Asymmetric Formation of Quaternary Carbon Centers Catalyzed by Novel Chiral 2,5-Dialkyl-7-phenyl-7-phosphabicyclo-[2.2.1]heptanes

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Many important biologically active compounds contain quaternary carbon centers. Efficient asymmetric syntheses of these compounds represent a significant challenge in organic chemistry.[1] Some catalytic synthetic methods directed toward this problem include proline-catalyzed aldol reactions,[2] Michael additions,[3] alkylations with phase-transfer catalysts,[4] palladium-catalyzed allylations,[5] Heck reactions,[6] Diels−Alder reactions,[7] and cyclopropanations.[8]

Recently, we prepared a new class of chiral monophosphines, 2,5-dialkyl-7-phenyl-7-phosphabicyclo[2.2.1]-heptanes (**1**, **2**, Figure 1). High enantioselectivities (>90% ee) have been obtained for Pd-catalyzed allylic alkylations[9] and phosphine-catalyzed [3 + 2] cycloadditions[10] using these species. The success of asymmetric phosphine-catalyzed [3 + 2] annulation between 2,3-butadienoates and electron-deficient olefins has prompted us to look at other phosphine-catalyzed reactions.[11] One such reaction, discovered by Trost, is the phosphine-catalyzed C−C bond formation at the γ-position of

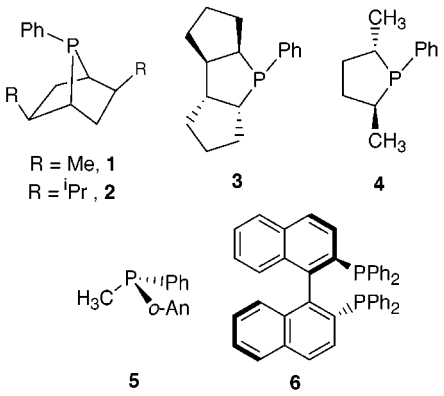

Figure 1. Chiral phosphines.

2-butynoates with malonate-type nucleophiles (Scheme 1).[12] The potential for asymmetric synthesis of quaternary carbon centers based on this transformation seemed to us to be an attractive synthetic strategy.

In this phosphine-catalyzed C−C bond-forming reaction, generation of electrophilic character at the γ-carbon of 2-butynoates creates a regiochemical complement to the Michael addition. The mechanistic rationale proposed by Trost is illustrated in Scheme 2. The first intermediate **7** comes from Michael addition of PPh_3 to ethyl 2-butynoate. Proton transfer within **7** generates **8**. Deprotonation of a pronucleophile by **8** produces a vinylphosphonium species **9** and the anionic nucleophile. Nucleophilic addition of this species to **9** leads to **10**. Facile proton transfer then affords **11** with subsequent elimination of PPh_3 to give the final γ-addition products.

Since some aspects of this γ-addition process are similar to the phosphine-catalyzed [3 + 2] cycloaddition discovered by Lu,[13] which we previously developed as an asymmetric reaction, we investigated the asymmetric version of this reaction using chiral phosphabicyclo[2.2.1]-heptanes **1** and **2** as catalysts (Table 1). Under conditions similar to those cited by Trost, moderate enantioselectivities (42−68% ee, Table 1, entries 1−4) have been obtained between ethyl 2-butynoate and several pronucleophiles with **1** as the catalyst; however, these reactions do not proceed at room temperature.

