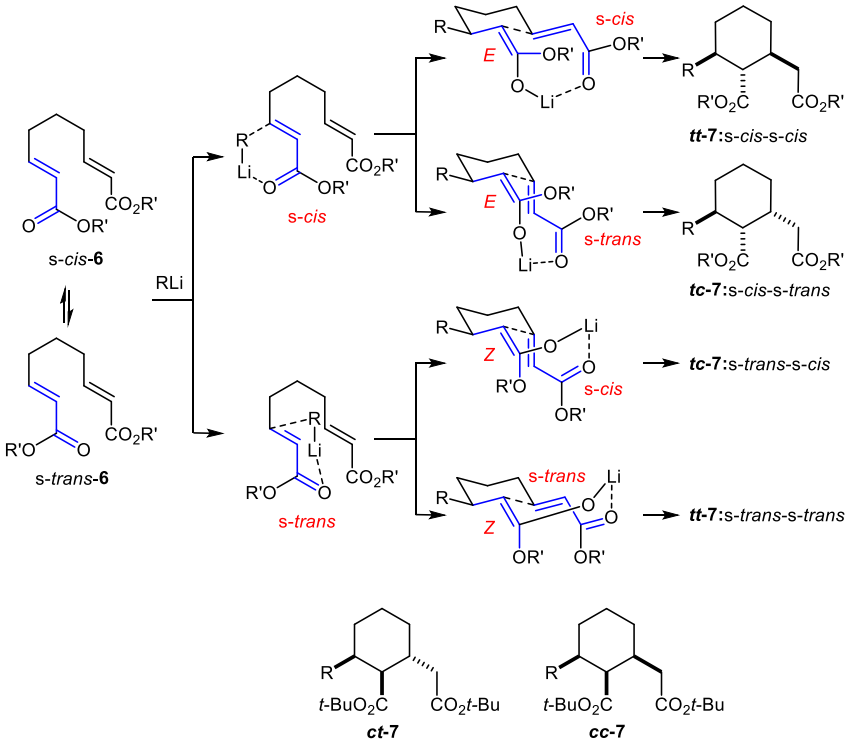
Although the similar cyclic reaction models were proposed by some other groups for the conjugate addition of lithium amide to s-*cis*-enoate,[2a,j,k] lithium-involved models with s-*trans*-enoate were also proposed for the conjugate addition of lithium enolate[11] and methyllithium.[12] Thus, determination of the reactive conformation of an α,β-unsaturated carbonyl compound in the conjugate addition of lithium reagent is still a formidable challenging target. Instead of direct identification of enolate geometry, conjugate addition and following Michael cyclization of the resulting enolate with intramolecular enoate were designed to identify the enolate geometry as shown in Scheme 2.



Scheme 1 Our proposal for chiral diether ligand **1**-mediated asymmetric conjugate addition of lithium reagents to α,β-unsaturated carbonyl compounds.

The asymmetric conjugate addition of organolithium[13,14] to C_2 symmetric nona-2,7-dienedioate **6** is a cascade reaction[15] to provide chiral cyclohexanes **2** bearing three contiguous chiral centers, stereochemistry of which provides us an insight into reactive conformation of alkenoates that undergo the conjugate addition (Scheme 2). The addition of organolithium to s-*cis*-**6** preferentially gives *E*-enolate via the cyclic

transition state, while that to s-*trans*-**6** leads to the *Z*-enolate. When the resulting *E*- and *Z*-enolates undergo subsequent conjugate addition to the internal alkenoate moiety with s-*cis* conformation, *trans*,*trans*-***tt*-7** (s-*cis*-s-*cis* product) and *trans*,*cis*-***tc*-7** (s-*trans*-s-*cis* product) should be obtained, respectively, and ***ct*-7** and ***cc*-7** would be quite minor products. The addition reaction of *E*- and *Z*-enolate through s-*trans* conformation would give ***tc*-7** (s-*cis*-s-*trans* product) and ***tt*-7** (s-*trans*-s-*trans* product) as major products, respectively. Herein, we report details of the stereochemistry of the asymmetric conjugate addition cascade preferentially giving ***tt*-7** as well as the preferred cyclic *s-cis* conformation of the alkenoates moieties.



Scheme 2. Products of conjugate addition-Michael cyclization cascade.

At the outset of our studies, the cascade reaction of phenyllithium with bis-BHA (2,6-di-*tert*-butyl-4-methoxyphenyl) enoate **6a** was attempted in the presence of **1** (eq 1).[4a] To a toluene solution of **1** (2 equiv) at –78 °C, were added solutions of phenyllithium (1.5 equiv) in cyclohexane–diethyl ether and then **6a** in toluene 20 min apart. After 20 min reaction, simple conjugate addition product **9a** with 87% ee was obtained in 56% yield along with recovered **6a** in 13% yield without production of desired cascade products **7**. Even when the reaction mixture was gradually warmed up from –78 °C, no cyclization took place below –20 °C, while production of 2,6-di-*tert*-butyl-4-methoxyphenol was observed, probably due to elimination from the intermediate lithium enolate at the elevated temperature.

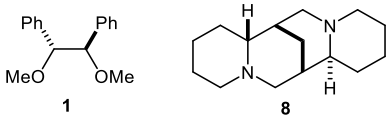
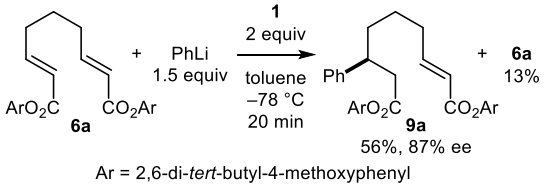


Figure 1 Chiral ligands for organolithium compounds.

