Tetrahedron: *Asymmetry* 25 (2014) 936–943

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Desymmetrization of *meso*-methylenecyclopropanes by a palladium-catalyzed asymmetric ring-opening bis(alkoxycarbonylation) reaction

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ARTICLE INFO

Article history:
Received 5 March 2014
Accepted 14 May 2014
Available online 23 June 2014

ABSTRACT

Desymmetrization of various *meso*-methylenecyclopropanes 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-methyleneglutarates with up to 60% ee. Desymmetrization of protected *meso*-(3-methylenecyclopropane-1,2-diyl)dimethanols was also carried out to give enantioenriched highly oxygen-functionalized α-methyleneglutarates.

1. Introduction

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 relatively 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 selective mono- and bis(alkoxycarbonylation) reactions of terminal olefins catalyzed by palladium in the presence of copper salts under a mixture 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 the direct introduction of two carbonyl groups and have developed the ring-opening reaction of methylenecyclopropanes to afford the corresponding α-methyleneglutarates.[5] In order to prepare optically active glutaric acid derivatives, the asymmetric ring-opening bis(alkoxycarbonylation) reaction of methylenecyclopropanes could be effective.[6–8] Herein we report the desymmetrization of *meso*-methylenecyclopropanes by a palladium-catalyzed ring-opening bis(alkoxycarbonylation) reaction in the presence of a chiral bioxazoline ligand.[9]

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 equiv of $PdCl_2$ and 0.5 equiv of $CuOTf(C_6H_6)_{0.5}$ 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.[9–11] The reaction proceeded very slowly to give methyl (1*R*,2*S*)-2-(3-methoxy-3-oxoprop-1-en-2-yl)cyclohexanecarboxylate **2** in 58% yield. The enantiomeric excess 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, the 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).[12] 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 a reverse stereodifferentiation (entry 8), while the other types of oxazoline ligands **4**–**6** gave poor enantiomeric excesses (entries 9–11). When the amount of $CuOTf(C_6H_6)_{0.5}$ was reduced, the chemical yield and enantiomeric excesses were slightly decreased (entry 4).

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http://dx.doi.org/10.1016/j.tetasy.2014.05.007
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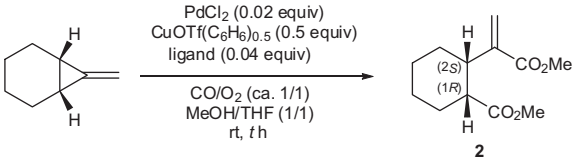
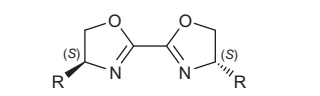
Table 1
Optimization of the reaction

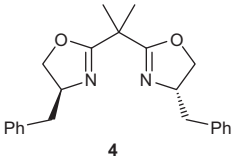


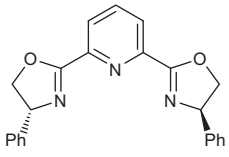
Entry	Ligand	*t* (h)	Yield (%)	ee[a] (%)
1	**3A**	41	58	37
2	**3B**	49	65	51
3	**3C**	60	53	60
4[b]	**3C**	59	50	56
5	**3D**	37	54	50
6	**3E**	37	57	43[c]
7	**3F**	47	47	8
8	**3G**	72	62	−45[d]
9	**4**	44	56	7
10	**5**	41	60	7
11	**6**	43	59	6

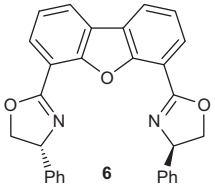
[a] Enantioselectivities were determined by HPLC analysis (DAICEL CHIRALPAK IA).
[b] The amount of $CuOTf(C_6H_6)_{0.5}$ was 0.01 equiv.
[c] This reaction was carried out by using (*R*,*R*)-**3E** as the ligand to give mainly (1*S*,2*R*)-**2**.
[d] This reaction was carried out by using (*R*,*R*)-**3G** as the ligand to give mainly (1*R*,2*S*)-**2**.