Because the nucleophilic addition of a phosphine to ethyl 2,3-butadienoate readily gives the intermediate **8** (Scheme 2), Lu et al.[14] have demonstrated that the C−C bond formation can be effected under mild conditions using ethyl 2,3-butadienoate instead of 2-butynoate. Using this alternative electrophile, we have studied the γ-addition reaction under various conditions by changing catalysts, additives, and substrates. Table 2 lists the results of this asymmetric reaction with several chiral phosphines (**1**−**6**). The new phosphines **1** and **2** (Table 2, entries 1−2) are more selective and active catalysts than the previously reported chiral phosphines **4**−**6** (Table 2, entries 4−6). Compared to the conformationally rigid dimethyl phosphabicyclo[2.2.1]heptane **1** (Table 2, entry 1, 74% ee), the corresponding five-membered ring phosphacycle **4**[15] gives much lower enantioselectivity

(1) For a recent review, see: Fuji, K. *Chem. Rev.* **1993**, *93*, 2037.
(2) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 496. (b) Agami, C.; Levisalles, J.; Puchot, C. *J. Chem. Soc., Chem. Commun.* **1985**, 441.
(3) (a) Hermann, K.; Wynberg, H. *J. Org. Chem.* **1979**, *44*, 2238. (b) Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. (c) Brunner, H.; Hammer, B. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 312. (d) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Am. Chem. Soc.* **1992**, *114*, 8295.
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(6) (a) Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1989**, *54*, 4738. (b) Kagechika, K.; Shibasaki, M. *J. Org. Chem.* **1991**, *56*, 4093. (c) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5836. (d) Ashimori, A.; Overman, L. E. *J. Org. Chem.* **1992**, *57*, 4571.
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(9) Chen, Z.; Jiang, Q.; Zhu, G.; Xiao, D.; Cao, P.; Guo, C.; Zhang, X. *J. Org. Chem.* **1997**, *62*, 4521.
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(12) Trost, B. M.; Li, C.-J. *J. Am. Chem. Soc.* **1994**, *116*, 3167.
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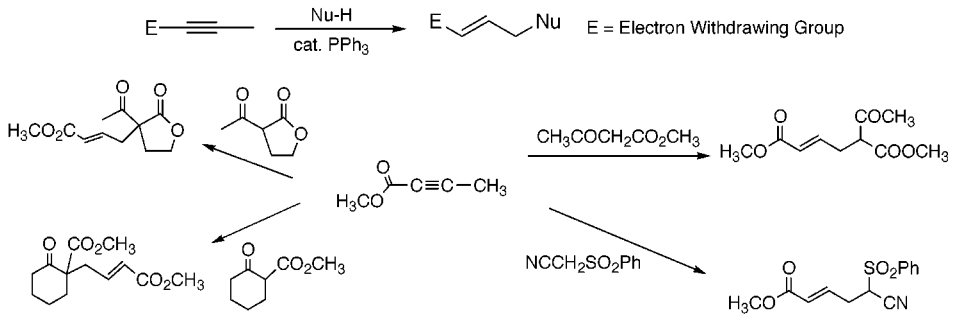
Scheme 1



Scheme 2

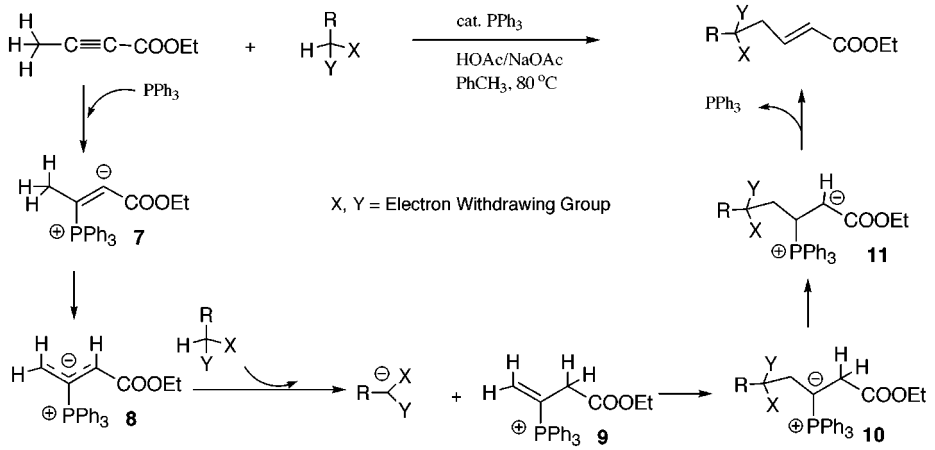
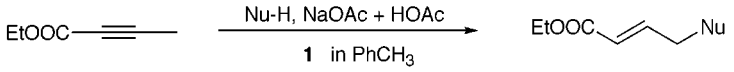
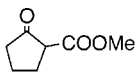
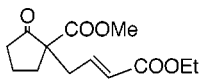
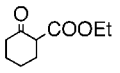
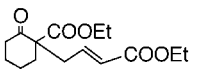
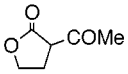
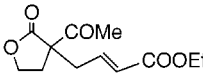