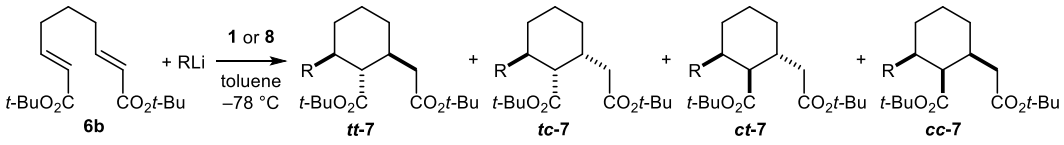


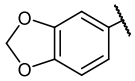
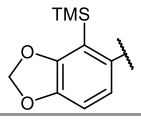
Equation 1

Then, di-*tert*-butyl ester **6b** of decrease steric hindrance was selected as a bis(enoate). To our delight, the reaction of **6b** and phenyllithium (3 equiv) complexed with **1** (4.2 equiv) was completed within 0.5 h to give desired cascade products *trans*,*trans*-cyclohexane ***tt*-7a** with 71% ee in 50% yield and *trans*,*cis*-cyclohexane ***tc*-7a** with 3% ee in 9% yield (Table 1, entry 1). The relative and absolute configuration of ***tt*-7a** was unambiguously determined by derivatization.[15b] The other diastereomers ***ct*-7** and ***cc*-7** were not obtained. It is noteworthy that **6b** mainly reacted with only one equivalent of phenyllithium. Even though **6b** was added into the solution of the excess amount of phenyllithium and **1**, only slight amount of double phenylated product **10a** (see eq 2) was produced (<10%). In contrast, when the reaction was conducted in THF as a solvent without **1**, **10a** was

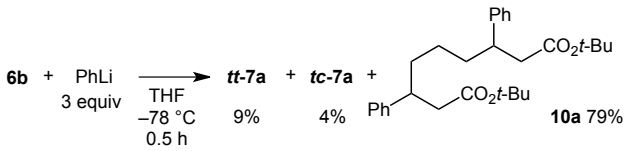
mainly produced (79% yield; eq 2), and only tiny amount of ***tt*-7a** and ***tc*-7a** were obtained (9% and 4% yields, respectively).[16] These results clearly indicate that chiral ligand **1** significantly accelerates the intramolecular conjugate addition of the enolate to the intramolecular enoate.

Table 1 Asymmetric conjugate addition cascade.[a]



Entry	Ligand	R	7	*tt*-7 Yield (%)	*tt*-7 ee (%)	*tc*-7 Yield (%)	*tc*-7 ee (%)	*ct*-7 Yield (%)	*cc*-7 Yield (%)
1[b]	**1**	Ph	**7a**	50	71[c]	9	3[c]	0	0
2	**8**	Ph	**7a**	75	23	0	-	0	0
3	**1**	Bu	**7b**	31	8	8	-	0	0
4	**8**	Bu	**7b**	91	86	0	-	0	0
5[b]	**1**		**7c**	40	74	10	72	0	0
6[b]	**1**		**7d**	68	99	18	88	0	0

[a] All reactions were carried out using RLi (3 equiv) and **1** or **8** (4.2 equiv). [b] Data from ref 15b. [c] The ee was determined after derivatization (see ref. 15b).



Equation 2

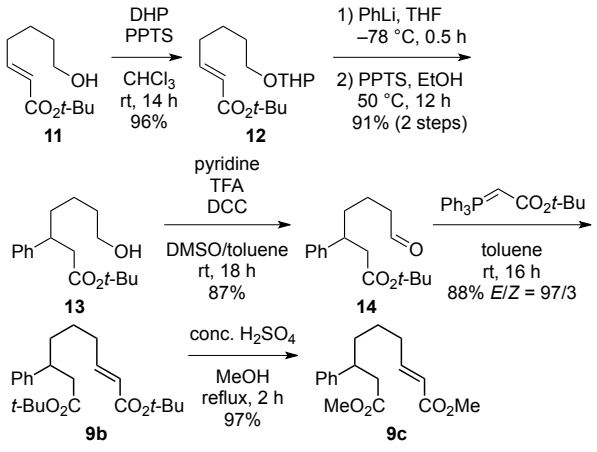
The asymmetric cascade cyclization reactions of aryl- and alkyllithiums were possible by using our chiral diether ligand **1** and (–)-sparteine (**8**) (Figure 1).[4a] Chiral diether **1** and (–)-sparteine (**8**) were complementary chiral ligands controlling the reactions of aryllithium and sp^3 organolithium butyllithium, respectively. The reaction of butyllithium was controlled by **8** to give ***tt*-7b** with 86% ee in 91% yield as a single diastereomer (entry 4), while the use of **1** as a chiral ligand produced ***tt*-7b** with miserable ee (8%) in 31% yield (entry 3). In the reaction of phenyllithium, **8** was a less effective chiral ligand than **1** to give ***tt*-7a** with low 23% ee (entry 2). Interestingly, the diastereoselection was perfectly controlled in the reactions using **8**, and neither ***tc*-7a** nor ***tc*-7b** was produced in entries 2 and 4.

For the reaction of an aryllithium, installation of a removable bulky substituent, such as a TMS group, at the *ortho*-position was effective to enhance the enantioselectivity (entries 5 and 6).[15b] It is noteworthy that the product cyclohexanes **7** bearing three contiguous stereogenic centers were useful for the asymmetric total synthesis of Amaryllidaceae alkaloids (–)-lycorine[15a] and (+)-β-lycorane.[15b]

In all these reactions in Table 1, only slight amount (<10% in total) of 1,2-addition products and 3,7-diaryl products **10** were produced. Importantly, chiral ligand **1** was quantitatively recovered without any loss of optical purity, and was reusable.

Based on the consideration made in Scheme 1, the formation of ***tt*-7**, having *trans*,*trans*-configuration, as the major product suggests two possibilities: (1) the first conjugate addition proceeded with s-*cis*-**6** to give *E*-enolate as an intermediate, which underwent the intramolecular conjugate addition with the alkenoate moiety in s-*cis* conformation, or (2) the first conjugate addition proceeded with s-*trans*-**6**, and the resulting *Z*-enolate undergoes the conjugate addition in s-*trans* conformation. Our studies then went to solve this problem.

