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Desymmetrization of meso-Methylene cyclopropanes by a Palladium-Catalyzed Asymmetric Ring-Opening Bis(alkoxycarbonylation) Reaction

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ABSTRACT

Desymmetrization of various meso-methylene cyclopropanes was accomplished by a palladium-catalyzed asymmetric ring-opening bis(alkoxycarbonylation) reaction employing a chiral bioxazoline ligand. The reaction proceeded smoothly in the presence of copper(I) triflate under carbon monoxide and oxygen at ambient pressure to give the corresponding optically active α-methylene glutarates with up to 60% ee. Desymmetrization of protected meso-(3-methylene cyclopropane-1,2-diyldimethanol was also carried out to give enantioenriched highly oxygen-functionalized α-methylene glutarates.

1. Introduction

The desymmetrization of meso-compounds has become a common strategy in asymmetric synthesis since it allows the formation of multiple stereogenic centers in one symmetry-breaking operation. Among the desymmetrization techniques, methods which involve the formation of new C–C bonds are quite useful for the synthesis of optically active natural products or biologically active substances.1,2

Carbonylation is an important reaction in organic synthesis as it provides an efficient means of making a variety of useful homologated carbonyl compounds.3 We have developed the selective mono- and bis(alkoxycarbonylation) reactions of terminal olefins catalyzed by palladium in the presence of copper salts under mixtures of carbon monoxide and oxygen at ambient pressure.4 We have also taken an interest in utilizing
cyclopropanes as three carbon units for the preparation of glutarates via direct introduction of two carbonyl groups and have developed the ring-opening reaction of methylenecyclopropanes to afford the corresponding α-methyleneglutarates. In order to prepare optically active glutaric acid derivatives, the asymmetric ring-opening bis(alkoxycarbonylation) reaction of methylenecyclopropanes would be effective. Herein we describe the desymmetrization of meso-methylenecyclopropanes by a palladium-catalyzed ring-opening bis(alkoxycarbonylation) reaction in the presence of a chiral bioxazoline ligand.

2. Results and Discussion

We initially performed the asymmetric bis(alkoxycarbonylation) reaction of 7-methylenebicyclo[4.1.0]heptane (1) in the presence of 0.02 equivalents of PdCl$_2$ and 0.5 equivalents of CuOTf(C$_6$H$_6$)$_{0.5}$ under carbon monoxide and oxygen (ca. 1:1 v/v) at ambient pressure in MeOH/THF using (S,S)-isopropyl-substituted bioxazoline 3A as a chiral ligand. The reaction proceeded very slowly to give methyl (1R, 2S)-2-(3-methoxy-3-oxoprop-1-en-2-yl)cyclohexanecarboxylate (2) in 58% yield. The optical yield of the obtained α-methyleneglutarate 2 was determined to be 37% ee by HPLC analysis (Table 1, Entry 1). The effect of various substituents at the 4- and 4’-positions of the bioxazoline ligand 3 was subsequently investigated. As shown in Table 1, use of the isobutyl-substituted ligand 3B resulted in enhanced stereoselectivity (Entry 2), while desymmetrization using the benzyl-substituted bioxazoline ligand 3C proceeded with a further improved enantioselectivity of 60% ee (Entry 3). The use of the 1- and 2-naphthylmethyl substituted ligands 3D and 3E, however, did not improve the selectivity (Entries 5 and 6), while the bulky tert-butyl-substituted ligand 3F was less effective (Entry 7). In addition, the phenyl-substituted ligand 3G resulted in the reverse stereodifferentiation (Entry 8), while the other types of oxazoline ligands 4–6 which we applied gave poor optical yields (Entries 9–11). When the amount of CuOTf(C$_6$H$_6$)$_{0.5}$ was reduced, the chemical yield and optical yields were slightly decreased (Entry 4).
Table 1. Optimization of Reaction Conditions

![Diagram of reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>t/h</th>
<th>Yield/%</th>
<th>ee/%&lt;sup&gt;a&lt;/sup&gt;</th>
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<td>37</td>
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<tr>
<td>3</td>
<td>3C</td>
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</tr>
<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3C</td>
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<td>56</td>
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<td>3E</td>
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<td>57</td>
<td>43&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
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<td>7</td>
<td>3F</td>
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<tr>
<td>8</td>
<td>3G</td>
<td>72</td>
<td>62</td>
<td>-45&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>44</td>
<td>56</td>
<td>7</td>
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<tr>
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<tr>
<td>11</td>
<td>6</td>
<td>43</td>
<td>59</td>
<td>6</td>
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</table>

<sup>a</sup>Enantioselectivities were determined by HPLC analysis (DAICEL CHIRALPAK IA).

<sup>b</sup>The amount of CuOTf(C<sub>6</sub>H<sub>6</sub>)<sub>0.5</sub> was 0.01 equivalent.

<sup>c</sup>Actual reaction was carried out by the use of (R,R)-3E as a ligand to mainly give (1S, 2R)-2.

<sup>d</sup>Actual reaction was carried out by the use of (R,R)-3G as a ligand to mainly give (1R, 2S)-2.