Table 1. Phosphine-Catalyzed Asymmetric γ-Addition[a]



Entry	Substrate (NuH)	T (°C)	Time (h)	Yield (%)	ee %[b]	Product	
1		80	16	76	59 (-)		(**12**)
2		50	72	57	68 (-)		
3		110	50	44	51 (+)		(**13**)
4		110	18	93	43 (-)		(**14**)

a: The reaction was carried out under N_2 with chiral phosphine **1** (30 mol%), NaOAc (50 mol%), acetic acid (50 mol%), ethyl 2-butynoate (100 mol%) and Nu-H (100 mol%). b: % ee was measured by GC with a γ-Dex column.

(Table 2, entry 4, 8% ee). This result is similar to that observed in the asymmetric phosphine-catalyzed [3 + 2] cycloaddition.[10] To rigidify the conformationally flexible five-membered ring in **4**, we have also synthesized a new chiral phosphacycle **3**, which has three fused five-membered rings. This phosphine was made from (1*R*,1′*R*)-bicyclopentyl-(2*S*,2′*S*)-diol[16] previously reported by us as shown in Figure 2. Moderate enantioselectivity has been obtained with phosphine **3** (Table 2, entry 3). Our study demonstrates that phosphine **1** is one of the most effective catalysts for the asymmetric γ-addition reaction. A rationale for the asymmetric C−C forming reaction is not available.

Additives and phosphine stoichiometry play important roles in this C−C bond-forming reaction. Table 3 summaries some experimental results with **1** as the catalyst. Higher catalyst loading accelerates the reaction (Table 3, entries 1, 2, and 4) with a slight loss of enantioselectivity. At lower temperatures (Table 3, entry 3, 0 °C, 81% ee), the reaction proceeds with higher enantioselectivity and much lower reaction rate than at room temperature. The catalytic reaction occurs much faster in the absence of acetic acid−sodium acetate (Table 3, entry 6) or in the presence of sodium acetate only (Table 3, entry 5). However, the enantioselectivities are significantly lower than those obtained with acetic acid−sodium acetate as

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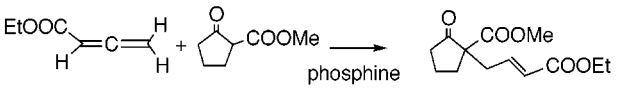
(16) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799.

Table 2. Asymmetric γ-Addition Catalyzed by Various Chiral Phosphines[a]



entry	phosphine	time	yield (%)	ee[b] (%)	rotation
1	**1**	27 h	76	74	−
2	**2**	27 h	80	69	−
3	**3**	18	71	35	+
4	**4**	4 d	58	8	−
5	**5**	5 d	66	20	+
6	**6**	>10 d	46	20	+

[a] The reaction was carried out under N_2 at rt in $PhCH_3$ with chiral phosphines (**1**−**6**) (10 mol %), NaOAc (50 mol %), AcOH (50 mol %), ethyl 2,3-butadienoate (100 mol %), and 2-methoxycarbonyl cyclopentanone (100 mol %). [b] % ee was measured by GC with a γ-Dex column.