Monophenyl adduct di-*tert*-butyl ester **9b** and dimethyl ester **9c** were prepared from (*E*)-*tert*-butyl 7-hydroxyhept-2-enoate **11** [17] (Scheme 3). Hydroxy group of **11** was protected by THP, and then conjugate addition of PhLi followed by deprotection of THP



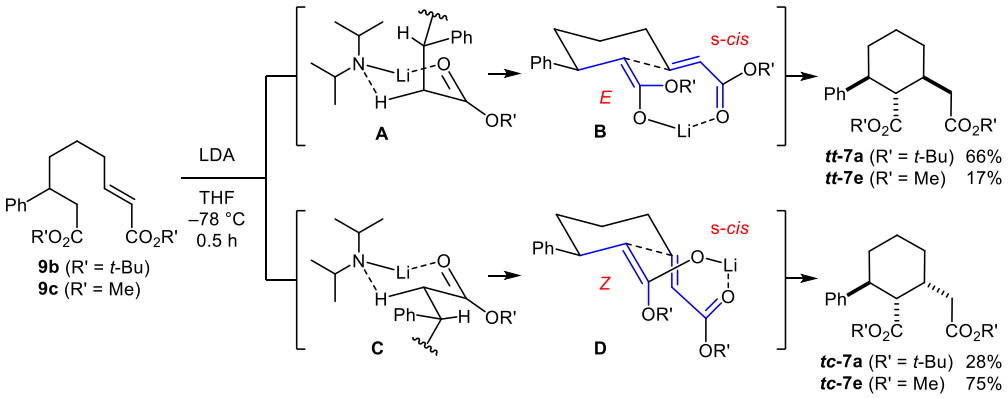
Scheme 3 Preparation of monophenyl adducts **9b** and **9c**.

group afforded **13**. Pfitzner–Moffatt oxidation of **13** and the following Wittig reaction gave **9b**. Dimethyl ester **9c** was prepared by *in situ* methyl esterification of **9b** under Fischer conditions.

Lithium enolate formation and then intramolecular Michael reaction of **9b** and **9c** was examined by treating with LDA (1.2 equiv) in THF at –78 °C (Scheme 4). The reaction of **9b** mainly produced ***tt*-7a**, which is also the main product of the cascade reaction of **6b**, in 66% yield along with ***tc*-7a** in 28% yield. In contrast, diastereoselectivity was opposite for **9c**, and ***tc*-7e** was obtained as a major product in 75% yield along with ***tt*-7e** as a minor product in 17% yield. The observed difference in diastereoselectivity certainly reflected the difference in the geometry of the lithium enolates that formed from **9b** and **9c**. Interestingly, the reaction of dimethyl dienedioate **6c** (R' = Me) with phenyllithium in THF at –78 °C gave *trans,trans*-product ***tt*-7e** in 19% yield as a major product and ***tc*-7e** in 3% yield, showing the same stereochemical tendency as that of di-*tert*-butyl bis(enoate) **6b**. These results clearly indicate that the geometry of the lithium enolate that formed by the deprotonation of **9b** should be the same as that formed by the conjugate addition of **6b**, whereas those should be different between dimethyl esters **9c** and **6c**.

The deprotonation of methyl ester **9c** probably proceeded via 6-membered transition state **C** according to the Ireland model,[18] where the 1,3-diaxial interaction between the α-substituent of the ester and the isopropyl group of LDA was avoided, to give enolates with *Z*-geometry. Hence, ***tc*-7e** was obtained as a major product via the conjugate addition through s-*cis* transition state **D**. Indeed, deprotonation of **9c** with LDA in 23% HMPA–THF,[18] under which an *E*-enolate should formed via an open transition state, led to the opposite diastereoselectivity, giving ***tt*-7e** as a major product in 21% yield along with ***tc*-7e** in 9% yield. The low yields were due to competitive γ-deprotonation of the alkenoate moiety giving rise to the corresponding deconjugated *Z*- and *E*-alkenoates in 28% and 6% yield, respectively.

Deprotonation of ketones by LDA preferentially gives *E*-enolate via analogous transition states to **A** to avoid steric repulsion between the two substituents on the carbonyl carbons.[18] Therefore, it is highly probable that the deprotonation of *tert*-butyl ester **9b** mainly proceeded via transition state **A** due to the bulkiness of the α-substituent and the *tert*-butoxy moiety, giving *E*-enolate. As a consequence, ***tt*-7a** was produced as a major product by subsequent intramolecular conjugate addition via s-*cis* transition state **B**. All these results lead to the conclusion that the lithium enolate intermediate should undergo the intramolecular conjugate addition in s-*cis* conformation, and consequently, that the both conjugate addition should proceed with the alkenoate moieties in s-*cis* conformation as proposed in the above possibility (1).



Scheme 4 Cyclization of Monophenyl Adducts **5b** and **5c** with LDA.

In summary, we have developed the chiral ligands-mediated asymmetric conjugate addition cascade of nonadienedioate with organolithiums to give cyclohexanes bearing three contiguous stereogenic centers with *trans,trans*-configuration in high optical purity. Based on the stereochemical consideration, the preferred alkenoate conformation in the conjugate addition was confirmed to be s-*cis* giving *E*-enolate. This methodology enables the formation of two C–C bonds and three stereogenic centers in one pot to give synthetically useful chiral cyclohexane derivatives.

All melting points are uncorrected. Silica gel was used for column chromatography. ^{1}H and ^{13}C NMR (500 and 125 MHz, respectively) were measured in $CDCl_3$ unless otherwise mentioned. Chemical shifts and coupling constants are presented in ppm δ relative to tetramethylsilane and Hz, respectively. The wavenumbers of maximum absorption peaks of IR spectroscopy are presented in cm^{-1}. Chiral ligand **1** was prepared as previously described,[19] while **8** is commercially available. Preparation and physical and spectroscopic data of **6b**, **7a**, **7c** and **7d** were previously reported. [15b]

(*E*,*E*)-Bis-(2,6-di-*tert*-butyl-4-methoxyphenyl) nona-2,7-dienedioate (6a)