![Structures](image)

3A: R = i-Pr  
3B: R = i-Bu  
3C: R = PhCH<sub>2</sub>  
3D: R = 1-NapCH<sub>2</sub>  
3E: R = 2-NapCH<sub>2</sub>  
3F: R = t-Bu  
3G: R = Ph
The asymmetric ring-opening reactions of the methylene cyclopropanes 7 and 9, with a fused 5- or 8-membered ring, were next investigated using the benzyl-substituted bioxazoline ligand 3C. The ring-opening reaction did not proceed at rt and, when the reaction temperature was increased to 60 °C, a complex mixture of products resulted (Eqs. 1 and 2). In the case of 9, the desired ring-opening product 10 was obtained in only 5% yield with 45% ee.

Next, in order to synthesize optically active oxygen-functionalized glutarate derivatives, meso-methylene cyclopropanes (11) with alkoxy methyl groups at the 1- and 2-positions were used as substrates. The desymmetrization reaction of the (benzyloxy)methyl-substituted methylene cyclopropane 11a using the bioxazoline ligand (S,S)-3C proceeded to afford the ring-opened product 12a in 70% yield, although unfortunately the enantiomeric excess was quite poor (Table 2, Entry 1). Employing the 1-naphthylmethyl-substituted ligand 3D gave very little improvement in the
stereoselectivity of the reaction (Entry 2), while the use of the phenyl-substituted bioxazoline ligand 3G resulted in reversal of the stereoselection in addition to continued low enantioselectivity (Entry 3). When the sterically bulky triphenylmethyl group was introduced in place of the benzyl group on 11a, however, desymmetrization proceeded more efficiently to give the oxygen-functionalized α-methylene glutarate 12b with 42% ee (Entry 4). The triphenylsilyl ether 11c allowed slightly improved enatioselectivity (Entry 5) and, when the tert-butyldiphenylsilyl ether 11d was subjected to the desymmetrization, the corresponding product 12d was obtained with a selectivity of 51% ee (Entries 6 and 7). By the use of phenyl bioxazoline ligand 3G, the reversal of enantioselection was again observed (Entry 8).

Table 2. Scope of Substrates

<table>
<thead>
<tr>
<th>Entry</th>
<th>R’</th>
<th>R (3)</th>
<th>t/h</th>
<th>Yield/%</th>
<th>ee/%</th>
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<tbody>
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<td>a</td>
<td>PhCH2 (3C)</td>
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<td>70</td>
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<tr>
<td>2</td>
<td>1-NapCH2</td>
<td>(3D)</td>
<td>24</td>
<td>47</td>
<td>22&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>(3G)</td>
<td>36</td>
<td>69</td>
<td>–28&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>Ph3Si</td>
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<td>PhCH2 (3C)</td>
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<tr>
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<td>t-BuPh2Si</td>
<td>d</td>
<td>PhCH2 (3C)</td>
<td>49</td>
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<td>1-NapCH2</td>
<td>(3D)</td>
<td>30</td>
<td>82</td>
<td>51&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>Ph</td>
<td>(3G)</td>
<td>71</td>
<td>76</td>
<td>–24&lt;sup&gt;a,b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Enantioselectivity was determined by HPLC analysis (DAICEL CHIRALPAK IA).

<sup>b</sup>Actual reaction was carried out by the use of (R,R)-3G as a ligand to mainly give the same enantiomer with that by the use of (S,S)-3C.

<sup>c</sup>Enantioselectivity was determined by HPLC analysis (DAICEL CHIRALPAK IC).
To establish the absolute configuration of 2, the compound was converted to 14 as follows. Enantiomerically rich 2 (60% ee) obtained by the use of (S,S)-benzyl-substituted bioxazoline ligand (S,S)-3C was reduced to the corresponding diol 13 with LiAlH₄. The diol was subsequently transformed into the bis-camphanic ester 14 by treatment with (1S)-camphanic chloride and Et₃N in the presence of a catalytic amount of 4-(N,N-dimethylamino)pyridine (DMAP) (Scheme 1). Recrystallization gave the diastereomERICally pure compound 14 and the absolute stereochemistry at each of its two chiral centers was determined (Figure 1) by X-ray crystallographic analysis. In this manner, the absolute configuration of 2 obtained by using the (4S,4’S)-benzyl-substituted bioxazoline ligand (S,S)-3C was determined to be 1R,2S. This assignment also demonstrated that the relative stereochemistry of the two substituents on the cyclohexane ring of 2 was cis. The absolute configuration of 10 was also tentatively assigned as 1R,2S. In the case of the 12 series of products shown in Table 2, the stereochemistries of the molecules were assumed to correspond to the same configurational arrangements as the substituents of 2 as depicted in Table 2, in which case the manner of chiral induction is similar to that which occurs in the bis(alkoxycarbonylation) reaction of 1 using (S,S)-3C.