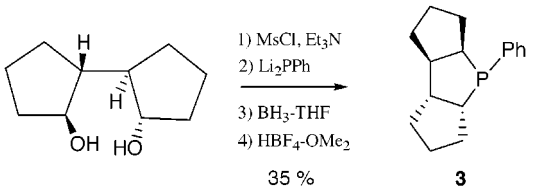
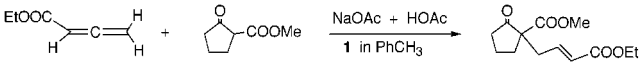


Figure 2. Synthesis of chiral phosphine **3**.

Table 3. Effect of Additives to the Phosphine-Catalyzed Asymmetric γ-Addition[a]



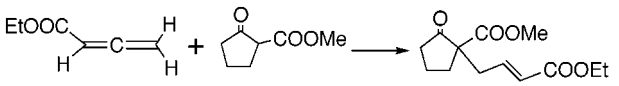
entry	**1** (mol %)	'NaOAc (mol %)	HOAc (mol %)	*T* (°C)	time	yield (%)	ee[b] (%)
1	35	50	50	rt	10 h	79	72
2	10	50	50	rt	27 h	76	74
3	10	50	50	0	10 d	67	81
4	5	50	50	rt	5 d	84	75
5	10	100	0	rt	5 h	84	54
6	10	0	0	rt	7 h	82	54
7	10	0	100	rt		NR	

[a] The reaction was carried out under N_2 with chiral phosphine **1**, ethyl 2,3-butadienoate (100 mol %), and 2-methoxycarbonyl cyclopentanone (100 mol %). [b] % ee was measured by GC with a γ-Dex column.

additives. In the presence of acetic acid, the reaction does not occur because the carbon nucleophile cannot be generated.

Since an enolate nucleophile is the putative intermediate in this asymmetric reaction, we have studied the effects of different countercations (Table 4). While enantioselectivity with various cations remains at the same level (Table 4, entries 1−5), the reactivity with Na^+, K^+, and Cs^+ are significantly higher than with Li^+ and NH_4^+. Overall, the reaction with Na^+ gives higher activity and selectivity (Table 4, entry 1). Under the optimized conditions with phosphine **1**, several different substrates have been tested for asymmetric C−C bond formation (Table 5). Changing the ester groups in the 2,3-butadienoates has no significant influence on the enantioselectivities (Table 5, entries 1−3). However, varying enantioselectivities have been observed with different pronucleophile structures. Lower enantioselectivities were obtained by replacing an ester group with a ketone (Table 5, entry 4 vs entry 2), or by substituting a cyclic ketone for a lactone (Table 5, entry 5 vs entry 4).

Table 4. Effect of Counter Cations to the Phosphine-Catalyzed Asymmetric γ-Addition[a]



entry	MOAc	time	yield (%)	ee[b] (%)
1	LiOAc	10 d	67	72 (−)
2	NaOAc	27 h	76	74 (−)
3	KOAc	20 h	82	67 (−)
4	CsOAc	20 h	84	70 (−)
5	NH_4OAc	7 d	62	70 (−)

[a] The reaction was carried out under N_2 at rt with chiral phosphines **1** (10 mol %), MOAc (50 mol %), AcOH (50 mol %), ethyl 2,3-butadienoate (100 mol %), and 2-methoxycarbonyl cyclopentanone (100 mol %). [b] % ee was measured by GC with γ-Dex column.

Moderate enantioselectivities have been obtained with a six-membered ring pronucleophile (Table 5, entry 6, 41% ee) and an acyclic pronucleophile (Table 5, entry 7, 45% ee).

In summary, we have developed new chiral phosphines as catalysts for the asymmetric C−C bond formation of quaternary carbon centers. Moderate to good enantioselectivities have been obtained with a variety of substrates. The present work provides potentially useful addition to phosphine-catalyzed asymmetric organic reactions.