To a stirred solution of triphenylphosphine (525 g, 2.0 mol) in toluene (1.0 L) was added ethyl bromoacetate (0.22 L, 2.0 mol) dropwise over 1 h at rt. After 5 h, the mixture was filtered. The residue was washed with toluene (1.0 L) and hexane (0.80 L), and then suspended in H_2O (4.0 L). To the suspension cooled in an ice-water bath, was added aqueous 10% NaOH (0.80 L) dropwise over 1 h. The suspension was filtered, and the residue was washed with H_2O (0.25 L × 3) to give ylide (643 g, 92%) as a white solid of mp 120–122 °C. To a stirred suspension of the ylide (572 g, 1.64 mol) in toluene (1.2 L) was dropwise added a solution of glutaraldehyde (65 g, 0.65 mol) in toluene (0.10 L) at rt. After 18 h, the mixture was filtered, and the residue was washed with hexane (0.50 L). The combined filtrate and washings were concentrated *in vacuo* to give unsaturated ester as an yellow oil (255 g). To a stirred solution of the ester in EtOH (0.32 L) was added a solution of NaOH (130 g, 3.3 mol) in H_2O (0.32 L) at rt. After 2 h, the mixture was concentrated *in vacuo*, and H_2O (0.40 L) was added. The mixture was filtered, and the filtrate was acidified with aqueous 10% HCl (0.70 L) to give dicarboxylic acid[20] as a white solid. The resulting white solid (47 g) was collected by filtration. To a solution of the carboxylic acid (200 mg, 1.09 mmol) and 2,6-di-*tert*-butyl-4-methoxyphenol (513 mg, 2.17 mmol) in toluene (3 mL) was added TFAA (0.92 mL, 6.5 mmol) at rt. After stirred for 6 days at 40 °C, the mixture was cooled in an ice-water bath, and aqueous 10% NaOH (6 mL) was dropwise added over 5 min. After stirred for 30 min at rt, the mixture was extracted with AcOEt (30 mL × 3). The combined organic layers were washed with 10% NaOH (40 mL), 10% HCl (40 mL), saturated $NaHCO_3$ (40 mL), and brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give brown oil (685 mg), which was purified by column chromatography (hexane/AcOEt = 20/1) to give the title compound (340 mg, 50%) as a white solid of mp 171.5–172.0 °C (MeOH) along with the following products: R_f = 0.2 (hexane/Et_2O = 6/1). ^{1}H NMR: 1.33 (s, 36H), 1.80 (quintet, J = 7.3, 2H), 2.39 (m, 4H), 3.80 (s, 6H), 6.13 (d, J = 15.6, 2H), 6.87 (s, 4H), 7.16 (dt, J = 15.6, 6.7, 2H). ^{13}C NMR: 26.1 (CH_2), 31.4 (CH_3), 31.6 (CH_2), 35.6 (C), 55.2 (CH_3), 111.6 (CH), 122.7 (CH), 141.4 (C), 143.5 (C), 150.3 (CH), 156.2 (C), 166.8 (C). IR ($CDCl_3$): 1730, 1650, 1590. EIMS *m/z*: 621 (M + H), 385, 329, 236. Anal. calcd for $C_{39}H_{56}O_6$: C, 75.45; H, 9.09. Found: C, 75.18; H, 9.04.

(*E*,*Z*)-Bis-(2,6-di-*tert*-butyl-4-methoxyphenyl) nona-2,7-dienedioate

A yellow oil (89 mg, 13%): R_f = 0.3 (hexane/Et_2O = 6/1). ^{1}H NMR: 1.30 (s, 18H), 1.33 (s, 18H), 1.70 (quintet, J = 7.6, 2H), 2.33 (m, 2H), 2.78 (m, 2H), 3.791 (s, 3H), 3.794 (s, 3H), 6.07 (d, J = 15.6, 1H), 6.14 (d, J = 11.3, 1H), 6.47 (dt, J = 11.3, 7.6, 1H), 6.85 (s, 2H), 6.87 (s, 2H), 7.14 (dt, J = 15.6, 6.7, 1H). ^{13}C NMR: 27.2 (CH_2), 28.6 (CH_2), 31.3 (CH_3), 31.4 (CH_3), 32.1 (CH_2), 35.5 (C), 35.6 (C), 55.17 (CH_3), 55.22 (CH_3), 111.5 (CH), 111.6 (CH), 120.8 (CH), 122.2 (CH), 141.2 (C), 141.5 (C), 143.5 (C), 143.6 (C), 150.9 (CH), 151.8 (CH), 156.18 (C), 156.22 (C), 166.6 (C), 166.9 (C). IR (neat): 1740, 1640, 1590. EIMS *m/z*: 621 (M + H), 385, 329, 236. Anal. calcd for $C_{39}H_{56}O_6$: C, 75.45; H, 9.09. Found: C, 75.42; H, 9.33.

(*Z*,*Z*)-Bis-(2,6-di-*tert*-butyl-4-methoxyphenyl) nona-2,7-dienedioate

A yellow oil (4 mg, 1%): R_f = 0.4 (hexane/Et_2O = 6/1). ^{1}H NMR: 1.24 (s, 36H), 1.55 (m, 2H), 2.66 (m, 4H), 3.72 (s, 6H), 6.00 (d, J = 11.3, 2H), 6.38 (dt, J = 11.3, 7.7, 2H), 6.78 (s, 4H). ^{13}C NMR: 27.9 (CH_2),–28.4 (CH_2), 31.4 (CH_3), 35.6 (C), 55.2 (CH_3), 111.6 (CH), 120.4 (CH), 141.3 (C), 143.5 (C), 152.3 (CH), 156.2 (C), 166.7 (C). IR (neat): 1740, 1640, 1590. EIMS *m/z*: 621 (M + H), 385, 329, 236. HRMS–EI (*m/z*): $[M]^+$ calcd for $C_{39}H_{56}O_6$, 620.4077; found, 620.4089.