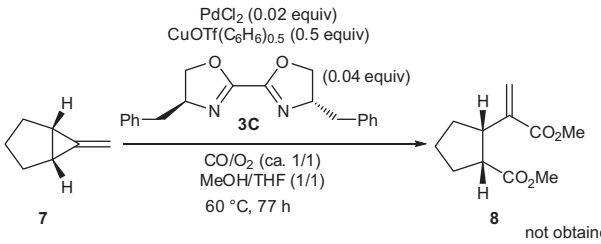
3A: R = *i*-Pr
3B: R = *i*-Bu
3C: R = $PhCH_2$
3D: R = 1-NapCH_2
3E: R = 2-NapCH_2
3F: R = *t*-Bu
3G: R = Ph



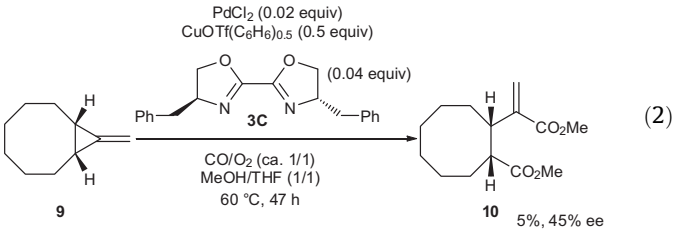




The asymmetric ring-opening reactions of the methylene cyclopropanes **7** and **9**, with a fused 5- or 8-membered ring, were next investigated using the benzyl-substituted bioxazoline ligand **3C**. The ring-opening reaction did not proceed at rt and, when the reaction temperature was increased to 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.



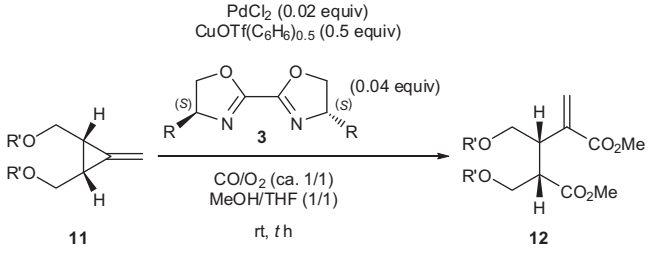
(1)



(2)

Next, in order to synthesize optically active oxygen-functionalized glutarate derivatives,[13] *meso*-methylene cyclopropanes **11** with alkoxymethyl 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 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 a reversal of the stereoselection in addition to continued low enantioselectivity (entry 3). When a sterically bulky triphenylmethyl group was introduced in place of the benzyl group on **11a**, desymmetrization proceeded more efficiently to give the oxygen-functionalized α-methyleneglutarate **12b** with 42% ee (entry 4). The triphenylsilyl ether **11c** gave slightly improved enatioselectivity (entry 5) and when the *tert*-butyldiphenylsily ether **11d** was subjected to desymmetrization, the corresponding product **12d** was obtained with a selectivity of 51% ee (entries 6 and 7). When using phenyl bioxazoline ligand **3G**, a reversal of enantioselection was again observed (entry 8).