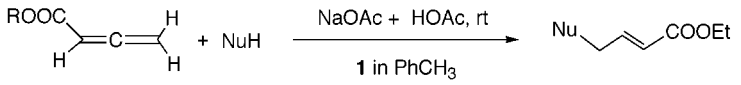
Experimental Section

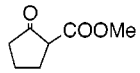
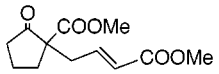
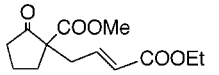
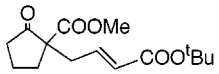
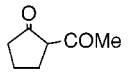
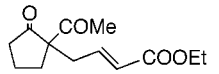
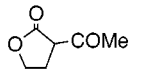
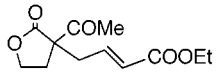
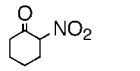
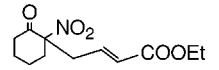
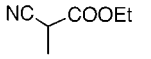
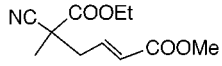
All reactions and manipulations were performed in a nitrogen-filled glovebox or using standard Schlenk techniques. Toluene was distilled from sodium benzophenone ketyl under nitrogen. Column chromatography was performed using EM silica gel 60(230−400 mesh). ^1H, ^{13}C, and ^{31}P NMR were recorded using 300 or 360 MHz NMR spectrometers. Chemical shifts are reported in ppm downfield from TMS with the solvent resonance as the internal standard. GC analyses were done using chiral capillary columns (Supelco γ-Dex 225 or β-Dex 120).

(1*R*,1′*R*)-Bicyclopentyl-(2*S*,2′*S*)-diol Bis(methanesulfonate). To a solution of (1*R*,1′*R*)-bicyclopentyl-(2*S*,2′*S*)-diol[16] (0.8 g, 4.65 mmol) and triethylamine (1.68 mL, 12.09 mmol) in CH_2Cl_2 (30 mL) was added dropwise a solution of methanesulfonyl chloride (0.76 mL, 9.92 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 30 min at 0 °C, the reaction mixture was stirred for an additional 2 h at room temperature and then quenched by saturated aqueous ammonium chloride solution (25 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic solution was dried over Na_2SO_4. After evaporation of the solvent, a white solid was obtained that was used directly for the next step: ^1H NMR ($CDCl_3$, 200 MHz) δ 5.01 (m, 2 H), 3.04 (s, 6 H), 2.17 (m, 2 H), 2.15−1.65 (m, 10 H), 1.43−1.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 86.8, 48.2, 38.4, 32.8, 27.4, 22.5.

3-BH_3. To phenylphosphine (0.39 mL, 3.55 mmol) in THF (50 mL) was added *n*-BuLi (4.9 mL of a 1.6 M solution in hexane, 7.8 mmol) via syringe at 0 °C over 2 min. The orange solution was warmed to room temperature and stirred for 1 h. To the resulting orange-yellow suspension was added a solution of (1*R*,1′*R*)-bicyclopentyl-(2*S*,2′*S*)-diol bis(methanesulfonate) (1.16 g, 3.55 mmol) in THF (30 mL) over 3 min. After the mixture was stirred overnight at room temperature, the pale-yellow suspension was hydrolyzed with saturated NH_4Cl solution. The mixture was extracted with ether (2 × 50 mL), and the combined organic extract was dried over anhydrous Na_2SO_4 and evaporated. The residue was dissolved in CH_2Cl_2 (30 mL) and treated with BH_3·THF (10 mL of a 1.0 M solution in THF, 10 mmol), and the mixture was stirred overnight. Workup required addition of saturated NH_4Cl solution and extraction with CH_2Cl_2 (30 mL). The combined organic extracts were dried over

Table 5. Chiral Phosphine-Catalyzed Asymmetric γ-Addition[a]