(*E*,*E*)-8-(2,6-di-*tert*-butyl-4-methoxyphenyloxycarbonyl)oct-2,7-dienoic acid

A yellow oil (58 mg, 14%): R_f = 0.1 (hexane/Et_2O = 6/1). ^{1}H NMR: 1.33 (s, 18H), 1.74 (m, 2H), 2.31 (m, 2H), 2.36 (m, 2H), 3.79 (s, 3H), 5.87 (d, J = 15.9, 1H), 6.11 (d, J = 15.9, 1H), 6.86 (s, 2H), 7.08 (dt, J = 15.9, 7.1, 1H), 7.13 (dt, J = 15.9, 6.7, 1H). ^{13}C NMR: 26.1 (CH_2), 31.3 (CH_3), 31.5 (CH_2), 31.6 (CH_2), 35.6 (C), 55.2 (CH_3), 111.6 (CH), 121.4 (CH), 122.7 (CH), 141.4 (C), 143.5 (C), 150.3 (CH), 150.7 (CH), 156.2 (C), 166.8 (C), 171.5 (C). IR (neat): 1730, 1700, 1640. EIMS *m/z*: 402 (M^+), 236. HRMS-EI (*m/z*): $[M]^+$ calcd for $C_{24}H_{34}O_5$, 402.2406; found, 402.2393.

General procedure for asymmetric conjugate addition cascade; (1*S*,2*S*,3*S*)- and (1*R*,2*S*,3*S*)-*tert*-butyl 2-*tert*-butoxycarbonyl-3-phenylcyclohexaneacetate (*tt*-7a and *tc*-7a) (Table 1, entry 1)

To a solution of **1** (10.2 g, 42 mmol) in toluene (260 mL) was added a solution of PhLi (1.83 M; 16.4 mL, 30 mmol) in cyclohexane–Et_2O (7/3) at –78 °C, and the resulting solution was stirred for 20 min at the same temperature. A solution of **6b** (2.96 g, 10 mmol) in toluene (20 mL) was added at –78 °C, and the mixture was stirred for 30 min at the same temperature. The reaction was quenched by the addition of saturated NH_4Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc. The combined organic layers were successively washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Column chromatography (hexane/EtOAc = 20/1) gave ***tt*-7a** (1.86 g, 50%) with 71% ee and ***tc*-7a** (339 mg, 9%) with 3% ee as white solids, and **1** (10.2 g, quantitative recovery) as a colorless solid.

(1*S*,2*R*,3*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)-3-butylcyclohexanacetate (*tt*-7b) (Table 1, entry 4)

R_f = 0.6 (hexane/EtOAc = 9/1). A colorless oil. 86% ee (HPLC: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 1000/1, 0.4 mL/min, 230 nm; major 14.5 min, minor 17.5 min). $[\alpha]_D^{25}$ +12.1 (*c* 2.01, benzene). ^{1}H NMR (C_6D_6): 0.63–1.50 (m, 10H), 0.88 (t, J = 7.3, 3H), 1.37

(s, 9H), 1.38 (s, 9H), 1.56 (m, 1H), 1.66 (m, 1H), 1.81 (t, J = 11.0, 1H), 1.95 (m, 1H), 2.11 (dd, J = 10.0, 15.0, 1H), 2.25 (m, 1H), 2.50 (dd, J = 3.1, 15.0, 1H). ^{13}C NMR (C_6D_6): 14.2 (CH_3), 23.3 (CH_2), 25.7 (CH_2), 28.08 (CH_3), 28.11 (CH_3), 28.6 (CH_2), 30.8 (CH_2), 31.5 (CH_2), 34.5 (CH_2), 38.0 (CH_2), 40.1 (CH), 40.9 (CH), 56.4 (CH), 79.6 (C), 79.7 (C), 171.4 (C), 174.3 (C). IR (neat): 1730. EIMS *m/z*: 355 (M + H), 298, 242. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 71.41; H, 11.04.

(1*R*,2*R*,3*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)-3-butylcyclohexanacetate (*tc*-7b) (Table 1, entry 3)

R_f = 0.6 (hexane/EtOAc = 9/1). A colorless oil. $[\alpha]_D^{25}$ –15.5 (*c* 0.51, $CHCl_3$). ^{1}H NMR: 0.88 (t, J = 7.0, 3H), 1.01 (m, 1H), 1.06 (m, 1H), 1.28 (m, 4H), 1.43 (s, 9H), 1.45 (s, 9H), 1.47 (m, 4H), 1.67 (m, 2H), 1.80 (m, 1H), 2.24 (dd, J = 4.3, 8.6, 1H), 2.28 (dd, J = 9.5, 15.3, 1H), 2.35 (dd, J = 5.2, 15.3, 1H), 2.41 (m, 1H). ^{13}C NMR: 14.1 (CH_3), 20.1 (CH_2), 22.9 (CH_2), 28.08 (CH_3), 28.11 (CH_3), 29.0 (CH_2), 29.1 (CH_2), 29.2 (CH_2), 32.3 (CH), 33.7 (CH_2), 34.0 (CH_2), 36.1 (CH), 51.5 (CH), 80.0 (C), 172.6 (C), 174.0 (C). IR (neat): 1720. EIMS *m/z*: 355 (M + H), 298, 242. Anal. Calcd for $C_{21}H_{38}O_4$: C, 71.14; H, 10.80. Found: C, 70.97; H, 10.52.

(*S*,*E*)-Bis(2,6-di-*tert*-butyl-4-methoxyphenyl) 5-phenylnona-2-enedioate (9a) (eq 1)

