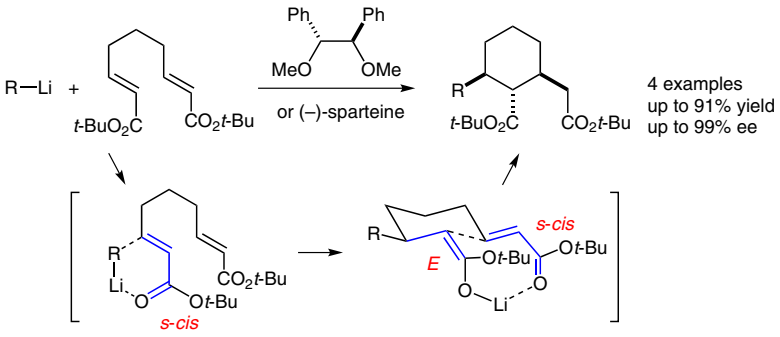
Synthesis K. Nishimura et al. Special Topic

Cyclic Model for the Asymmetric Conjugate Addition of Organolithiums with Enoates

Katsumi Nishimura[a]
Naoshi Fukuyama[a]
Mitsuaki Yamashita[a]
Takaaki Sumiyoshi[a]
Yasutomo Yamamoto[b]
Ken-ichi Yamada[a]
Kiyoshi Tomioka[*a,b]

[a] Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan
[b] Faculty of Pharmaceutical Sciences, Doshisha Women's College of Liberal Arts, Kodo, Kyotanabe 610-0395, Japan
ktomioka@dwc.doshisha.ac.jp



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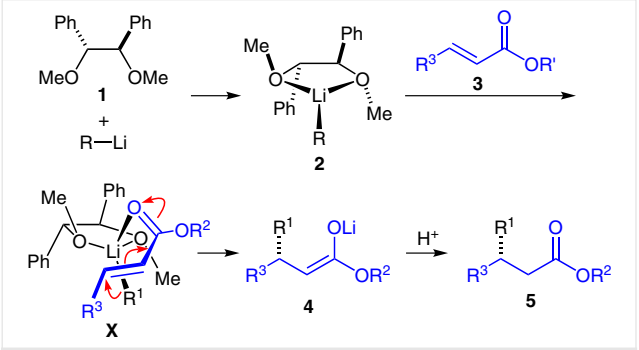
Abstract The chiral diether ligand controlled asymmetric conjugate addition of organolithiums to nona-2,7-dienedioates preferentially proceeds via the *s-cis* conformation with coordination of the carbonyl oxygen atom to the lithium to give a lithium *E*-enolate intermediate. Subsequent intramolecular conjugate addition of the enolate also proceeds via a cyclic transition state involving the lithium and the *s-cis*-enoate, resulting in *trans*,*trans*-trisubstituted cyclohexanes with high enantiomeric excesses and yields.

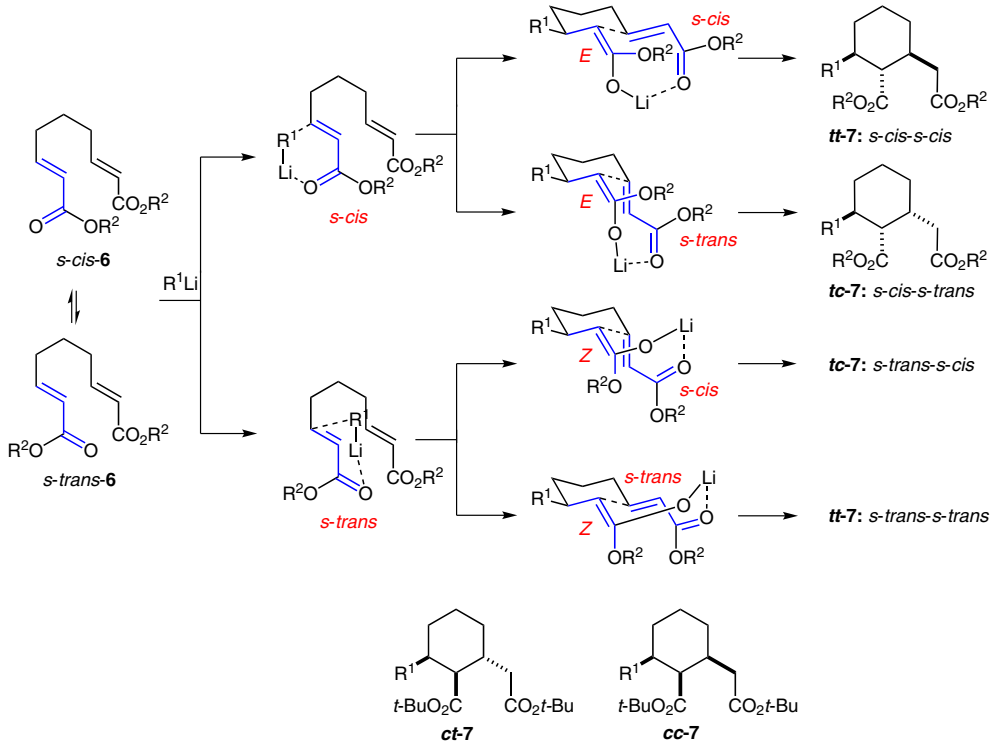
Key words chiral ligand, asymmetric synthesis, organolithiums, conjugate addition, cascade reaction