Entry	NuH	R	Yield (%)	ee %[b]	Product[c]	
1		Me	80[d]	73 (-)		(**15**)
2		Et	76	74 (-)		(**12**)
3		*t*-Bu	74	75 (-)		(**16**)
4		Et	67	56 (+)		(**17**)
5		Et	83	48 (+)		(**14**)
6		Et	31	41 (-)		(**18**)
7		Me	47	45 (+)		(**19**)

a: The reaction was carried out under N_2 at rt. with chiral phosphines **1** (10 mol%), NaOAc (50 mol %), AcOH (50 mol%), 2,3-butadienoate (100 mol%), Nu-H (100 mol %). b: % ee was measured by GC with γ-dex, β-dex columns. c: All compounds have been fully characterized spectroscopically and their elemental composition established by high resolution mass spectrometry. d: The reaction was carried out at 0 °C.

anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The residue was subjected to silica gel chromatography, eluting with hexanes/CH_2Cl_2 (3:1) to afford the product as a white solid: yield 0.35 g (38%); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.80−7.65 (m, 2 H), 7.55−7.35 (m, 3 H), 3.00−2.10 (m, 4 H), 2.00−1.30 (m, 12 H), 1.30−0.20 (m, 3H); ^{13}C NMR ($CDCl_3$ 90 MHz) δ 132.2 (d, ^2J(PC) = 8.0 Hz), 130.8 (d, ^4J(PC) = 2.3 Hz), 129.3 (d, ^1J(PC) = 45.2 Hz), 128.6 (d, ^3J(PC) = 9.2 Hz), 53.5 (d, ^2J(PC) = 5.1 Hz), 52.6 (d, ^2J(PC) = 6.0 Hz), 45.3 (d, ^1J(PC) = 35.9 Hz), 41.0 (d, ^1J(PC) = 37.1 Hz), 32.3 (d, ^2J(PC) = 5.1 Hz), 32.0 (d, ^2J(PC) = 6.6 Hz), 28.1 (d, ^3J(PC) = 5.0 Hz), 27.8 (d, ^3J(PC) = 4.8 Hz), 26.1 (d, ^3J(PC) = 6.7 Hz), 25.8 (d, ^3J(PC) = 6.0 Hz); ^{31}P NMR ($CDCl_3$, 146 MHz) δ 48.1 (q, br, ^1J(PB) = 53 Hz).

Preparation of Compound 3. To a solution of **3**−BH_3 (0.293 g, 1.34 mmol) in CH_2Cl_2 (8 mL) was added tetrafluoroboric acid−dimethyl ether complex (0.69 mL, 5.69 mmol) dropwise via syringe at −5 °C. After the addition, the reaction mixture was allowed to warm slowly to room temperature and was stirred for 20 h. When ^{31}P NMR showed the reaction was complete, the mixture was diluted with CH_2Cl_2 and neutralized with saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with CH_2Cl_2. The combined organic solution was washed with brine and water and then dried over Na_2SO_4. Evaporation of the solvent gave a pure phosphine product **3**: yield 0.256 g (92%); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.46−7.42 (m, 2 H), 7.35−7.26 (m, 3 H), 2.93−2.77 (m, 2 H), 2.50−2.40 (m, 2 H), 2.09−2.01 (m, 1 H), 1.87−1.42 (m, 10 H), 1.28−1.19 (m, 1 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 139.3 (d, ^1J (PC) = 23.8 Hz), 132 (d, ^2J(PC) = 17.1 Hz), 127.9 (d, ^3J(PC) = 5.3 Hz), 127.4, 54.5 (d, J = 2.0 Hz), 53.3, 44.9 (d, J = 13.4 Hz), 44.1 (d, J = 6.6 Hz), 32.5 (m), 32.2, 31.9, 29.1 (d, J = 5.2 Hz), 26.1, 25.6 (d, J = 7.9 Hz); ^{31}P NMR ($CDCl_3$, 146 MHz) δ 16.3.