Scheme 1. Conversion of 2 into 14
Although the precise mechanism of the present reaction is still an open question, one possible transition state during the desymmetrization of meso-methylenecyclopropane using the benzyl-substituted ligand $\{(S,S)\}-3C$ is shown in Schemes 2 and 3, based on the absolute stereochemistry assigned above. Copper salt might work not only as an oxidant, but also as a co-catalyst to generate Pd-CO$_2$Me species C as previously proposed.\textsuperscript{9b} That is, CuOTf reacts with CO and MeOH successively to give the CuCO$_2$Me species, from which CO$_2$Me group was transferred to palladium chloride to generate complex C with the chiral ligand 3C. Furthermore, CuOTf also reacts with C to afford a cationic palladium intermediate D, in which olefin strongly coordinate to the palladium metal (Scheme 2). The following carbopalladation proceeds from the anti direction relative to the R substituents, to give a terminal palladium intermediate E regioselectively avoiding steric congestion of the olefin component (Scheme 3).\textsuperscript{14} Desymmetrization then occurs as the result of differentiation of the ring cleavage reaction via either path (a) or (b). In the transition state $T_{cis}$, steric hindrance between R and the palladium complex moiety prevents the cis elimination pathway from proceeding. During trans elimination, there is steric congestion between the benzyl group of the bioxazoline ligand 3C and the cyclopropane moiety in the transition state $T_b$ and therefore the predominant enantiomer in the final product may arise from cleavage reaction (a) via transition state $T_a$ by a trans-β-carbon elimination pathway.\textsuperscript{15} Subsequent to this, a second alkoxycarbonylation can take place with retention of the carbon center to afford enantiomer A, which corresponds to product (1R,2S)-2 obtained from the reaction of the cyclohexane-fused
methylene cyclopropane 1. The cause of the observed reversal of enatiom differentiation with the use of the phenyl-substituted ligand 3G is still not well understood.

Scheme 2. A Proposed Pathway toward Generation of Pd-CO₂Me species

Scheme 3. A Proposed Transition State
3. Conclusions

In conclusion, we have realized the desymmetrization of meso-methylene cyclopropanes by a palladium-catalyzed asymmetric ring-opening bis(alkoxycarbonylation) reaction to afford optically active α-methylene glutarates with up to 60% ee. This asymmetric carbonylation method provides a useful starting point for the synthesis of optically active oxygen-functionalized substrates.

4. Experimental Section

**General Method.** $^1$H NMR spectroscopy was performed in CDCl$_3$ using a JEOL ECS 400 NMR (400 MHz) spectrometer. Chemical shifts ($\delta$) were determined relative to TMS ($\delta=0$ ppm) as an internal standard. $^{13}$C NMR spectroscopy was performed in CDCl$_3$ on a JEOL ECS 400 NMR (100 MHz) spectrometer and chemical shifts ($\delta$) were determined relative to CDCl$_3$ ($\delta=77.0$ ppm) as an internal standard. IR spectra were acquired on a JASCO FT/IR-230 spectrometer. Melting points were determined on a micro-melting apparatus (Yanagimoto–Seisakusho) and were uncorrected. The specific optical rotations were recorded on a JASCO DIP-370 spectrometer. HPLC was performed using chiral column with JASCO PU980 plus JASCO UV970. X-ray crystallography was carried out using Mo-K$_\alpha$ radiation. Elemental analysis was performed on a Yanaco CHN Corder MT-5 elemental analyzer. Mass spectra were obtained using JMS-700 and JMS-T100TD mass spectrometers. All solvents were distilled prior to use and stored over drying agents. Merck silica gel 60 PF254 (Art. 7749), Cica silica gel 60N spherical neutral (37563-84), and JAIGL-SIL (s-043-15) were used for thin-layer chromatography (TLC), flash column chromatography, and recycle HPLC, respectively.

Methylenecyclopropanes 1, 7, 9, and 11a were prepared by literature procedures. Oxygen-functionalized methylenecyclopropanes 11b, 11c, and 11d were prepared from 3-(methylenecyclopropane-1,2-diyl)dimethanol by following procedures.

**1,2-Bis((trityloxy)methyl)-3-methylenecyclopropane (11b)**
A DMF (3 mL) solution of 3-(methylene)cyclopropane-1,2-diyl)dimethanol\(^{18}\) (572 mg, 5 mmol) was added to a mixture of trityl chloride (3.07 g, 11 mmol) and 4-(dimethylamino)pyridine (1.83 g, 15 mmol) in DMF (9 mL) at rt under a nitrogen atmosphere, and the mixture was stirred overnight at rt. Trityl chloride (1.12 g, 4 mmol) was added to the reaction mixture, and the solution was stirred overnight at 80 °C. This mixture was subsequently poured into a mixture of ice and water, and extracted with Et\(_2\)O, after which the combined extracts were washed with H\(_2\)O and brine, dried over Na\(_2\)SO\(_4\), and evaporated under reduced pressure. The residue was purified by recrystallization from toluene to give the corresponding methylene)cyclopropane 11b (2.00 g, 62%) as a solid. m.p. 158 °C (toluene). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 1.91\text{-}1.98 \text{ (m, 2H)}, 2.92\text{-}2.98 \text{ (m, 2H)}, 3.11\text{-}3.15 \text{ (m, 2H)}, 5.43 \text{ (t, } J = 1.8 \text{ Hz, 2H)}, 7.17\text{-}7.21 \text{ (m, 18H)}, 7.31\text{-}7.37 \text{ (m, 12H)}; \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 19.6, 62.5, 86.4, 104.2, 126.8, 127.7, 128.6, 136.6, 144.2; IR (KBr) 3056, 3031, 2973, 2922, 2872, 1595, 1491, 1446, 1385, 1208, 1179, 1157, 1047, 1028, 891, 764, 738, 706 \text{ cm}^{-1};\) elemental analysis calcd (%) for C\(_{44}\)H\(_{38}\)O\(_2\): C 88.26, H 6.40; found: C 87.96, H 6.47.