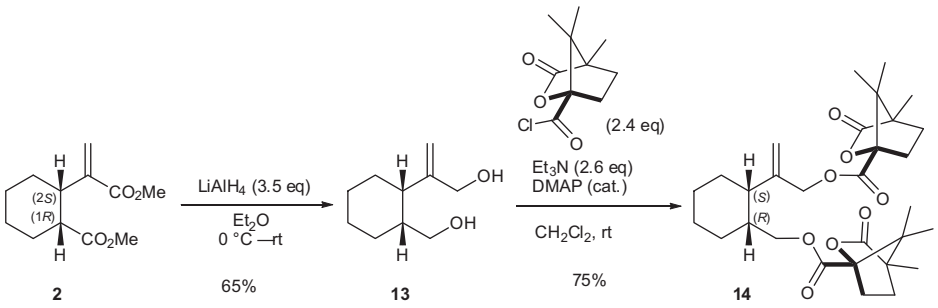
Table 2
Scope of the substrates



Entry	R′		R **3**	*t* (h)	Yield (%)	ee (%)
1	$PhCH_2$	**a**	$PhCH_2$ **3C**	43	70	18[a]
2			1-NapCH_2 **3D**	24	47	22[a]
3			Ph **3G**	36	69	−28[a,b]
4	Ph_3C	**b**	$PhCH_2$ **3C**	67	65	42[a]
5	Ph_3Si	**c**	$PhCH_2$ **3C**	72	48	48[c]
6	*t*-$BuPh_2Si$	**d**	$PhCH_2$ **3C**	49	67	51[a]
7			1-NapCH_2 **3D**	30	82	51[a]
8			Ph **3G**	71	76	−24[a,b]

[a] Enantioselectivitiy was determined by HPLC analysis (DAICEL CHIRALPAK IA).
[b] This reaction was carried out by using (*R*,*R*)-**3G** as a ligand to give mainly the same enantiomer as that when using (*S*,*S*)-**3C**.
[c] Enantioselectivitiy was determined by HPLC analysis (DAICEL CHIRALPAK IC).

In order to establish the absolute configuration of **2**, the compound was converted into **14** as follows. Enantiomerically enriched **2** (60% ee) obtained by using (*S*,*S*)-benzyl-substituted bioxazoline ligand (*S*,*S*)-**3C** was reduced into the corresponding diol **13** with $LiAlH_4$. The diol was subsequently transformed into the bis-camphanic ester **14** by treatment with (1*S*)-camphanic chloride



Scheme 1. Conversion of **2** into **14**.

and Et_3N 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 stereogenic centers was determined (Fig. 1) by X-ray crystallographic analysis. In this manner, the absolute configuration of **2** obtained by using the (4*S*,4′*S*)-benzyl-substituted bioxazoline ligand (*S*,*S*)-**3C** was determined to be (1*R*,2*S*). 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 (1*R*,2*S*). In the case of products **12** 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 the chiral induction is similar to that which occurs in the bis(alkoxycarbonylation) reaction of **1** using (*S*,*S*)-**3C**.