The asymmetric conjugate addition of a carbonucleophile to an electron-deficient olefin is one of the most attractive and powerful methods for the asymmetric construction of a carbon–carbon bond.[1] It is advantageous that the initial product of asymmetric conjugate addition of an organolithium to an α,β-unsaturated carbonyl compound is a chiral lithium enolate which can thus further react with an electrophile to form an additional bond. The conformation of the α,β-unsaturated carbonyl compound, namely *s-cis* or *s-trans*, is responsible for the facial selectivity of the conjugate addition and also for the *E*,*Z* geometry of the resulting enolate, which should then govern 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 studying the external chiral ligand controlled asymmetric conjugate addition reaction of a variety of lithiated nucleophiles, such as organolithiums, lithium ester enolates, lithium thiolates and lithium amides, to linear α,β-unsaturated imines,[3] enoates[4–6] and nitroolefins.[7] Our NMR studies have revealed that chiral diether ligand **1** and a lithium reagent form a 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 be situated on the up and down faces of the chelation, avoiding steric repulsion by the phenyl groups on the chiral centers (Scheme 1).[9] The reaction of complex **2** with an enoate **3** affords the 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 the cyclic reaction model **X**, in which the lithium atom is coordinated by the carbonyl oxygen atom of the *s-cis*-enoate on the olefin side. The olefin moiety is placed in the less crowded space, avoiding steric repulsion by the two methyl groups of **2** (Scheme 1).[3a,b,5b,10] Then, the R^1 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 the *s-trans*-enoate, instead of *s-cis*, was involved in the reaction, the *Z*-enolate with the opposite absolute configuration would result.



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



Scheme 2 Possible products of the conjugate addition–Michael cyclization cascade

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

The asymmetric conjugate addition of an organolithium[13,14] to a C_2-symmetric nona-2,7-dienedioate **6** is a cascade reaction,[15] providing a chiral cyclohexane **7** bearing three contiguous chiral centers, the stereochemistry of which provides an insight into the reactive conformation of the alkenoate that undergoes the conjugate addition (Scheme 2). The addition of an organolithium to *s-cis*-**6** preferentially gives *E*-enolate via a 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 the *E*- and *Z*-enolates through the *s-trans* conformation would give ***tc*-7** (*s-trans-s-cis* product) and ***tt*-7** (*s-trans-s-trans* product) as the major products, respectively. Herein, we report details of the stereochemistry of the asymmetric conjugate addition cascade preferentially giving ***tt*-7**, as well as confirmation of the preferred cyclic *s-cis* conformation of the alkenoate moieties.

At the outset of our studies, the cascade reaction of phenyllithium with bis(2,6-di-*tert*-butyl-4-methoxyphenyl) dienedioate **6a** was attempted in the presence of ligand **1** (Figure 1 and Equation 1).[4a] Thus, 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 minutes apart. After reaction for 20 minutes, simple conjugate addition product **9a** with 87% ee was obtained in 56% yield, along with 13% of recovered **6a**, without production of the desired cascade product **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.

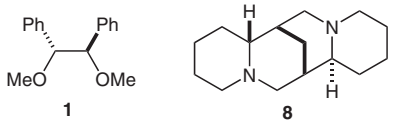
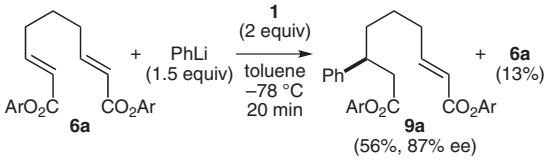
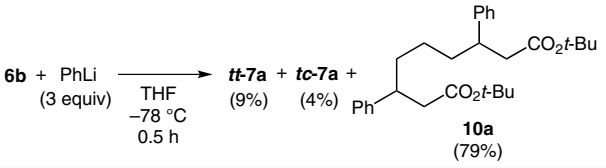