1,2-Bis-((triphenylsilyloxy)methyl)-3-methylene)cyclopropane (11c)

To a suspension of NaH (60% dispersion in mineral oil, 310 mg, 7.8 mmol) in DMF (14 mL), 3-(methylene)cyclopropane-1,2-diyl)dimethanol (355 mg, 3.1 mmol) in DMF (3 mL) was added at 0 °C. After the evolution of hydrogen gas ceased, 4-(N,N-dimethylamino)pyridine (17 mg, 0.13 mmol) and a DMF (3 mL) solution of chlorotriphenylsilane (2.245 g, 7.6 mmol) were added, and the reaction mixture was stirred at rt for 3 d. The reaction mixture was poured into a mixture of ice and water, and the insoluble substance was filtered through a bed of Celite. The filtrate was extracted with Et\(_2\)O, and the combined extracts were washed by H\(_2\)O and brine, dried over Na\(_2\)SO\(_4\), and condensed under reduced pressure. The residue was purified by column chromatography (SiO\(_2\), hexane/AcOEt = 3/1) to give 11c (1.745 g, 93%) as a solid. m.p. 129 °C (hexane/AcOEt). \(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta = 1.94\text{-}1.96 \text{ (m, 2H)}, 3.79\text{-}3.81 \text{ (m, 4H)}, 5.27 \text{ (t, } J = 1.84 \text{ Hz, 2H)}, 7.26\text{-}7.46 \text{ (m, 30H)}; \(^1\)C NMR (CDCl\(_3\), 100 MHz): \(\delta = 22.2, 62.3, 104.1, 127.8, 129.9, 135.2, 135.4, 136.0; IR (KBr) 3066, 3008, 2911, 2871, 1588, 1485, 1427, 1387, 1308, 1253, 1188, 1158, 1119, 997, 887, 806, 740, 713 \text{ cm}^{-1};\) elemental analysis calcd (%) for C\(_{42}\)H\(_{38}\)O\(_2\)Si\(_2\): C 79.95, H
1,2-Bis-((tert-butyldiphenylsilyloxy)methyl)-3-methylenecyclopropane (11d)

To a suspension of NaH (60% dispersion in mineral oil, 430 mg, 11 mmol) in THF (6 mL), 3-(methylene cyclopropane-1,2-diyl)dimethanol (410 mg, 4 mmol) in THF (3 mL) was added at 0 °C. After the evolution of hydrogen gas ceased, tetrabutylammonium iodide (66 mg, 0.2 mmol) and a THF (3 mL) solution of tert-butyldichlorodiphenylsilane (2.93 g, 11 mmol) were added, and the reaction mixture was stirred at rt for 1 d. Water was added, and the insoluble substance was filtered through a bed of Celite. The filtrate was extracted with Et₂O, and the combined extracts were washed by H₂O and brine, dried over Na₂SO₄, and condensed under reduced pressure. The residue was purified by column chromatography (SiO₂, hexane/AcOEt = 5/1) to give 11d (1.89 g, 89%) as an oil.

1H NMR (CDCl₃, 400 MHz): \( \delta = 1.01 \) (s, 18H), 1.90–1.95 (m, 2H), 3.68 (ddd, \( \delta = 11.0, 6.9, 2.3 \) Hz, 2H), 3.73 (ddd, \( \delta = 11.0, 7.3, 2.3 \) Hz, 2H), 5.35 (dd, \( \delta = 2.3, 1.8 \) Hz, 2H), 7.30–7.36 (m, 8H), 7.36–7.43 (m, 4H), 7.61–7.67 (m, 8H); 13C NMR (CDCl₃, 100 MHz): \( \delta = 19.1, 22.1, 26.8, 62.6, 103.8, 127.6, 129.49, 129.52, 133.7, 133.8, 135.5, 135.6, 136.6 \); IR (neat) 3070, 2958, 2930, 2857, 1589, 1472, 1427, 1389, 1112, 1074, 823, 739, 702 cm⁻¹; HRMS (EI): \( m/z \) calcld for C₃₈H₄₆O₂Si₂: 590.30364 [M]⁺; found: 590.30370.

The ligands (S,S)-3D and (R,R)-3E were prepared by literature procedures for the synthesis of other bioxazoline ligands starting from (S)-2-amino-3-(1-naphthalenyl)-1-propanol and (R)-2-amino-3-(2-naphthalenyl)-1-propanol, respectively.