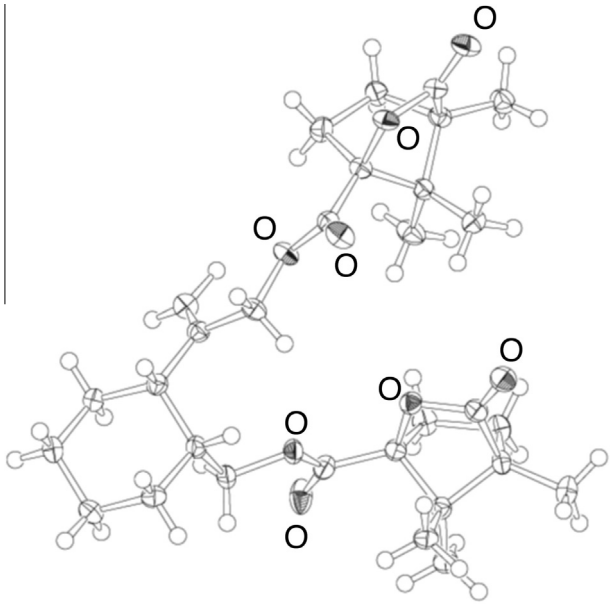
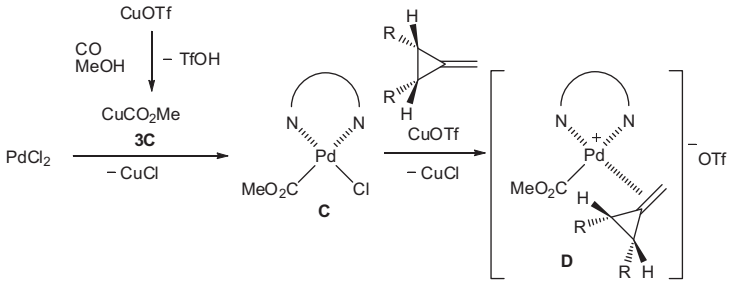
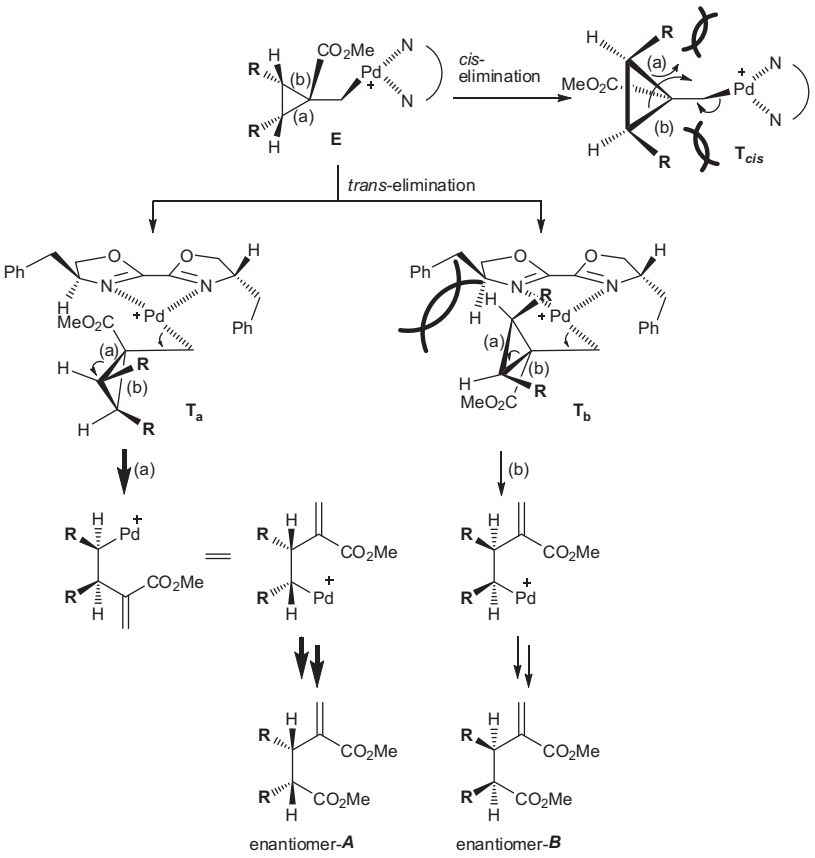


Figure 1. X-ray crystal structure of compound **14**.

Although the precise mechanism of the present reaction is still unknown, 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. The copper salt might work not only as an oxidant, but also as a co-catalyst to generate Pd-CO_2Me species **C** as previously proposed,[9b] that is, CuOTf reacts with CO and MeOH successively to give the $CuCO_2Me$ species, from which the CO_2Me group was transferred into 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 the olefin strongly coordinates 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 with the olefin component (Scheme 3).[14] Desymmetrization then occurs due to differentiation of the ring cleavage reaction via either path (a) or (b). In the transition state $\mathbf{T}_{cis}$, the 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 $\mathbf{T_b}$ and therefore the predominant enantiomer in the final product may arise from cleavage reaction (a) via transition state $\mathbf{T_a}$ by a *trans*-β-carbon elimination pathway.[15] Subsequent to this, a second alkoxycarbonylation can take place with retention of the carbon center to afford enantiomer ***A***, which corresponds to product (1*R*,2*S*)-**2** obtained from the reaction of the cyclohexane-fused methylenecyclopropane **1**. The cause of the observed reversal of enatiodifferentiation with the use of the phenyl-substituted ligand **3G** is still not well understood.



Scheme 2. A proposed pathway toward the generation of a Pd-CO_2Me species.



Scheme 3. Proposed transition states.