Figure 1 Chiral ligands for organolithium compounds



Equation 1

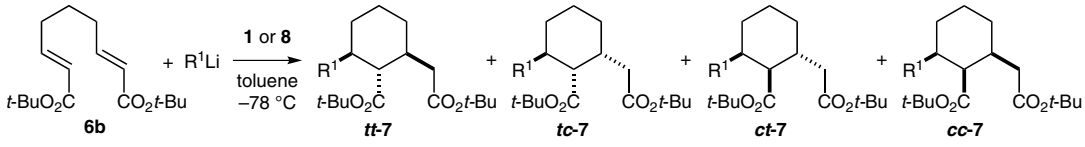
Then, di-*tert*-butyl ester **6b** of decreased steric hindrance was selected as the bis(enoate). To our delight, the reaction of **6b** and phenyllithium (3 equiv) complexed with ligand **1** (4.2 equiv) was completed within 30 minutes to give the desired cascade products *trans*,*trans*-cyclohexane ***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** (R^1 = Ph), were not obtained. It is noteworthy that **6b** mainly reacted with only 1 equivalent of phenyllithium; even though **6b** was added into the solution of an excess amount of phenyllithium and ligand **1**, only a slight amount of double phenylated product **10a** (see Equation 2) was produced (<10%). In contrast, when the reaction was conducted in tetrahydrofuran as a solvent without **1**, **10a** was mainly produced (79% yield, Equation 2), and only tiny amounts of ***tt*-7a** and ***tc*-7a** were obtained (9% and 4% yield, respectively).[16] These results clearly indicate that chiral ligand **1** significantly accelerates the intramolecular conjugate addition of the enolate to the intramolecular enoate.

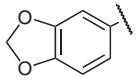
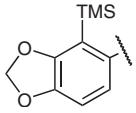


Equation 2

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 the aryllithium and the 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 (Table 1, entry 4), while the use of **1** as the 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 (Table 1, entry 2). Interestingly, the diastereoselection was perfectly controlled in the reactions using **8**, and neither ***tc*-7a** nor ***tc*-7b** was produced (Table 1, entries 2 and 4).

Table 1 Asymmetric Conjugate Addition Cascade[a]



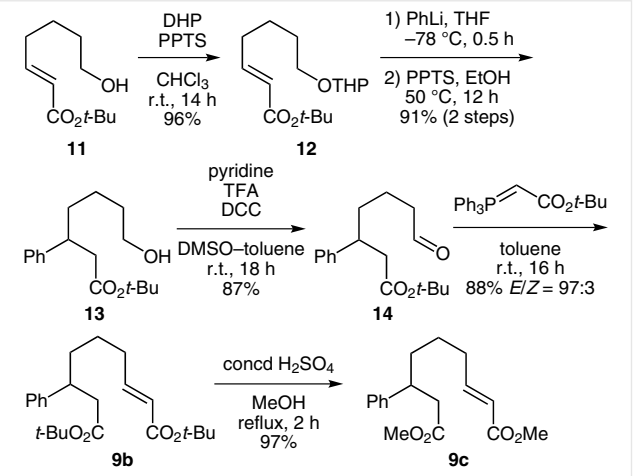
Entry	Ligand	R^1	7	*tt*-7		*tc*-7		*ct*-7	*cc*-7
				Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	Yield (%)
1[b]	**1**	Ph	**7a**	50	71[c]	9	3[c]	0	0
2	**8**	Ph	**7a**	75	23	0	–	0	0
3	**1**	Bu	**7b**	31	8	8	–	0	0
4	**8**	Bu	**7b**	91	86	0	–	0	0
5[b]	**1**		**7c**	40	74	10	72	0	0
6[b]	**1**		**7d**	68	99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

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

For the reaction of an aryllithium, installation of a removable bulky substituent, such as a trimethylsilyl group, at the *ortho* position was effective in enhancing the enantioselectivity (Table 1, 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 the Amaryllidaceae alkaloids (–)-lycorine[15a] and (+)-β-lycorane.[15b]