R_f = 0.3 (hexane/Et_2O = 4/1). 87% ee (HPLC: Daicel Chiralpak AD-H, hexane/*i*-PrOH = 100/1, 0.5 mL/min, 254 nm; minor 39.4 min, major 42.8 min). The absolute configuration was tentatively assigned by analogy. The yield was based on ^{1}H NMR and the specific rotation was not measured because **9a** was inseparable from chiral ligand **1**. The structure was identified by comparing its ^{1}H and ^{13}C NMR with those of (±)-**9a** that was prepared from **6a** and phenyllithium (1.5 equiv) without **1** in THF at –78 °C and fully characterized: ^{1}H NMR: 1.06 (s, 9H), 1.29 (s, 9H), 1.30 (m, 9H), 1.32 (m, 9H), 1.37 (m, 1H), 1.43 (m, 1H), 1.75 (m, 1H), 1.86 (m, 1H), 2.26 (m, 2H), 2.90 (dd, J = 6.1, 17.7, 1H), 2.97 (dd, J = 7.6, 17.7, 1H), 3.23 (m, 1H), 3.76 (s, 3H), 3.79 (s, 3H), 6.00 (d, J = 15.9, 1H), 6.79 (d, J = 3.1, 1H), 6.83 (d, J = 3.1, 1H), 6.85 (s, 2H), 7.06 (dt, J = 15.9, 6.7, 1H), 7.20–7.31 (m, 5H). ^{13}C NMR: 25.6 (CH_2), 31.0 (CH_3), 31.3 (CH_3), 32.1 (CH_2), 35.2 (C), 35.4 (C), 35.46 (CH_2), 35.51 (C), 40.8 (CH), 43.0 (CH_2), 55.1 (CH_3), 111.5 (CH), 122.1 (CH), 126.6 (CH), 127.8 (CH), 128.5 (CH), 143.2 (C), 143.4 (C), 143.45 (C), 143.48 (C), 151.2 (CH), 156.1 (C), 166.8 (C), 172.3 (C). IR ($CHCl_3$): 1750, 1730, 1650, 1590. FABMS *m/z*: 699 (M + H), 463. Anal. calcd for $C_{45}H_{62}O_6$: C, 77.33; H, 8.94. Found: C, 77.09; H, 8.94.

Conjugate addition cascade in the absence of chiral ligand in THF (eq 2 and note 16); Di-*tert*-butyl 3,7-diphenylnonandioate (10a)

A 1.73 M cyclohexane–Et_2O solution of PhLi (17.3 mL, 30 mmol) was diluted with THF (260 mL), and to the solution, was added a solution of **6b** (2.96 g, 10 mmol) in THF (40 mL) at –78 °C. After 0.5 h, MeOH (10 mL) and saturated NH_4Cl (200 mL) were successively added. The mixture was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, and then dried over Na_2SO_4. Concentration followed by column chromatography (hexane/EtOAc = 15/1) gave (±)-***tt*-7a** (344 mg, 9%) and (±)-***tc*-7a** (138 mg, 4%) as white solids, and the title compound (3.57 g, 79%) as a colorless oil: R_f = 0.4 (hexane/EtOAc = 9/1). ^{1}H NMR: 1.00–1.05 (m, 2H), 1.27 (s, 18H), 1.51–1.63 (m, 4H), 2.40 (dd, J = 8.6, 15.0, 2H), 2.47 (dd, J = 7.0, 15.0, 2H), 2.94 (m, 2H,), 7.07–7.29 (m, 10H). ^{13}C NMR: 24.7 (CH_2), 24.9 (CH_2), 27.9 (CH_3), 36.2 (CH_2), 42.18 (CH), 42.23 (CH), 42.9 (CH_2), 43.0 (CH_2), 80.1 (C), 126.21 (CH), 126.24 (CH), 127.50 (CH), 127.52 (CH), 128.18 (CH), 128.21 (CH), 144.0 (C), 144.1 (C), 171.6 (C), 171.7 (C). IR (neat): 1730. FABMS *m/z*: 453 (M + H). HRMS–FAB (m/*z*): $[M + H]^+$ calcd for $C_{29}H_{41}O_4$, 453.3005; found, 453.2998.

Alternative method (note 16): To a solution of **6b** (296 mg, 1.0 mmol) in THF (30 mL) was added a 1.83 M cyclohexane–Et_2O solution of PhLi (1.07 mL, 2.0 mmol) at –78 °C. After 0.5 h, MeOH (1 mL) and saturated NH_4Cl (40 mL) were successively added. The mixture was extracted with EtOAc. The organic layer was washed with saturated $NaHCO_3$ and brine, and dried over Na_2SO_4. Concentration followed by column chromatography (hexane/EtOAc = 20/1) gave (±)-***tt*-7a** (197 mg, 52%) and (±)-***tc*-7a** (16 mg, 5%) as white solids, and **10a** (37 mg, 8%) as a colorless oil. Recrystallization of (±)-***tt*-7a** from MeOH gave colorless needles of mp 82–83 °C.

Preparation of monophenyl adducts 9b and 9c (Scheme 3); (*E*)-*tert*-butyl 7-(tetrahydro-2*H*-pyran-2-yloxy)hept-2-enoate (12)

To a solution of (*E*)-*tert*-butyl 7-hydroxyhept-2-enoate (**11**)[17] (2.22 g, 11 mmol) in dry $CHCl_3$ (45 mL) were added 3,4-dihydro-2*H*-pyran (1.5 mL, 17 mmol) and then PPTS (280 mg, 1.1 mmol) in $CHCl_3$ (5 mL). The mixture was stirred for 14 h at rt, and diluted with Et_2O (60 mL). The whole was washed with half saturated NaCl (80 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*, and the resulting colorless oil (3.09 g) was purified by column chromatography (hexane/AcOEt = 3/1) to give the title compound (3.02 g, 96%) as a colorless oil: R_f = 0.7 (hexane/AcOEt = 2/1). ^{1}H NMR: 1.48 (s, 9H), 1.50–1.62 (m, 8H), 1.71 (m, 1H), 1.83 (m, 1H), 2.21 (m, 2H), 3.39 (m, 1H), 3.50 (m, 1H), 3.75 (m, 1H), 3.86 (m, 1H), 4.57 (m, 1H), 5.75 (d, J = 15.6, 1H), 6.86 (dt, J = 15.6, 7.0, 1H). ^{13}C NMR: 19.6 (CH_2), 24.8 (CH_2), 25.4 (CH_2), 28.1 (CH_3), 29.2 (CH_2), 30.7 (CH_2), 31.8 (CH_2), 62.3 (CH_2), 67.1 (CH_2), 79.9 (C), 98.8 (CH), 123.1 (CH), 147.6 (CH), 166.0 (C). IR (neat): 1710, 1650. EIMS *m/z*: 283 (M – H), 227. Anal. calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.61; H, 10.15.