3. Conclusion

In conclusion, we have realized the desymmetrization of *meso*-methylenecyclopropanes by a palladium-catalyzed asymmetric ring-opening bis(alkoxycarbonylation) reaction to afford optically active α-methyleneglutarates 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

4.1. General method

^{1}H NMR spectroscopy was performed in $CDCl_3$ using a JEOL ECS 400 NMR (400 MHz) spectrometer. Chemical shifts (δ) were determined relative to TMS (δ = 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 (δ) were determined relative to $CDCl_3$ (δ = 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 are uncorrected. Optical rotations were recorded on a JASCO DIP-370 spectrometer. HPLC was performed using a chiral column with JASCO PU980 plus JASCO UV970. X-ray crystallography was carried out using Mo-Kα 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 60 N 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**,[16] **7**,[16] **9**,[16] and **11a**[17] were prepared by literature procedures. Oxygen-functionalized methylenecyclopropanes **11b**, **11c**, and **11d** were prepared from 3-(methylenecyclopropane-1,2-diyl)dimethanol by the following procedures.

4.2. 1,2-Bis((trityloxy)methyl)-3-methylenecyclopropane 11b

A DMF (3 mL) solution of 3-(methylenecyclopropane-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 then 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_2O, after which the combined extracts were washed with H_2O and brine, dried over Na_2SO_4, and evaporated under reduced pressure. The residue was purified by recrystallization from toluene to give the corresponding methylenecyclopropane **11b** (2.00 g, 62%) as a solid. Mp 158 °C (toluene). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.91–1.98 (m, 2H), 2.92–2.98 (m, 2H), 3.11–3.15 (m, 2H), 5.43 (t, J = 1.8 Hz, 2H), 7.17–7.21 (m, 18H), 7.31–7.37 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 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 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.

4.3. 1,2-Bis-((triphenylsilyloxy)methyl)-3-methylenecyclopropane 11c

To a suspension of NaH (60% dispersion in mineral oil, 310 mg, 7.8 mmol) in DMF (14 mL), 3-(methylenecyclopropane-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_2O, and the combined extracts were washed by H_2O and brine, dried over Na_2SO_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. Mp 129 °C (hexane/AcOEt). ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.94–1.96 (m, 2H), 3.79–3.81 (m, 4H), 5.27 (t, 2H, *J* = 1.84 Hz), 7.26–7.46 (m, 30H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 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 cm^{-1}; elemental analysis calcd (%) for $C_{42}H_{38}O_2Si_2$: C 79.95, H 6.07; found: C 79.79, H 6.10.

4.4. 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-(methylenecyclopropane-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*-butylchlorodiphenylsilane (2.93 g, 11 mmol) were added, and the reaction mixture was stirred at rt for 1 d. Water was then added, and the insoluble substance was filtered through a bed of Celite. The filtrate was extracted with Et_2O, and the combined extracts were washed by H_2O and brine, dried over Na_2SO_4, and condensed under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/AcOEt = 5:1) to give **11d** (1.89 g, 89%) as an oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.01 (s, 18H), 1.90–1.95 (m, 2H), 3.68 (ddd, *J* = 11.0, 6.9, 2.3 Hz, 2H), 3.73 (ddd, *J* = 11.0, 7.3, 2.3 Hz, 2H), 5.35 (dd, *J* = 2.3, 1.8 Hz, 2H), 7.30–7.36 (m, 8H), 7.36–7.43 (m, 4H), 7.61–7.67 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 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* calcd for $C_{38}H_{46}O_2Si_2$: 590.30364 $[M]^+$; found: 590.30370.

Ligands (*S*,*S*)-**3D** and (*R*,*R*)-**3E** were prepared by literature procedures[10a,19] described for the synthesis of other bioxazoline ligands starting from (*S*)-2-amino-3-(1-naphthalenyl)-1-propanol and (*R*)-2-amino-3-(2-naphthaleny)-1-propanol,[20] respectively.