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

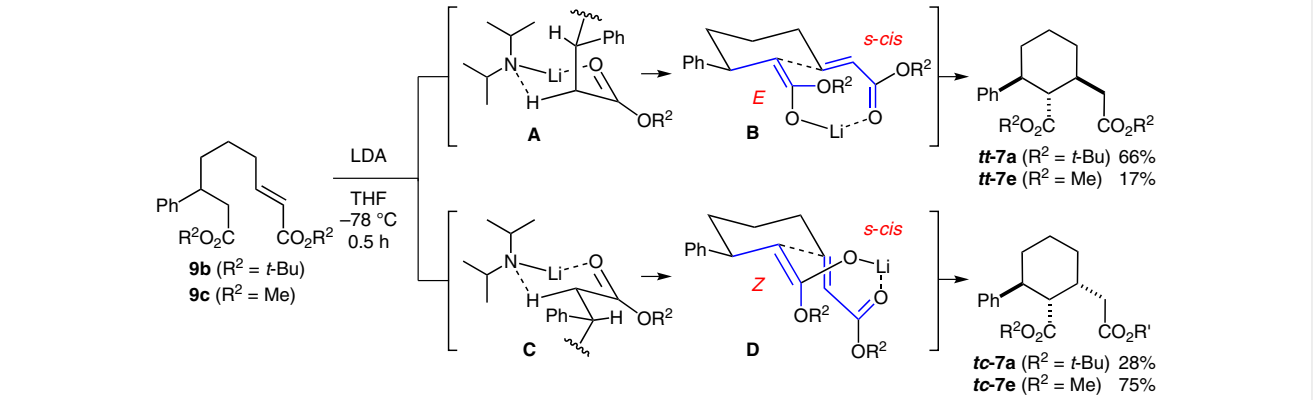


Scheme 3 Preparation of monophenyl adducts **9b** and **9c**

The di-*tert*-butyl ester **9b** and dimethyl ester **9c** of the monophenyl adduct were prepared from *tert*-butyl (*E*)-7-hydroxyhept-2-enoate (**11**)[17] (Scheme 3). The hydroxy group of **11** was protected with a tetrahydropyran-2-yl group, and then conjugate addition of phenyllithium followed by deprotection afforded **13**. Pfitzner–Moffatt oxidation of **13** and subsequent 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 lithium diisopropylamide (1.2 equiv) in tetrahydrofuran 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, the diastereoselectivity was opposite for **9c**, and ***tc*-7e** was obtained as the major product in 75% yield along with ***tt*-7e** as the minor product in 17% yield. The observed difference in diastereoselectivity certainly reflects the difference in the geometry of the lithium enolates that are formed from **9b** and **9c**. Interestingly, the reaction of dimethyl (*E*,*E*)-nona-2,7-dienedioate (**6c**) with phenyllithium in tetrahydrofuran at –78 °C gave *trans*,*trans*-product ***tt*-7e** (R^2 = Me) in 19% yield as the 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 is formed by the deprotonation of **9b** should be the same as that formed by the conjugate addition of **6b**, whereas those enolate geometries formed from dimethyl esters **9c** and **6c** should be different.

The deprotonation of methyl ester **9c** probably proceeds via six-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 lithium diisopropylamide is avoided, to give the enolate



Scheme 4 Cyclization of monophenyl adducts **9b** and **9c** with lithium diisopropylamide

with *Z* geometry. Hence, ***tc*-7e** is obtained as the major product via conjugate addition through the *s-cis* transition state **D**. Indeed, deprotonation of **9c** with lithium diisopropylamide in 23% hexamethylphosphoramide in tetrahydrofuran,[18] conditions under which an *E*-enolate should be formed via an open transition state, led to the opposite diastereoselectivity, giving ***tt*-7e** as the major product in 21% yield along with ***tc*-7e** in 9% yield. The low yields are 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 lithium diisopropylamide preferentially gives the *E*-enolates via analogous transition states to **A** to avoid steric repulsion between the two substituents on the carbonyl carbon.[18] Therefore, it is highly probable that the deprotonation of *tert*-butyl ester **9b** mainly proceeds via transition state **A** due to the bulkiness of the α-substituent and the *tert*-butoxy moiety, giving an *E*-enolate. As a consequence, ***tt*-7a** is produced as the major product by subsequent intramolecular conjugate addition via *s-cis* transition state **B**. All of these results lead to the conclusion that the lithium enolate intermediate should undergo the intramolecular conjugate addition in the *s-cis* conformation and, consequently, that both conjugate additions should proceed with the alkenoate moieties in the *s-cis* conformation as proposed in possibility (1) above.

In summary, we have developed a chiral ligand mediated asymmetric conjugate addition cascade reaction of nonadienedioates with organolithiums to give cyclohexanes bearing three contiguous stereogenic centers with *trans*,*trans* configuration in high optical purity. Based on stereochemical considerations, the preferred alkenoate conformation in the conjugate addition was confirmed to be *s-cis* giving *E*-enolate. This methodology enables the formation of two carbon–carbon 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 spectra (500 and 125 MHz, respectively) were measured on a JEOL EX-500 instrument in the solvents indicated. Chemical shifts and coupling constants are presented in ppm (δ) relative to tetramethylsilane and Hz, respectively. IR spectra were recorded on a Shimadzu IR-435 spectrophotometer and the wavenumbers of maximum absorption peaks are presented in cm^{-1}. Chiral ligand **1** was prepared as previously described,[19] while **8** is commercially available. The preparation and physical and spectroscopic data of **6b**, **7a**, **7c** and **7d** have been previously reported.[15b]

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

To a stirred solution of Ph_3P (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 r.t. 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 aq 10% NaOH (0.80 L) dropwise over 1 h. The suspension was filtered, and the residue was washed with H_2O (3 × 0.25 L) to give ylide (643 g, 92%) as a white solid; 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 r.t. 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 a 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 r.t. 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 aq 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 dicarboxylic 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 r.t. After being stirred for 6 d at 40 °C, the mixture was cooled in an ice–water bath, and aq 10% NaOH (6 mL) was dropwise added over 5 min. After being stirred for 30 min at r.t., the mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 10% NaOH (40 mL), 10% HCl (40 mL), sat. $NaHCO_3$ (40 mL) and brine (40 mL), then dried over Na_2SO_4 and concentrated in vacuo to give a brown oil (685 mg), which was purified by column chromatography (hexane–EtOAc, 20:1) to give **6a** along with three additional products, as listed below.

Compound 6a

White solid; yield: 340 mg (50%); mp 171.5–172.0 °C (MeOH).