Typical Experimental Procedure for the γ-Addition Reaction. A mixture of ethyl 2,3-butadienoate (56 mg, 0.5 mmol), 2-methoxycarbonyl cyclopentanone (74 mg, 0.5 mmol), chrial phosphine **1** (0.1M in toluene, 0.5 mL, 0.05 mmol), acetic acid (15 mg, 0.25 mmol), and sodium acetate (20 mg, 0.25 mmol) in 5 mL of toluene was stirred at room temperature under nitrogen. The reaction was monitored by TLC. After the reaction was complete, enantioselectivity was determined by GC using a chiral capilliary column [Supelco γ-Dex-225 (0.25 mm × 30 m)]. The solvent was removed, and the residue was purified by column chromatography on silica gel to give 97 mg of 2-(methoxycarbonyl)-2-[3′-(ethoxycarbonyl)-2′(*E*)-propen-1′-yl]-cyclopentanone (76% yield, 74% ee).

2-(Methoxycarbonyl)-2-[3′-(ethoxycarbonyl)-2′(*E*)-propen-1′-yl]cyclopentanone (12): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.77 (dt, J = 7.66, 15.53 Hz, 1H), 5.85 (dt, J = 1.35, 15.54 Hz, 1H), 4.15 (q, J = 7.13 Hz, 2H), 3.7 (s, 3H), 2.84−2.78 (m, 1H), 2.48−2.39 (m, 3H), 2.28−2.21 (m, 1H), 2.01−1.87 (m, 3H), 1.26 (t, J = 7.13 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 213.5, 170.8, 165.8, 142.8, 125.2, 60.3, 59.4, 52.7, 37.7, 35.9, 32.4, 19.5, 14.2; HRMS calcd for $C_{13}H_{18}O_5$ 254.1154 (M^+), found 254.1152.

2-(Ethoxycarbonyl)-2-[3′-(ethoxycarbonyl)-2′(*E*)-propen-1′-yl]cyclohexanone (13): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.83 (dt, J = 7.7, 15.6 Hz, 1 H), 5.79 (dt, J = 1.4, 15.60 Hz, 1 H), 4.08 (m, 4 H), 2.72−2.65 (m, 1 H), 2.49−2.41 (m, 4 H), 2.09−2.01 (m, 1 H), 1.74−1.51 (m, 3 H), 1.49−1.42 (m, 1 H), 1.27−1.20 (m, 6 H); ^{13}C NMR (($CDCl_3$, 90 MHz) δ 206.6, 170.9, 165.8, 143.4, 124.6, 61.5, 60.6, 60.2, 40.9, 37.5, 36.0, 27.3, 22.4, 14.2, 14.0; HRMS calcd for $C_{15}H_{22}O_5$ 282.1467 (M^+), found: 282.1460.

2-Acetyl-2-[3′-(ethoxycarbonyl)-2′(*E*)-propen-1′-yl]-γ-butyrolactone (14): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.65 (dt, J = 7.4, 15.5 Hz, 1 H), 5.89 (dt, J = 1.4, 15.5 Hz, 1 H), 4.31−4.25 (m, 1 H), 4.20−4.11 (m, 3 H), 2.90−2.82 (m, 2 H), 2.75−2.69 (m, 1 H), 2.30 (s, 3 H), 2.11−2.02 (m, 1 H), 1.24 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 201.2, 174.5, 165.3, 140.5, 126.1, 66.3, 60.6, 60.5, 36.8, 29.0, 25.6, 14.1; HRMS calcd for $C_{12}H_{16}O_5$ 240.0998 (M^+), found 240.0999.

2-(Methoxycarbonyl)-2-[3′-(methoxycarbonyl)-2′(*E*)-propen-1′-yl]cyclopentanone (15): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.80 (dt, J = 7.6, 15.6 Hz, 1 H), 5.88 (dt, J = 1.3, 15.6 Hz, 1 H), 3.72 (s, 6 H), 2.86−2.79 (m, 1 H), 2.51−2.41 (m, 3 H), 2.31−2.23 (m, 1 H), 2.09−1.88 (m, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 202.9, 160.2, 155.7, 132.7, 114.1, 48.9, 42.1, 40.9, 27.2, 25.4, 21.9, 8.9; HRMS calcd for $C_{12}H_{16}O_5$ 240.0998 (M^+), found 240.0987.