***tert*-Butyl 7-hydroxy-3-phenylheptanoate (13)**

To a solution of PhLi (1.45 M; 2.1 mL, 3.0 mmol) in dry THF (8 mL) was added a solution of **12** (284 mg, 1.0 mmol) in dry THF (2 mL) at –78 °C. The mixture was stirred for 30 min at the same temperature, and MeOH (2 mL) and then saturated NH_4Cl (20 mL) were added. The whole was extracted with AcOEt (20 mL × 3), and the combined organic layers were washed with saturated $NaHCO_3$ (40 mL) and brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give yellow oil (432 mg) including a phenyl adduct. To a solution of the yellow oil in EtOH (8 mL) was added PPTS (25 mg, 0.1 mmol). After stirred for 12 h at 50 °C, the mixture was concentrated *in vacuo* and diluted with H_2O (40 mL). The whole was extracted with Et_2O (30 mL × 3), and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give yellow oil (335 mg), which was purified by column chromatography (hexane/AcOEt = 2/1) to give the title compound (254 mg, 91% over 2 steps) as a colorless oil: R_f = 0.1 (hexane/AcOEt = 5/1). ^{1}H NMR: 1.21–1.27 (m, 2H), 1.30 (s, 9H), 1.49–1.67 (m, 4H), 1.60 (s, 1H), 2.47 (dd, *J* = 8.3, 14.7, 1H), 2.54 (dd, *J* = 7.3, 14.7, 1H), 3.03 (m, 1H), 3.57 (t, *J* = 6.4, 2H), 7.18–7.28 (m, 5H). ^{13}C NMR: 23.4 (CH_2), 27.8 (CH_3), 32.5 (CH_2), 36.0 (CH_2), 42.4 (CH), 42.9 (CH_2), 62.6 (CH_2), 80.2 (C), 126.3 (CH), 127.5 (CH), 128.2 (CH), 143.9 (C), 171.7 (C). IR (neat): 3400, 1720. EIMS *m/z*: 222 (M + H – *t*-Bu), 205. Anal. calcd for $C_{17}H_{26}O_3$: C, 73.34; H, 9.41. Found: C, 73.54; H, 9.62.

tert-Butyl 7-formyl-3-phenylhexanoate (14)

To a solution of **13** (27.9 g, 0.10 mol) in dry toluene and DMSO (330 mL each), were added pyridine (8.1 mL, 0.10 mol), TFA (3.9 mL, 0.050 mol), and then DCC (62 g, 0.30 mol) at rt. The mixture was stirred for 18 h at rt, diluted with toluene (1 L), and filtered. The filtrate was washed with H_2O (1 L × 2) and brine (1 L), dried over Na_2SO_4, and concentrated *in vacuo* to give yellow oil (76.8 g), which was purified by column chromatography (hexane/ AcOEt = 10/1) to give the title compound (24 g, 87%) as a colorless oil: R_f = 0.5 (hexane/AcOEt = 3/1). ^{1}H NMR: 1.30 (s, 9H), 1.45–1.70 (m, 4H), 2.37 (m, 2H), 2.48 (dd, *J* = 8.3, 15.0, 1H), 2.54 (dd, *J* = 7.4, 14.7, 1H), 3.04 (m, 1H), 7.18–7.29 (m, 5H), 9.68 (s, 1H). ^{13}C NMR: 19.9 (CH_2), 27.8 (CH_3), 35.5 (CH_2), 42.3 (CH), 42.8 (CH_2), 43.6 (CH_2), 80.3 (C), 126.5 (CH), 127.5 (CH), 128.4 (CH), 143.4 (C), 171.4 (C), 202.3 (CH). IR (neat): 1730, 1710. EIMS *m/z*: 220 (M + H – *t*-Bu). Anal. calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.62; H, 8.88.

(*E*)-Di-*tert*-butyl 7-phenylnona-2-enedioate (9b)

To a suspension of *tert*-butyl triphenylphosphoranylideneacetate (40 g, 0.11 mol) in toluene (140 mL) was added a solution of **14** (24.0 g, 87 mmol) in toluene (40 mL) over 10 min. The mixture was stirred for 16 h at rt, diluted with hexane (100 mL), and filtered. Concentration of the filtrate *in vacuo* gave yellow oil (34.7 g), which was purified by column chromatography (hexane/AcOEt = 20/1) to give the title compound (*E*:*Z* = 97:3; 28.4 g, 88%) as a colorless oil: R_f = 0.6 (hexane/AcOEt = 4/1). ^{1}H NMR: 1.27 (m, 1H), 1.30 (s, 9H), 1.46 (s, 9H), 1.60 (m, 1H), 1.65 (m, 2H), 2.11 (m, 2H,), 2.47 (dd, *J* = 8.3, 14.7, 1H), 2.52 (dd, *J* = 7.0, 14.7, 1H), 3.02 (m, 1H), 5.67 (d, *J* = 15.6, 1H), 6.76 (dt, *J* = 15.6, 7.6, 1H), 7.15–7.30 (m, 5H). ^{13}C NMR: 25.8 (CH_2), 27.9 (CH_3), 28.1 (CH_3), 31.8 (CH_2), 35.7 (CH_2), 42.3 (CH), 42.9 (CH_2), 79.9 (C), 80.2 (C), 123.1 (CH), 126.4 (CH), 127.5 (CH), 128.3 (CH), 143.7 (C), 147.4 (CH), 165.9 (C), 171.5 (C). IR (neat): 1720, 1650. EIMS *m/z*: 375 (M + H), 340, 318. Anal. calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 74.04; H, 9.31.

(*E*)-Dimethyl 7-phenylnona-2-enedioate (9c)

To a solution of **9b** (374 mg, 1.0 mmol) in MeOH (12 mL) was added conc. H_2SO_4 (0.05 mL) at rt. The mixture was heated under reflux for 2 h and neutralized by the addition of 10% Na_2CO_3 (0.5 mL). The whole was extracted with Et_2O (30 mL × 3), and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the title compound (280 mg, 97%) as a yellow oil: R_f = 0.5 (hexane/AcOEt = 3/1). ^{1}H NMR: 1.28 (m, 1H), 1.33 (m, 1H), 1.65 (m, 2H), 2.14 (m, 2H), 2.58 (dd, *J* = 8.0, 15.6, 1H), 2.62 (dd, *J* = 7.3, 15.6, 1H), 3.09 (m, 1H), 3.58 (s, 3H), 3.71 (s, 3H), 5.75 (d, *J* = 15.6, 1H), 6.87 (dt, *J* = 15.6, 7.1, 1H), 7.15–7.31 (m, 5H). ^{13}C NMR: 25.7 (CH_2), 31.9 (CH_2), 35.4 (CH_2), 41.5 (CH_2), 41.9 (CH), 51.3 (CH_3), 51.4 (CH_3), 121.0 (CH), 126.5 (CH), 127.3 (CH), 128.5 (CH), 143.5 (C), 149.0 (CH), 166.9 (C), 172.6 (C). IR (neat): 1740, 1720, 1660. EIMS *m/z*: 290 (M^+), 258. Anal. calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.51; H, 7.64.