R_f = 0.2 (hexane–Et_2O, 6:1).

IR ($CDCl_3$): 1730, 1650, 1590 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 36 H), 1.80 (quintet, *J* = 7.3 Hz, 2 H), 2.39 (m, 4 H), 3.80 (s, 6 H), 6.13 (d, *J* = 15.6 Hz, 2 H), 6.87 (s, 4 H), 7.16 (dt, *J* = 15.6, 6.7 Hz, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *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.

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

Yellow oil; yield: 89 mg (13%).

R_f = 0.3 (hexane–Et_2O, 6:1).

IR (neat): 1740, 1640, 1590 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 18 H), 1.33 (s, 18 H), 1.70 (quintet, *J* = 7.6 Hz, 2 H), 2.33 (m, 2 H), 2.78 (m, 2 H), 3.791 (s, 3 H), 3.794 (s, 3 H), 6.07 (d, *J* = 15.6 Hz, 1 H), 6.14 (d, *J* = 11.3 Hz, 1 H), 6.47 (dt, *J* = 11.3, 7.6 Hz, 1 H), 6.85 (s, 2 H), 6.87 (s, 2 H), 7.14 (dt, *J* = 15.6, 6.7 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *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.

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

Yellow oil; yield: 4 mg (1%).

R_f = 0.4 (hexane–Et_2O, 6:1).

IR (neat): 1740, 1640, 1590 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.24 (s, 36 H), 1.55 (m, 2 H), 2.66 (m, 4 H), 3.72 (s, 6 H), 6.00 (d, *J* = 11.3 Hz, 2 H), 6.38 (dt, *J* = 11.3, 7.7 Hz, 2 H), 6.78 (s, 4 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *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

Yellow oil; yield: 58 mg (14%).

R_f = 0.1 (hexane–Et_2O, 6:1).

IR (neat): 1730, 1700, 1640 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.33 (s, 18 H), 1.74 (m, 2 H), 2.31 (m, 2 H), 2.36 (m, 2 H), 3.79 (s, 3 H), 5.87 (d, *J* = 15.9 Hz, 1 H), 6.11 (d, *J* = 15.9 Hz, 1 H), 6.86 (s, 2 H), 7.08 (dt, *J* = 15.9, 7.1 Hz, 1 H), 7.13 (dt, *J* = 15.9, 6.7 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *m*/*z* = 402 $[M]^+$, 236.

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{24}H_{34}O_5$: 402.2406; found: 402.2393.

***tert*-Butyl (1*S*,2*S*,3*S*)- and (1*R*,2*S*,3*S*)-2-(*tert*-Butoxycarbonyl)-3-phenylcyclohexaneacetate (*tt*-7a and *tc*-7a; Table 1, Entry 1); Typical Procedure for the Asymmetric Conjugate Addition Cascade**

To a solution of ligand **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 di-*tert*-butyl (*E*,*E*)-nona-2,7-dienedioate (**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 sat. NH_4Cl (200 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were successively washed with sat. $NaHCO_3$ (200 mL) and brine (200 mL), dried over Na_2SO_4 and concentrated. Column chromatography (hexane–EtOAc, 20:1) gave ***tt*-7a** [yield: 1.86 g (50%); 71% ee] and ***tc*-7a** [yield: 339 mg (9%); 3% ee] as white solids, and **1** (10.2 g, quantitative recovery) as a colorless solid.

***tert*-Butyl (1*S*,2*R*,3*S*)-2-(*tert*-Butoxycarbonyl)-3-butylcyclohexaneacetate (*tt*-7b; Table 1, Entry 4)**

Colorless oil; yield: 323 mg (91%) from **6b** (296 mg, 1 mmol); 86% ee [HPLC (Daicel Chiralcel OD-H column, hexane–*i*-PrOH, 1000:1, 0.4 mL/min, 230 nm): t_R = 14.5 (major), 17.5 (minor) min].

$[\alpha]_D^{25}$ +12.1 (*c* 2.01, benzene).

R_f = 0.6 (hexane–EtOAc, 9:1).

IR (neat): 1730 cm^{-1}.

^1H NMR (500 MHz, C_6D_6): δ = 0.63–1.50 (m, 10 H), 0.88 (t, *J* = 7.3 Hz, 3 H), 1.37 (s, 9 H), 1.38 (s, 9 H), 1.56 (m, 1 H), 1.66 (m, 1 H), 1.81 (t, *J* = 11.0 Hz, 1 H), 1.95 (m, 1 H), 2.11 (dd, *J* = 10.0, 15.0 Hz, 1 H), 2.25 (m, 1 H), 2.50 (dd, *J* = 3.1, 15.0 Hz, 1 H).

^{13}C NMR (125 MHz, C_6D_6): δ = 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).

MS (EI): *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.