(S,S)-4,4'-Bis(1-naphthalenylmethyl)-4,4',5,5'-tetrahydro-2,2'-bioxazole (3D): m.p. 149 °C (hexane/AcOEt); \([\alpha]_D^{25} = -5\) (c 0.9, CHCl₃); 1H NMR (CDCl₃, 400 MHz): \( \delta = 3.00 \) (dd, \( \delta = 14.2, 10.1 \) Hz, 2H), 3.88 (dd, \( \delta = 14.2, 4.1 \) Hz, 2H), 4.289 (d, 2H, \( \delta = 8.2 \) Hz), 4.294 (d, 2H, \( \delta = 9.2 \) Hz), 4.77–4.85 (m, 2H), 7.34 (d, \( \delta = 6.9 \) Hz, 2H), 7.41 (dd, \( \delta = 8.2, 6.9 \) Hz, 2H), 7.48–7.57 (m, 4H), 7.76 (d, \( \delta = 7.8 \) Hz, 2H), 7.86 (d, \( \delta = 8.2 \) Hz, 2H), 8.09 (d, \( \delta = 8.2 \) Hz, 2H); 13C NMR (CDCl₃, 100 MHz): \( \delta = 38.5, 67.2, 73.1, 123.4, 125.4, 125.8, 126.3, 126.8, 127.7, 128.9, 131.7, 133.1, 133.9, 155.2 \); IR (KBr) 3045, 2953, 2885, 1613, 1508, 1472, 1395, 1308, 1228, 1131, 1093, 1075, 953, 795, 776, 740 cm⁻¹; HRMS (ESI-TOF): \( m/z \) calcld for C₂₈H₂₄N₂O₂Na: 443.1736 [M+Na]⁺; found:
(R,R)-4,4'-Bis(2-naphthalenylmethyl)-4,4',5,5'-tetrahydro-2,2'-bioxazole (3E):

m.p. 173 °C (hexane/AcOEt); [α]D

1H NMR (CDCl3, 400 MHz): δ = 2.85 (dd, J = 13.8, 9.2 Hz, 2H), 3.42 (dd, J = 13.8, 4.6 Hz, 2H), 4.21 (t, J = 8.2 Hz, 2H), 4.37 (dd, J = 10.1, 8.2 Hz, 2H), 4.67–4.75 (m, 2H), 7.34 (d, J = 8.2 Hz, 2H), 7.42–7.48 (m, 4H), 7.63 (s, 2H), 7.77–7.81 (m, 6H); 13C NMR (CDCl3, 100 MHz): δ = 41.2, 68.1, 72.7, 125.6, 126.2, 127.3, 127.5, 127.6, 128.4, 132.3, 133.5, 134.6, 155.1; IR (KBr) 3055, 2897, 1613, 1508, 1479, 1363, 1135, 1084, 1054, 944, 901, 861, 758, 735 cm


A Representative Procedure for the Asymmetric Bis(alkoxycarbonylation) Reaction of 1 (Table 1, Entry 3): Under an Ar atmosphere, CuOTf(C6H6)0.5 (253 mg, 1.0 mmol) was placed in a flask, and a MeOH (12 mL) solution of 7-methylenebicyclo[4.1.0]heptane (1) (217 mg, 2.0 mmol) and a THF (12 mL) solution of (S,S)-3C (26 mg, 0.08 mmol) were added. To the mixture, PdCl2 (7.1 mg, 0.04 mmol) was added. The Ar atmosphere was replaced with CO/O2 (ca. 1/1, v/v), and the reaction mixture was stirred for 60 h at rt. A saturated aq solution of NaHCO3 was added to the reaction mixture at rt, and the insoluble substance was filtered off. After the filtrate was extracted with AcOEt, the combined extracts were washed with water and brine, dried over Na2SO4, and condensed in vacuo. The residue was purified by TLC on SiO2 (hexane/AcOEt = 7/1, v/v) to give 2 (237 mg, 53%) with a selectivity of 60% ee.

In a similar manner, the glutaric acid dimethyl esters 10, and 12, were prepared from the corresponding methylenecyclopropanes 9, and 11, respectively.

(1R,2S)-Methyl 2-(3-methoxy-3-oxo-1-propen-2-yl)cyclohexanecarboxylate (2):

Compound 2 (237 mg, 53%) was obtained as an oil. [α]D

1H NMR (CDCl3, 400 MHz): δ = 1.29–1.43 (m, 1H), 1.49–1.61 (m, 2H), 1.59–1.73 (m, 2H), 1.81–1.90 (m, 2H).
1H), 1.91–2.04 (m, 2H), 2.75–2.84 (m, 1H), 3.04–3.09 (m, 1H), 3.55 (s, 3H), 3.77 (s, 3H), 5.58 (s, 1H), 6.23 (s, 1H); 13C NMR (CDCl₃, 100 MHz) δ = 21.6, 25.68, 25.72, 28.3, 39.4, 42.6, 50.7, 51.8, 124.8, 142.7, 167.5, 174.4; IR (neat) 2949, 2859, 1735, 1720, 1437, 1281, 1247, 1194, 1165, 1143, 1030, 995, 949, 937, 819 cm⁻¹; HRMS (EI): m/z calcd for C₁₂H₁₈O₄: 226.12051 [M⁺]; found: 226.12062.