4.5. (*S*,*S*)-4,4′-Bis(1-naphthalenylmethyl)-4,4′,5,5′-tetrahydro-2,2′-bioxazole 3D

Mp 149 °C (hexane/AcOEt); $[\alpha]_D^{25}$ = −5 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 3.00 (dd, *J* = 14.2, 10.1 Hz, 2H), 3.88 (dd, *J* = 14.2, 4.1 Hz, 2H), 4.289 (d, 2H, *J* = 8.2 Hz), 4.294 (d, 2H, *J* = 9.2 Hz), 4.77–4.85 (m, 2H), 7.34 (d, *J* = 6.9 Hz, 2H), 7.41 (dd, *J* = 8.2, 6.9 Hz, 2H), 7.48–7.57 (m, 4H), 7.76 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H), 8.09 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 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* calcd for $C_{28}H_{24}N_2O_2Na$: 443.1736 $[M+Na]^+$; found: 443.1739.

4.6. (*R*,*R*)-4,4′-Bis(2-naphthalenylmethyl)-4,4′,5,5′-tetrahydro-2,2′-bioxazole 3E

Mp 173 °C (hexane/AcOEt); $[\alpha]_D^{25}$ = −26 (*c* 0.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, 822, 758, 735 cm^{-1}; HRMS (ESI-TOF): *m*/*z* calcd for $C_{28}H_{24}N_2O_2Na$: 443.1736 $[M+Na]^+$; found: 443.1734.

4.7. A representative procedure for the asymmetric bis(alkoxycarbonylation) reaction of 1 (Table 1, entry 3)

Under an argon atmosphere, $CuOTf(C_6H_6)_{0.5}$ (253 mg, 1.0 mmol) was placed in a flask, and an 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, $PdCl_2$ (7.1 mg, 0.04 mmol) was added. The argon atmosphere was replaced with CO/O_2 (ca. 1:1, v/v), and the reaction mixture was stirred for 60 h at rt. A saturated aq solution of $NaHCO_3$ was then 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 Na_2SO_4, and condensed in vacuo. The residue was purified by TLC on SiO_2 (hexane/AcOEt = 7:1, v/v) to give **2** (237 mg, 53%) with a selectivity of 60% ee.

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

4.8. (1*R*,2*S*)-Methyl 2-(3-methoxy-3-oxo-1-propen-2-yl)cyclohexanecarboxylate 2

Compound **2** (237 mg, 53%) was obtained as an oil. $[\alpha]_D^{25}$ = −49 (*c* 0.6, EtOH). The ee was determined to be 60% by HPLC (DAICEL CHIRALPAK IA×2, hexane/AcOEt = 50:1, 0.5 mL/min, 220 nm, major 54 min and minor 50 min); ^{1}H NMR ($CDCl_3$, 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, 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); ^{13}C NMR ($CDCl_3$, 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, 1628, 1437, 1281, 1247, 1194, 1165, 1143, 1030, 995, 949, 937, 819 cm^{-1}; HRMS (EI): *m*/*z* calcd for $C_{12}H_{18}O_4$: 226.12051 $[M]^+$; found: 226.12062.

4.9. (1*R*,2*S*)-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 carbonylation using $PdCl_2$ (1.8 mg, 0.01 mmol), $CuOTf(C_6H_6)_{0.5}$ (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. $[\alpha]_D^{25}$ = −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); ^{1}H NMR ($CDCl_3$, 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 (ddd, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{14}H_{22}O_4$: 254.15181 $[M]^+$; found: 254.15194.

4.10. (2*S*,3*S*)-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 carbonylation using $PdCl_2$ (1.8 mg, 0.01 mmol), $CuOTf(C_6H_6)_{0.5}$ (65 mg, 0.26 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. $[\alpha]_D^{25}$ = +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); ^{1}H NMR ($CDCl_3$, 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 (dd, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{24}H_{28}O_6$: 412.18859 $[M]^+$; found: 412.18843.