***tert*-Butyl (1*R*,2*R*,3*S*)-2-(*tert*-Butoxycarbonyl)-3-butylcyclohexaneacetate (*tc*-7b; Table 1, Entry 3)**

Colorless oil; yield: 27 mg (8%) from **6b** (296 mg, 1 mmol).

$[\alpha]_D^{25}$ –15.5 (*c* 0.51, $CHCl_3$).

R_f = 0.6 (hexane–EtOAc, 9:1).

IR (neat): 1720 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 3 H), 1.01 (m, 1 H), 1.06 (m, 1 H), 1.28 (m, 4 H), 1.43 (s, 9 H), 1.45 (s, 9 H), 1.47 (m, 4 H), 1.67 (m, 2 H), 1.80 (m, 1 H), 2.24 (dd, *J* = 4.3, 8.6 Hz, 1 H), 2.28 (dd, *J* = 9.5, 15.3 Hz, 1 H), 2.35 (dd, *J* = 5.2, 15.3 Hz, 1 H), 2.41 (m, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *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.

Bis(2,6-di-*tert*-butyl-4-methoxyphenyl) (*S*,*E*)-7-Phenylnon-2-enedioate (9a; Equation 1)

The absolute configuration of **9a** was tentatively assigned by analogy. The yield was based on ^1H NMR and the specific rotation was not measured because **9a** was inseparable from chiral ligand **1**. The structure was identified by comparing its ^1H and ^{13}C NMR spectra with those of (±)-**9a** that was prepared from **6a** and PhLi (1.5 equiv) without **1** in THF at –78 °C and fully characterized.

Yield: 389 mg (56%) from **6a** (620 mg, 1 mmol); 87% ee [HPLC (Daicel Chiralpak AD-H column, hexane–*i*-PrOH, 100:1, 0.5 mL/min, 254 nm): t_R = 39.4 (minor), 42.8 (major) min].

R_f = 0.3 (hexane–Et_2O, 4:1).

IR ($CHCl_3$): 1750, 1730, 1650, 1590 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.06 (s, 9 H), 1.29 (s, 9 H), 1.30 (m, 9 H), 1.32 (m, 9 H), 1.37 (m, 1 H), 1.43 (m, 1 H), 1.75 (m, 1 H), 1.86 (m, 1 H), 2.26 (m, 2 H), 2.90 (dd, *J* = 6.1, 17.7 Hz, 1 H), 2.97 (dd, *J* = 7.6, 17.7 Hz, 1 H), 3.23 (m, 1 H), 3.76 (s, 3 H), 3.79 (s, 3 H), 6.00 (d, *J* = 15.9 Hz, 1 H), 6.79 (d, *J* = 3.1 Hz, 1 H), 6.83 (d, *J* = 3.1 Hz, 1 H), 6.85 (s, 2 H), 7.06 (dt, *J* = 15.9, 6.7 Hz, 1 H), 7.20–7.31 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (FAB): *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.

Di-*tert*-butyl 3,7-Diphenylnonanedioate (10a)

Conjugate Addition Cascade in the Absence of Chiral Ligand in Tetrahydrofuran (Equation 2)[16]

A solution of PhLi in cyclohexane–Et_2O (1.73 M; 17.3 mL, 30 mmol) was diluted with THF (260 mL), and to this solution was added a solution of di-*tert*-butyl dienedioate **6b** (2.96 g, 10 mmol) in THF (40 mL) at –78 °C. After 0.5 h, MeOH (10 mL) and sat. NH_4Cl (200 mL) were successively added. The mixture was extracted with EtOAc (3 × 120 mL). The organic layer was washed with sat. $NaHCO_3$ (200 mL) and brine (200 mL), and then dried over Na_2SO_4. Concentration followed by column chromatography (hexane–EtOAc, 15:1) gave (±)-***tt*-7a** [yield: 344 mg (9%)] and (±)-***tc*-7a** [yield: 138 mg (4%)] as white solids, and **10a** [yield: 3.57 g (79%)] as a colorless oil.

R_f = 0.4 (hexane–EtOAc, 9:1).

IR (neat): 1730 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.00–1.05 (m, 2 H), 1.27 (s, 18 H), 1.51–1.63 (m, 4 H), 2.40 (dd, *J* = 8.6, 15.0 Hz, 2 H), 2.47 (dd, *J* = 7.0, 15.0 Hz, 2 H), 2.94 (m, 2 H), 7.07–7.29 (m, 10 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (FAB): *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[16]

To a solution of di-*tert*-butyl dienedioate **6b** (296 mg, 1.0 mmol) in THF (30 mL) was added a solution of PhLi in cyclohexane–Et_2O (1.83 M; 1.07 mL, 2.0 mmol) at –78 °C. After 0.5 h, MeOH (1 mL) and sat. NH_4Cl (40 mL) were successively added. The mixture was extracted with EtOAc (3 × 30 mL). The organic layer was washed with sat. $NaHCO_3$ (40 mL) and brine (40 mL), and dried over Na_2SO_4. Concentration followed by column chromatography (hexane–EtOAc, 20:1) gave (±)-***tt*-7a** [yield: 197 mg (52%)] and (±)-***tc*-7a** [yield: 16 mg (5%)] as white solids, and **10a** [yield: 37 mg (8%)] as a colorless oil. Recrystallization of (±)-***tt*-7a** from MeOH gave colorless needles; mp 82–83 °C.