(1R,2S)-Methyl 2-(3-methoxy-3-oxo-1-propen-2-yl)cyclooctanecarboxylate (10): 9-Methylenebicyclo[6.1.0]nonane (9) (68 mg, 0.50 mmol) was subjected to the carbonylation using PdCl₂ (1.8 mg, 0.01 mmol), CuOTf(C₆H₆)₀.₅ (63 mg, 0.25 mmol), and ligand (S,S)-3C (7 mg, 0.02 mmol) in MeOH/THF (3 mL/3 mL) at 60 °C for 47 h. Compound 10 (6 mg, 5%) was obtained as an oil. [α]₂⁵D –11 (c 0.1, EtOH); The ee was determined to be 45% by HPLC (DAICEL CHIRALPAK IA×2, hexane/EtOH = 400/1, 0.5 mL/min, 220 nm, major 42 min and minor 38 min); ¹H NMR (CDCl₃, 400 MHz): δ = 1.51–1.71 (m, 7H), 1.71–1.84 (m, 2H), 1.84–1.93 (m, 2H), 1.93–2.05 (m, 1H), 2.82–2.90 (m, 1H), 3.32 (dd, J = 11.5, 3.6, 3.2 Hz, 1H), 3.57 (s, 3H), 3.76 (s, 3H), 5.57 (s, 1H), 6.25 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz) δ = 25.5, 26.4, 26.7, 26.9, 28.2, 29.4, 37.4, 46.0, 51.1, 52.0, 124.8, 143.7, 167.8, 175.5; IR (neat) 2922, 2851, 1725, 1685, 1627, 1436, 1268, 1192, 1168 cm⁻¹; HRMS (EI): m/z calcd for C₁₄H₂₂O₄: 254.15181 [M⁺]; found: 254.15194.

(2S,3S)-Dimethyl 2,3-bis((benzyloxy)methyl)-4-methylenepentanedioate (12a): 1,2-Bis((benzyloxy)methyl)-3-methylenecyclopropane (11a) (148 mg, 0.50 mmol) was subjected to the carbonylation using PdCl₂ (1.8 mg, 0.01 mmol), CuOTf(C₆H₆)₀.₅ (65 mg, 0.25 mmol), and ligand (R,R)-3G (6 mg, 0.02 mmol) in MeOH/THF (3 mL/3 mL) at rt for 36 h. Compound 12a (142 mg, 69%) was obtained as an oil. [α]₂⁵D +6 (c 1.3, EtOH); The ee was determined to be 28% by HPLC (DAICEL CHIRALPAK IA×2, hexane/EtOH = 100/1, 0.5 mL/min, 254 nm, major 82 min and minor 88 min); ¹H NMR (CDCl₃, 400 MHz): δ = 3.14 (ddd, J = 10.1, 8.7, 4.6 Hz, 1H), 3.28 (dt, J = 10.1, 6.4 Hz, 1H), 3.49 (ddd, J = 9.6, 4.6 Hz, 1H), 3.52-3.64 (m, 3H), 3.62 (s, 3H), 3.69 (s, 3H), 4.41 (d, J = 12.4 Hz, 2H), 4.45 (d, J = 12.4 Hz, 1H), 4.47 (d, J = 12.4 Hz, 1H), 5.68 (s, 1H), 6.29 (s, 1H), 7.22–7.35 (m, 10H); ¹³C NMR (CDCl₃, 100 MHz) δ = 41.7, 47.1, 51.7, 51.9, 70.0, 71.1, 72.8, 72.9, 127.46, 127.49, 127.52 127.6, 127.8, 128.3, 129.6, 137.9, 138.1, 138.4, 166.8, 174.0; IR (neat) 2951, 2863, 1738, 1719, 1626, 1454, 1436, 1363, 1270, 1197, 1156, 1100, 1028, 739, 699 cm⁻¹; HRMS (EI): m/z calcd for C₂₄H₂₈O₆: 412.18859 [M⁺]; found: 412.18843.
(3S,4S)-Dimethyl 2-methylene-3,4-bis((trityloxy)methyl)pentanedioate (12b):
1,2-Bis((trityloxy)methyl)-3-methylene cyclopropane (11b) (299 mg, 0.50 mmol) was subjected to the carbonylation using PdCl₂ (1.8 mg, 0.01 mmol), CuOTf(C₆H₆)₀.₅ (65 mg, 0.25 mmol), and ligand (S,S)-3C (7 mg, 0.02 mmol) in MeOH/THF (3 mL/3 mL) at rt for 67 h. Compound 12b (234 mg, 65%) was obtained as a solid. [α]²⁵°D +5 (c 0.5, EtOH); The ee was determined to be 42% by HPLC (DAICEL CHIRALPAK IA, hexane/EtOH = 50/1, 0.5 mL/min, 254 nm, major 28 min and minor 31 min); m.p. 146 °C (recrystallized from CHCl₃/Hex); ¹H NMR (CDCl₃, 400 MHz): δ 2.98–3.06 (m, 1H), 3.06–3.12 (m, 2H), 3.12–3.26 (m, 3H), 3.15 (s, 3H), 3.57 (s, 3H), 6.09 (s, 1H), 7.18–7.25 (m, 18H), 7.30–7.35 (m, 12H); ¹³C NMR (CDCl₃, 100 MHz) δ = 41.4, 46.8, 51.4, 51.6, 63.3, 64.1, 86.5, 126.8, 126.9, 127.55, 127.59, 128.5, 128.6, 143.7, 166.6, 173.9; IR (KBr) 3056, 3022, 2949, 2877, 1741, 1725, 1626, 1597, 1491, 1448, 1325, 1224, 1193, 1153, 1078, 764, 747, 706 cm⁻¹; HRMS (ESI-TOF): m/z calcd for C₄₈H₄₄O₆Na: 739.3036 [M+Na]+; found: 739.3038.