2-(Methoxycarbonyl)-2-[3′-(*tert*-butoxycarbonyl)-2′(*E*)-propen-1′-yl]cyclopentanone (16): ^{1}H NMR ($CDCl_3$ 360 MHz) δ 6.68 (dt, J = 7.6, 15.5 Hz, 1 H), 5.80 (dt, J = 1.3, 15.5 Hz, 1 H), 3.71 (s, 3 H), 2.84−2.78 (m, 1 H), 2.50−2.39 (m, 3 H), 2.29−2.20 (m, 1 H), 2.05−1.90 (m, 3 H), 1.31 (s, 9 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 213.8, 170.9, 165.3, 141.6, 126.9, 80.5, 59.5, 52.8, 37.8, 35.8, 32.3, 28.1, 19.5; HRMS calcd for $C_{15}H_{22}O_5$ 209.0814 (M^+ − O-*t*-Bu), found 209.0853.

2-Acetyl-2-[3′-(ethoxycarbonyl)-2′(*E*)-propen-1′-yl]cyclopentanone (17): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.61 (dt, J = 7.7, 15.5 Hz, 1 H), 5.80 (dt, J = 1.4, 15.5 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 2.78−2.72 (m, 1 H), 2.60−2.57 (m, 1 H), 2.51−2.48 (m, 1 H), 2.29−2.13 (m, 2 H), 2.08 (s, 3 H), 1.89−1.82 (m, 2 H), 1.73−1.67 (m, 1 H), 1.20 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 214.6, 202.8, 165.5, 142.1, 125.0, 67.6, 60.3, 38.1, 36.8, 30.4, 26.0, 19.2, 14.0; HRMS calcd for $C_{13}H_{18}O_4$ 238.1205 (M^+), found: 238.1207.

2-Nitro-2-[3′-(ethoxycarbonyl)-2′(*E*)-propen-1′-yl]cyclohexanone (18): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.77 (dt, J = 7.7, 15.6 Hz, 1 H), 5.86 (dt, J = 1.3, 15.5 Hz, 1 H), 4.16 (q, J = 7.1 Hz, 2 H), 2.97−2.74 (m, 3 H), 2.61−2.57 (m, 2 H), 2.06−2.03 (m, 1 H), 1.83−1.67 (m, 4 H), 1.26 (t, J = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 199.4, 165.3, 139.3, 126.7, 95.9, 60.5, 39.6, 37.9, 36.2, 26.6, 21.2, 14.2; HRMS calcd for $C_{12}H_{17}NO_5$: 255.1107 (M^+), found 255.1094.

Methyl 5-(ethoxycarbonyl-)5-cyano-2(*E*)-hexenoate (19): ^{1}H NMR ($CDCl_3$, 360 MHz) δ 6.83 (dt, J = 9.2,18.7 Hz, 1 H), 5.95 (dt, J = 1.4, 18.7 Hz, 1 H), 4.23 (q, J = 8.6 Hz, 2 H), 3.69 (s, 3 H), 2.81−2.74 (m, 1 H), 2.65−2.58 (m, 1 H), 1.58 (s, 3 H), 1.27 (t, J = 8.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 90 MHz) δ 168.2, 165.7, 139.8, 126.3, 118.9, 63.1, 51.6, 43.0, 39.9, 23.0, 13.9; HRMS calcd for $C_{11}H_{15}NO_4$ 225.1001 (M^+), found 225.1003.

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Supporting Information Available: A modified synthetic procedure of (1*S*,2*R*,4*S*,5*R*)-(+)-2,5-dimethylcyclohexane-1,4-diol, an intermediate for the synthesis of **1**, and NMR spectra of compounds **3** and **12**−**19** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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