Monophenyl Adducts 9b and 9c (Scheme 3)

tert-Butyl (*E*)-7-(Tetrahydro-2*H*-pyran-2-yloxy)hept-2-enoate (12)

To a solution of *tert*-butyl (*E*)-7-hydroxyhept-2-enoate (**11**)[17] (2.22 g, 11 mmol) in anhydrous $CHCl_3$ (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 r.t., and then diluted with Et_2O (60 mL). The whole was washed with half-sat. 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–EtOAc, 3:1) to give **12** as a colorless oil; yield: 3.02 g (96%).

R_f = 0.7 (hexane–EtOAc, 2:1).

IR (neat): 1710, 1650 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 1.50–1.62 (m, 8 H), 1.71 (m, 1 H), 1.83 (m, 1 H), 2.21 (m, 2 H), 3.39 (m, 1 H), 3.50 (m, 1 H), 3.75 (m, 1 H), 3.86 (m, 1 H), 4.57 (m, 1 H), 5.75 (d, *J* = 15.6 Hz, 1 H), 6.86 (dt, *J* = 15.6, 7.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *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 anhydrous THF (8 mL) was added a solution of **12** (284 mg, 1.0 mmol) in anhydrous THF (2 mL) at –78 °C. The mixture was stirred for 30 min at the same temperature, and MeOH (2 mL) and then sat. NH_4Cl (20 mL) were added. The whole was extracted with EtOAc (3 × 20 mL), and the combined organic layers were washed with sat. $NaHCO_3$ (40 mL) and brine (40 mL), dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil (432 mg) which included a phenyl adduct. To a solution of the yellow oil in EtOH (8 mL) was added PPTS (25 mg, 0.1 mmol). After being 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 (3 × 30 mL), and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil (335 mg), which was purified by column chromatography (hexane–EtOAc, 2:1) to give **13** as a colorless oil; yield: 254 mg (91% over 2 steps).

R_f = 0.1 (hexane–EtOAc, 5:1).

IR (neat): 3400, 1720 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.21–1.27 (m, 2 H), 1.30 (s, 9 H), 1.49–1.67 (m, 4 H), 1.60 (s, 1 H), 2.47 (dd, *J* = 8.3, 14.7 Hz, 1 H), 2.54 (dd, *J* = 7.3, 14.7 Hz, 1 H), 3.03 (m, 1 H), 3.57 (t, *J* = 6.4 Hz, 2 H), 7.18–7.28 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *m*/*z* = 222 $[M + H - t\text{-Bu}]^+$, 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 6-Formyl-3-phenylhexanoate (14)

To a solution of **13** (27.9 g, 0.10 mol) in anhydrous 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 r.t. The mixture was stirred for 18 h at r.t., then diluted with toluene (1 L) and filtered. The filtrate was washed with H_2O (2 × 1 L) and brine (1 L), dried over Na_2SO_4 and concentrated in vacuo to give a yellow oil (76.8 g), which was purified by column chromatography (hexane–EtOAc, 10:1) to give **14** as a colorless oil; yield: 24 g (87%).

R_f = 0.5 (hexane–EtOAc, 3:1).

IR (neat): 1730, 1710 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.30 (s, 9 H), 1.45–1.70 (m, 4 H), 2.37 (m, 2 H), 2.48 (dd, *J* = 8.3, 15.0 Hz, 1 H), 2.54 (dd, *J* = 7.4, 14.7 Hz, 1 H), 3.04 (m, 1 H), 7.18–7.29 (m, 5 H), 9.68 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *m*/*z* = 220 $[M + H - t\text{-Bu}]^+$.

Anal. Calcd for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.62; H, 8.88.

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

To a suspension of *tert*-butyl (triphenylphosphoranylidene)acetate (40 g, 0.11 mmol) in toluene (140 mL) was added a solution of **14** (24.0 g, 87 mol) in toluene (40 mL) over 10 min. The mixture was stirred for 16 h at r.t., then diluted with hexane (100 mL) and filtered. Concentration of the filtrate in vacuo gave a yellow oil (34.7 g), which was purified by column chromatography (hexane–EtOAc, 20:1) to give **9b** as a colorless oil; yield: 28.4 g (88%); *E*/*Z* = 97:3.

R_f = 0.6 (hexane–EtOAc, 4:1).

IR (neat): 1720, 1650 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.27 (m, 1 H), 1.30 (s, 9 H), 1.46 (s, 9 H), 1.60 (m, 1 H), 1.65 (m, 2 H), 2.11 (m, 2 H), 2.47 (dd, *J* = 8.3, 14.7 Hz, 1 H), 2.52 (dd, *J* = 7.0, 14.7 Hz, 1 H), 3.02 (m, 1 H), 5.67 (d, *J* = 15.6 Hz, 1 H), 6.76 (dt, *J* = 15.6, 7.6 Hz, 1 H), 7.15–7.30 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *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.