(3S,4S)-Dimethyl 2-methylene-3,4-bis((triphenylsilyloxy)methyl)pentanedioate (12c):
1,2-Bis((triphenylsilyloxy)methyl)-3-methylene cyclopropane (11c) (252 mg, 0.4 mmol) was subjected to the carbonylation using PdCl₂ (1.4 mg, 0.008 mmol), CuOTf(C₆H₆)₀.₅ (60 mg, 0.2 mmol), and ligand (S,S)-3C (5.1 mg, 0.016 mmol) in MeOH/THF (2 mL/2 mL) at rt for 72 h. 12c (145 mg, 48%) was obtained as a solid. [α]²⁵°D +6 (c 1.5, CHCl₃); The ee was determined to be 48% by HPLC (DAICEL CHIRALPAK IC, hexane/EtOH = 100/1, 0.5 mL/min, 254 nm, major 13.5 min and minor 15.4 min); m.p. 124 °C (AcOEt/hexane); ¹H NMR (CDCl₃, 400 MHz): δ = 3.07 (ddd, J = 10.6, 8.7, 4.6 Hz, 1H), 3.17–3.22 (m, 1H), 3.43 (s, 3H), 3.53 (s, 3H), 3.75–3.82 (m, 3H), 3.91 (dd, J = 10.1, 8.7 Hz, 1H), 5.39 (s, 1H), 6.13 (s, 1H), 7.33–7.45 (m, 18H), 7.52–7.56 (m, 10H), 7.63–7.65 (m, 2H); ¹³C NMR (CDCl₃, 100 MHz) δ = 42.7, 48.8, 51.4, 51.7, 63.9, 64.4, 127.8, 128.0, 129.96, 130.01, 133.7, 135.3, 135.4, 137.9, 166.8, 173.9; IR (KBr) 3068, 2946, 2867, 1740, 1721, 1703, 1622, 1588, 1485, 1428, 1382, 1333, 1255, 1119, 996, 835, 741, 714 cm⁻¹; elemental analysis calcd (%) for C₄₆H₄₄O₆Si₂: C, 73.76; H, 5.92; found: C, 73.57; H, 6.03.
(2S,3S)-Dimethyl

2,3-bis((tert-butyldiphenylsilyloxy)methyl)-4-methylenepentanedioate (12d):

1,2-Bis((tert-butyldiphenylsilyloxy)methyl)-3-methylene cyclopropane (11d) (296 mg, 0.50 mmol) was subjected to the carbonylation using PdCl₂ (1.9 mg, 0.01 mmol), CuOTf(C₆H₆)₀.₅ (61 mg, 0.24 mmol), and ligand (S,S)-3D (9 mg, 0.02 mmol) in MeOH/THF (3 mL/3 mL) at rt for 30 h. Compound 12d (289 mg, 82%) was obtained as an oil. [α]₂⁵_D +3 (c 1.9, EtOH); The ee was determined to be 51% by HPLC (DAICEL CHIRALPAK IA×2, hexane/EtOH = 100/1, 0.5 mL/min, 254 nm, major 17 min and minor 19 min); ¹H NMR (CDCl₃, 400 MHz): δ = 0.99 (s, 18H), 3.08 (ddd, J = 11.0, 8.7, 4.1 Hz, 1H), 3.16 (ddd, J = 11.0, 6.4, 4.1 Hz, 1H), 3.59 (dd, J = 10.5, 4.1 Hz, 1H), 3.65 (dd, J = 10.0, 4.1 Hz, 1H), 3.68 (dd, J = 10.5, 6.4 Hz, 1H), 3.61 (s, 3H), 3.62 (s, 3H), 3.82 (dd, J = 10.0, 8.7 Hz, 1H), 5.39 (s, 1H), 6.18 (s, 1H), 7.31–7.44 (m, 12H), 7.54–7.64 (m, 8H); ¹³C NMR (CDCl₃, 100 MHz) δ = 19.0, 19.1, 26.5, 26.6, 42.5, 48.4, 51.4, 51.7, 51.9, 172.5, 175.4; IR (neat) 3071, 3049, 2931, 2857, 1736, 1720, 1624, 1472, 1428, 1252, 1194, 1154, 1111, 822, 841, 702 cm⁻¹; HRMS (EI): m/z calcld for C₄₂H₅₂O₆Si₂: 708.33025 [M⁺]; found: 708.33076.

Methyl 7-(2-methoxy-2-oxoethyl)bicyclo[4.1.0]heptane-7-carboxylate (15)¹¹:

7-Methylenebicyclo[4.1.0]heptane (1) (106 mg, 0.98 mmol) was subjected to the carbonylation using PdCl₂ (3.6 mg, 0.02 mmol), and CuOTf(C₆H₆)₀.₅ (127 mg, 0.50 mmol) in MeOH/THF (6 mL/6 mL) at rt for 36 h. Compound 2 (87 mg, 39%) and compound 15 (44 mg, 20%) were obtained. 15: an oil; ¹H NMR (CDCl₃, 400 MHz): δ = 1.16–1.51 (m, 6H), 1.71–1.78 (m, 2H), 1.90–2.05 (m, 2H), 2.67 (s, 2H), 3.62 (s, 3H), 3.71 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ = 18.6, 21.5, 22.7, 27.5, 30.6, 51.7, 51.9, 172.5, 175.4; IR (neat) 2969, 2931, 2857, 1758, 1723, 1672, 1435, 1411, 1359, 1309, 1276, 1200, 1172, 1131, 1068, 1043, 1012, 930, 879, 848, 780, 697 cm⁻¹; HRMS (EI): m/z calcld for C₁₂H₁₈O₄: 226.12051 [M⁺]; found: 226.12040.