4.11. (3*S*,4*S*)-Dimethyl 2-methylene-3,4-bis((trityloxy)methyl)-pentanedioate 12b

1,2-Bis((trityloxy)methyl)-3-methylenecyclopropane **11b** (299 mg, 0.50 mmol) was subjected to carbonylation using $PdCl_2$ (1.8 mg, 0.01 mmol), $CuOTf(C_6H_6)_{0.5}$ (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. $[\alpha]_D^{25}$ = +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); mp 146 °C (recrystallized from $CHCl_3$/Hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.98–3.06 (m, 1H), 3.06–3.12 (m, 2H), 3.12–3.26 (m, 3H), 3.55 (s, 3H), 3.57 (s, 3H), 5.35 (s, 1H), 6.09 (s, 1H), 7.18–7.25 (m, 18H), 7.30–7.35 (m, 12H); ^{13}C NMR ($CDCl_3$, 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 $C_{48}H_{44}O_6Na$: 739.3036 $[M+Na]^+$; found: 739.3038.

4.12. (3*S*,4*S*)-Dimethyl 2-methylene-3,4-bis((triphenylsilyloxy)-methyl)pentanedioate 12c

1,2-Bis((triphenylsilyloxy)methyl)-3-methylenecyclopropane **11c** (252 mg, 0.4 mmol) was subjected to carbonylation using $PdCl_2$ (1.4 mg, 0.008 mmol), $CuOTf(C_6H_6)_{0.5}$ (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. $[\alpha]_D^{25}$ = +6 (*c* 1.5, $CHCl_3$). 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); mp 124 °C (AcOEt/hexane); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{46}H_{44}O_6Si_2$: C, 73.76; H, 5.92; found: C, 73.57; H, 6.03.

4.13. (2*S*,3*S*)-Dimethyl 2,3-bis((*tert*-butyldiphenylsilyloxy)-methyl)-4-methylenepentanedioate 12d

1,2-Bis((*tert*-butyldiphenylsilyloxy)methyl)-3-methylenecyclopropane **11d** (296 mg, 0.50 mmol) was subjected to carbonylation using $PdCl_2$ (1.9 mg, 0.01 mmol), $CuOTf(C_6H_6)_{0.5}$ (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. $[\alpha]_D^{25}$ = +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); ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 19.0, 19.1, 26.5, 26.6, 42.5, 48.4, 51.4, 51.7, 63.9, 64.2, 127.5, 127.6, 129.49, 129.55, 129.64, 133.1, 133.2, 135.39, 135.45, 135.50, 138.0, 166.7, 174.1; IR (neat) 3071, 3049, 2931, 2857, 1736, 1720, 1624, 1472, 1428, 1252, 1194, 1154, 1111, 822, 741, 702 cm^{-1}; HRMS (EI): m/z calcd for $C_{42}H_{52}O_6Si_2$: 708.33025 $[M]^+$; found: 708.33076.

4.14. 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 carbonylation using $PdCl_2$ (3.6 mg, 0.02 mmol), and $CuOTf(C_6H_6)_{0.5}$ (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. Compound **15**: an oil; ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 calcd for $C_{12}H_{18}O_4$: 226.12051 $[M]^+$; found: 226.12040.

4.15. (1*S*,4*R*)-2-((1*S*,2*R*)-2-((((1*S*,4*R*)-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 $LiAlH_4$ (65 mg, 1.75 mmol) in Et_2O (5 mL) was added dropwise an Et_2O (3 mL) solution of **2** (113 mg, 0.50 mmol, 60% ee) at 0 °C under an N_2 atmosphere. The resulting mixture was gradually warmed to rt and stirred overnight at rt, and then treated with a saturated aq Na_2SO_4 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 CH_2Cl_2 (3 mL) solution of (*S*)-camphanic chloride (171 mg, 0.79 mmol) was added to a mixture of diol **13** (51 mg, 0.33 mmol), triethylamine (0.12 mL, 0.86 mmol), and 4-(dimethylamino)pyridine