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

To a solution of **9b** (374 mg, 1.0 mmol) in MeOH (12 mL) was added concd H_2SO_4 (0.05 mL) at r.t. The mixture was heated under reflux for 2 h, then neutralized by the addition of 10% Na_2CO_3 (0.5 mL). The whole was extracted with Et_2O (3 × 30 mL) and the combined organic layers were washed with brine (40 mL), dried over Na_2SO_4 and concentrated in vacuo to give **9c** as a yellow oil; yield: 280 mg (97%).

R_f = 0.5 (hexane–EtOAc, 3:1).

IR (neat): 1740, 1720, 1660 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.28 (m, 1 H), 1.33 (m, 1 H), 1.65 (m, 2 H), 2.14 (m, 2 H), 2.58 (dd, *J* = 8.0, 15.6 Hz, 1 H), 2.62 (dd, *J* = 7.3, 15.6 Hz, 1 H), 3.09 (m, 1 H), 3.58 (s, 3 H), 3.71 (s, 3 H), 5.75 (d, *J* = 15.6 Hz, 1 H), 6.87 (dt, *J* = 15.6, 7.1 Hz, 1 H), 7.15–7.31 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *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 anhydrous THF (3 mL) were added a solution of BuLi in hexane (1.56 M; 0.77 mL, 1.2 mmol) and, after 20 min, a solution of **9b** (374 mg, 1.0 mmol) in anhydrous 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 sat. NH_4Cl (40 mL) were added. The whole was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 10% HCl (40 mL), H_2O (40 mL), sat. $NaHCO_3$ (40 mL) and brine (40 mL), then dried over Na_2SO_4 and concentrated in vacuo to give a pale yellow solid (388 mg), which was purified by column chromatography (hexane–EtOAc, 9:1) to give a 7:3 mixture of ***tt*-7a** and ***tc*-7a** as a white solid; yield: 351 mg (94%).

Cyclization of 9c (Scheme 4)

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

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

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

To TFA (3.4 mL, 45 mmol) was added ***tc*-7a** (167 mg, 0.45 mmol) at r.t. The mixture was stirred for 0.5 h at r.t. 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 AcOH (10 drops), and the whole was concentrated. The resulting residue was purified by column chromatography (hexane–EtOAc, 4:1) to give ***tc*-7e** as a white solid.

Yield: 129 mg (99%); mp 62–64 °C; 3% ee [HPLC (Daicel Chiralcel OJ column, hexane–*i*-PrOH, 100:1, 0.5 mL/min, 254 nm): t_R = 30.0 (major), 36.0 (minor) min].

$[\alpha]_D^{25}$ –12.2 (*c* 1.12, $CHCl_3$).

R_f = 0.4 (hexane–EtOAc, 4:1).

IR (Nujol): 1720 cm^{-1}.

^1H NMR (500 MHz, CD_3OD): δ = 1.45 (m, 1 H), 1.61 (m, 2 H), 1.70 (m, 1 H), 1.73 (m, 1 H), 1.83 (m, 1 H), 2.50 (dd, *J* = 7.7, 16.2 Hz, 1 H), 2.63 (dd, *J* = 6.5, 16.2 Hz, 1 H), 2.73 (m, 1 H), 2.91 (dt, *J* = 4.0, 12.2 Hz, 1 H), 3.00 (dd, *J* = 4.0, 12.2 Hz, 1 H), 3.37 (s, 3 H), 3.64 (s, 3 H), 7.12–7.22 (m, 5 H).

^{13}C NMR (125 MHz, CD_3OD): δ = 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).

MS (EI): *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** from ***tt*-7a** (182 mg, 0.49 mmol); colorless oil; yield: 135 mg (96%); 71% ee [HPLC (Daicel Chiralcel OJ column, hexane–*i*-PrOH, 100:1, 0.5 mL/min, 254 nm): t_R = 30.0 (minor), 42.7 (major) min].

$[\alpha]_D^{25}$ +23.2 (*c* 1.08, $CHCl_3$).

R_f = 0.4 (hexane–EtOAc, 4:1).

IR (neat): 1740, 1720 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.16 (m, 1 H), 1.52 (m, 2 H), 1.87 (m, 2 H), 1.93 (m, 1 H), 2.16 (dd, *J* = 8.9, 14.7 Hz, 1 H), 2.23 (m, 1 H), 2.33 (dd, *J* = 3.4, 14.7 Hz, 1 H), 2.38 (t, *J* = 11.3 Hz, 1 H), 2.82 (dt, *J* = 3.4, 11.3 Hz, 1 H), 3.35 (s, 3 H), 3.67 (s, 3 H), 7.15–7.27 (m, 5 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 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).

MS (EI): *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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Supporting Information

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