Cyclization of 9b (Scheme 4)

To a solution of *i*-Pr_2NH (0.17 mL, 1.2 mmol) in dry THF (3 mL) were added a 1.56 M hexane solution of BuLi (0.77 mL, 1.2 mmol) and, after 20 min, a solution of **9b** (374 mg, 1.0 mmol) in dry THF (2 mL) at –78 °C under argon atmosphere. The mixture was stirred for 15 min at the same temperature, and MeOH (10 mL) and then saturated NH_4Cl (40 mL) were added. The whole was extracted with AcOEt (30 mL × 3). The combined organic layers were washed with 10% HCl (40 mL), H_2O (40 mL), saturated $NaHCO_3$ (40 mL), and brine (40 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give a pale yellow solid (388 g), which was purified by column chromatography (hexane/AcOEt = 9/1) to give a 7:3 mixture of ***tt*-7a** and ***tc*-7a** (351 mg, 94%) as a white solid.

Cyclization of 9c (Scheme 4)

The above procedure using **9c** (290 mg, 1.0 mmol) and purification by column chromatography (hexane/AcOEt = 5/1) gave an 18:82 mixture of ***tt*-7e** and ***tc*-7e** (266 mg, 92%) as a white solid.

The compounds ***tt*-7e** and ***tc*-7e** were inseparable and characterized by being prepared from ***tt*-7a** and ***tc*-7a**, respectively.

(1*R*,2*S*,3*S*)-Methyl 2-(methoxycarbonyl)-3-phenylcyclohexaneacetate (*tc*-7e)

To TFA (3.4 mL, 45 mmol) was added ***tc*-7a** (167 mg, 0.45 mmol) at rt. The mixture was stirred for 0.5 h at rt and concentrated *in vacuo* to give a white solid, which was dissolved in MeOH (20 mL). To the solution was added a solution of CH_2N_2 in Et_2O until no more N_2 gas evolved. To the yellow solution was added HOAc (10 drops), and the whole was concentrated. The resulting residue was purified by column chromatography (hexane/EtOAc = 4/1) to give the title compound (129 mg, 99%) as a white solid of mp 62–64 °C: R_f = 0.4 (hexane/EtOAc = 4/1). 3% ee (HPLC: Daicel Chiralcel OJ, hexane/*i*-PrOH = 100/1, 0.5 mL/min, 254 nm; major 30.0 min, minor 36.0 min). $[\alpha]_D^{25}$ –12.2 (*c* 1.12, $CHCl_3$). ^{1}H NMR (CD_3OD): 1.45 (m, 1H), 1.61 (m, 2H), 1.70 (m, 1H), 1.73 (m, 1H), 1.83 (m, 1H), 2.50 (dd, *J* = 7.7, 16.2, 1H), 2.63 (dd, *J* = 6.5, 16.2, 1H), 2.73 (m, 1H), 2.91 (dt, *J* = 4.0, 12.2, 1H), 3.00 (dd, *J* = 4.0, 12.2, 1H), 3.37 (s, 3H), 3.64 (s, 3H), 7.12–7.22 (m, 5H). ^{13}C NMR (CD_3OD): 21.7 (CH_2), 31.5 (CH_2), 34.0 (CH), 34.2 (CH_2), 35.9 (CH_2), 41.8 (CH), 51.8 (CH_3), 52.1 (CH_3), 52.6 (CH), 127.3 (CH), 128.4 (CH), 129.3 (CH), 146.1 (C), 175.0 (C), 175.7 (C). IR (Nujol): 1720. EIMS *m/z*: 290 (M^+), 259, 230. Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.30; H, 7.61.

Methyl (1*S*,2*S*,3*S*)-2-(Methoxycarbonyl)-3-phenylcyclohexaneacetate (*tt*-7e)

The same procedure as that from ***tc*-7a** to ***tc*-7e** gave ***tt*-7e** with 71% ee in 96% yield from ***tt*-7a** with 71% ee as colorless oil: $[\alpha]^{25}_D$ +23.2 (*c* 1.08, $CHCl_3$). The ee was determined by HPLC (Daicel Chiralcel OJ, hexane/*i*PrOH = 100/1, 0.5 mL/min, 254 nm; minor 30.0 min, major 42.7 min).

A colorless oil. R_f = 0.4 (hexane/AcOEt = 4/1). ^{1}H NMR: 1.16 (m, 1H), 1.52 (m, 2H), 1.87 (m, 2H), 1.93 (m, 1H), 2.16 (dd, *J* = 8.9, 14.7, 1H), 2.23 (m, 1H), 2.33 (dd, *J* = 3.4, 14.7, 1H), 2.38 (t, *J* = 11.3, 1H), 2.82 (dt, *J* = 3.4, 11.3, 1H), 3.35 (s, 3H), 3.67 (s, 3H), 7.15–7.27 (m, 5H). ^{13}C NMR: 25.5 (CH_2), 31.2 (CH_2), 33.4 (CH_2), 37.1 (CH), 39.4 (CH_2), 47.4 (CH), 51.1 (CH_3), 51.5 (CH_3), 55.9 (CH), 126.5 (CH), 127.2 (CH), 128.3 (CH), 143.7 (C), 172.4 (C), 174.4 (C). IR (neat): 1740, 1720. EIMS *m/z*: 290 (M^+), 259, 230. Anal. calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.20; H, 7.50.

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