(5 mg, 0.03 mmol) in CH_2Cl_2 (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 H_2O and brine, dried over Na_2SO_4, and condensed under reduced pressure. The residue was purified by TLC on SiO_2 (hexane/AcOEt = 3:2) to give the corresponding ester (131 mg, 75%) as a mixture of diastereomers as a solid. Recrystallization (Et_2O/hexane) gave more diastereomerically pure ester (66 mg). The substrate obtained 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 Et_2O. $[\alpha]_D^{25} = -11$ (c 0.1, EtOH); mp 135 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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, 1314, 1271, 1227, 1166, 1106, 1064, 995, 928, 913 cm^{-1}; HRMS (ESI-TOF): m/z calcd for $C_{30}H_{42}O_8Na$: 553.2777 [M+Na]$^+$; found: 553.2779. Crystal data: $C_{30}H_{42}O_8$, FW. 530.66, monoclinic, $P2_1$, a = 11.049(2), b = 10.876(2), c = 12.586(2) Å, V = 1375.7(5) Å^3, β = 114.556(4)°, Z = 2. D_{calcd} = 1.281 g/cm^3. R = 0.057 (R_w = 0.069) for 5515 reflections with $I > 3.00\sigma(I)$ 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.

Acknowledgements

The present work was financially supported in part by a Grant-in-Aid for Scientific Research on Priority Areas 'Advanced Molecular Transformations of Carbon Resources' from The Ministry of Education, Culture, Sports, Science, and Technology (MEXT) Japan and a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (JSPS).

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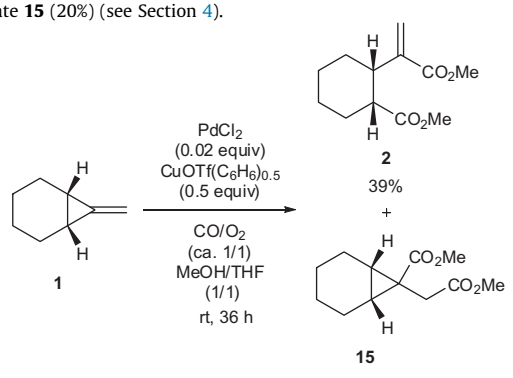
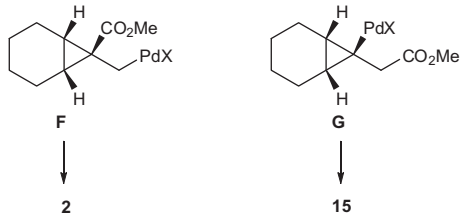
11. It was found that the bis(alkoxycarbonylation) reaction of **1** without chiral ligand **3C** afforded not only **2** (39%), but also a considerable amount of succinate **15** (20%) (see Section 4).



12. In this reaction, **15**[11] was not isolated after the purification procedure.
13. Examples of biologically active oxygen-functionalized α-alkylidene-β,γ-oxygen-functionalized glutarates: (a) Velten, R.; Klostermeyer, D.; Steffan, B.; Steglich, W.; Kuschel, A.; Anke, T. *J. Antibiot.* **1994**, *47*, 1017–1024; (b) McPhail, K.; Davies-Coleman, M. T. *Tetrahedron* **1997**, *53*, 4655–4660; (c) Chai, X.-Y.; Sun, J.-F.; Tang, L.-Y.; Yang, X.-W.; Li, Y.-Q.; Huang, H.; Zhou, X.-F.; Yang, B.; Liu, Y. *Chem. Pharm. Bull.* **2010**, *58*, 1391–1394; (d) Tan, J.-J.; Tan, J.-M.; Tan, C.-H.; Qu, S.-J.; Zhu, D.-Y. *Nat. Prod. Res.* **2012**, *26*, 1213–1217; (e) Valente, S.; Xu, Z.; Bana, E.; Zwergel, C.; Mai, A.; Jacob, C.; Meiser, P.; Bagrel, D.; Silva, A. M. S.; Kirsch, G. *Eur. J. Org. Chem.* **2013**, 2869–2877.
14. In the bis(alkoxycarbonylation) reaction in the absence of bioxazoline ligand **3C**, carbopalladation by chiral ligand-free palladium catalyst might proceed in a non-regioselective manner to give both the terminal intermediate **F** and the internal palladium intermediate **G** which produced succinate **15**[11] by the

second alkoxycarbonylation. 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 the proximal cyclopropane C—C bond through oxidative addition to a methylenecyclopropane[21] cannot be ruled out.
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