(1S,4R)-2-((1S,2R)-2-(((1S,4R)-4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carbonyl)oxy)methyl)cyclohexyl)allyl

4,7,7-trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylate (14):

To a suspension of LiAlH₄ (65 mg, 1.75 mmol) in Et₂O (5 mL) was added dropwise an
Et₂O (3 mL) solution of 2 (113 mg, 0.50 mmol, 60% ee) at 0 °C under N₂ atmosphere. The resulting mixture was gradually warmed to rt and stirred overnight at rt, and then treated with a saturated aq Na₂SO₄ solution (0.5 mL). The insoluble substance was filtered through a bed of Celite, followed by washing with AcOEt, and the filtrate was concentrated in vacuo. Separation of the residue by column chromatography (hexane/AcOEt = 1/1, v/v) afforded the corresponding diol 13 (51 mg, 65%) as an oil. A CH₂Cl₂ (3 mL) solution of (S)-camphanic chloride (171 mg, 0.79 mmol) was added to a mixture of the diol 13 (51 mg, 0.33 mmol), triethylamine (0.12 mL, 0.86 mmol), and 4-(dimethylamino)pyridine (5 mg, 0.03 mmol) in CH₂Cl₂ (3 mL) at rt under a nitrogen atmosphere and the mixture was stirred overnight at rt. The reaction was quenched by the addition of an aqueous solution of 1 M HCl aq (1.5 mL), and the mixture was subsequently extracted with AcOEt. The combined extracts were washed by H₂O and brine, dried over Na₂SO₄, and condensed under reduced pressure. The residue was purified by TLC on SiO₂ (hexane/AcOEt = 3:2) to give the corresponding ester (131 mg, 75%) as a mixture of diastereomer as a solid. Recrystallization (Et₂O/hexane) gave more diastereomerically pure ester (66 mg). The obtained substrate was further separated by recycle HPLC (hexane/AcOEt = 3:1) to give almost diastereomerically pure product (20 mg). Diastereomerically pure 14 was obtained by recrystallization from Et₂O. [α]D²⁵ –11 (c 0.1, EtOH); m.p. 135 °C (Et₂O). ¹H NMR (CDCl₃, 400 MHz): δ = 0.94 (s, 3H), 0.98 (s, 3H), 1.05 (s, 3H), 1.07 (s, 3H), 1.11 (s, 3H), 1.12 (s, 3H), 1.21–1.73 (m, 8H), 1.80–2.09 (m, 6H), 2.26–2.36 (m, 2H), 2.36–2.49 (m, 2H), 4.15 (dd, J = 11.0, 4.6 Hz, 1H), 4.24 (dd, J = 11.0, 9.2 Hz, 1H), 4.70 (d, J = 13.3 Hz, 1H), 4.84 (d, J = 13.3 Hz, 1H), 4.97 (s, 1H), 5.20 (s, 1H); ¹³C NMR (CDCl₃, 100 MHz): δ = 9.7, 16.7, 20.5, 25.2, 25.9, 27.6, 28.9, 30.5, 30.6, 34.3, 41.1, 54.1, 54.2, 54.7, 54.8, 63.66, 63.74, 67.2, 91.08, 91.13, 113.7, 144.9, 167.2, 167.6, 178.17, 178.25; IR (KBr) 2968, 2933, 2857, 1795, 1751, 1718, 1649, 1453, 1399, 1359, 1348, 1332, 1316, 1271, 1227, 1166, 1106, 1064, 995, 928, 913 cm⁻¹; HRMS (ESI-TOF): m/z calcd for C₃₀H₄₂O₈Na: 553.2777 [M+Na]⁺; found: 553.2779. Crystal data: C₃₀H₄₂O₈, FW 530.66, monoclinic, P₂₁, a = 11.049(2), b = 10.876(2), c = 12.586(2) Å, V = 1375.7(5)Å³, β = 114.556(4)°, Z = 2. Dcalc = 1.281 g/cm³. R = 0.057 (Rw = 0.069) for 5515 reflections with I > 3.000σ(I) and 344 variable parameters. CCDC-985876 (14) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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References


6. Examples of catalytic asymmetric desymmetrization of *meso*-methylene cyclopropanes; see references 2b, 2f, 2g and 7b.


11. It was found that bis(alkoxycarbonylation) reaction of 1 without chiral ligand 3C afforded not only 2 (39%) but also a considerable amount of a succinate 15 (20%) (see Experimental Section).

12. In this reaction, 15\textsuperscript{11} was not isolated after the purification procedure.


14. In the bis(alkoxycarbonylation) reaction in the absence of bioxazoline ligand 3C, carbopalladation by chiral ligand-free palladium catalyst might proceed in non-regioselective manner to give both the terminal intermediate F and the internal palladium intermediate G which produced the succinate $15^{11}$ by the second alkoxy carbonylation. To the contrary, the palladium coordinated by bioxazoline ligand 3C might be bulky enough to afford the terminal palladium intermediate E, regioselectively.

15. At present, an alternative pathway via cleavage of proximal cyclopropane C–C bond through oxidative addition to methylenecyclopropane$^{21}$ could not be ruled out.


