Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 19 (2008) 1106–1113

Pd-catalyzed asymmetric allylic alkylation of 2-substituted cycloalkenyl carbonates using a chiral diaminophosphine oxide: (S,R_P)-Ph-DIAPHOX

Long Jin, Tetsuhiro Nemoto, Hiroshi Nakamura and Yasumasa Hamada*

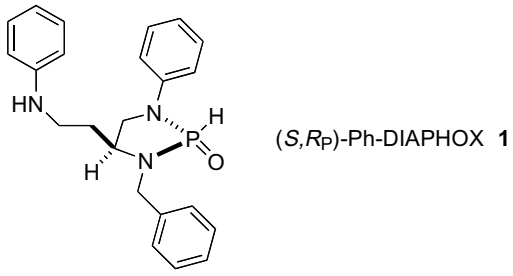
Graduate School of Pharmaceutical Sciences, Chiba University, Yayoi-cho, Inage-ku, Chiba 263-8522, Japan

Received 14 March 2008; accepted 26 March 2008

Abstract—A Pd-catalyzed asymmetric allylic alkylation of 2-substituted cycloalkenyl carbonates using a chiral diaminophosphine oxide is described. Asymmetric allylic substitution of various cyclic substrates proceeded using 5 mol % of Pd catalyst, 10 mol % of (S,R_P)-Ph-DIAPHOX **1**, 10 mol % of LiOAc, and *N*,*O*-bis(trimethylsilyl)acetamide (BSA), to afford the corresponding products in excellent yields with up to 92% ee.

1. Introduction

Pd-catalyzed asymmetric allylic substitution of cycloalkenyl alcohol derivatives is one of the most powerful methods for introducing chirality on the allylic carbon in a cyclic framework. The cyclic products obtained from this type of reaction can be utilized as versatile chiral building blocks for organic synthesis. Therefore, various reaction systems using carbon nucleophiles, nitrogen nucleophiles, and oxygen nucleophiles, have been developed.[1] There are many reports of asymmetric allylic substitution using simple cycloalkenyl alcohol derivatives as substrates. However, only limited success in the asymmetric allylic substitution of 2-substituted cycloalkenyl alcohol derivatives has been reported so far.[2–4] We recently reported the Pd-catalyzed asymmetric allylic amination of various 2-substituted cycloalkenyl alcohol derivatives using chiral diaminophosphine oxide preligands: DIAPHOXs (Fig. 1). Primary amines, secondary amines, and aromatic amines are applicable to this reaction system, and cycloalkenyl amines with a substituent at the 2-position were obtained in excellent yield and enantioselectivity.[5] In contrast, the asymmetric allylic alkylation with dimethyl malonate proceeded slowly under the same reaction conditions, affording the corresponding product with only moderate yield and enantioselectivity (e.g., Table 1, entry 1). We anticipated that we could overcome this drawback by tuning the reaction conditions. Herein, we report an asymmetric allylic alkylation of 2-substituted cycloalkenyl carbonates with malonate nucleophiles[6] using the Pd-DIAPHOX catalyst system.[7,8] Further transformations of the reaction adducts into chiral heterocyclic compounds with a quaternary stereocenter are also described.



(S,R_P)-Ph-DIAPHOX **1**

Figure 1.

2. Results and discussion

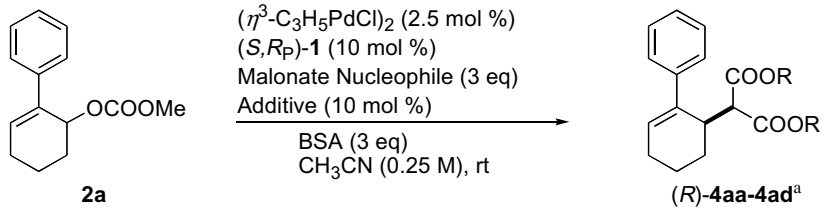
2.1. Asymmetric allylic alkylation of 2-substituted cycloalkenyl carbonates using the Pd-DIAPHOX catalyst system

We first optimized the reaction conditions using asymmetric allylic alkylation of 2-phenylcyclohexenyl carbonate **2a** with malonate nucleophiles (Table 1). Using 2.5 mol % of

* Corresponding author. Tel./fax: +81 43 290 2987; e-mail: hamada@p.chiba-u.ac.jp

0957-4166/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2008.03.027

Table 1. Optimization of the reaction conditions



2a (*R*)-**4aa-4ad**[a]

Entry	Nucleophile	Additive	Product	Time	Yield[b] (%)	ee[c] (%)
1	$CH_2(COOMe)_2$ **3a**	—	**4aa**	48	43	68
2	$CH_2(COOMe)_2$ **3a**	LiOAc	**4aa**	4	94	80
3	$CH_2(COOMe)_2$ **3a**	NaOAc	**4aa**	4	95	67
4	$CH_2(COOMe)_2$ **3a**	KOAc	**4aa**	4	93	66
5	$CH_2(COOMe)_2$ **3a**	$Mg(OAc)_2$	**4aa**	96	55	80
6	$CH_2(COOMe)_2$ **3a**	$Zn(OAc)_2$	**4aa**	96	40	81
7	$CH_2(COOEt)_2$ **3b**	LiOAc	**4ab**	4	94	85
8	$CH_2(COO\textit{t}\text{-}Bu)_2$ **3c**	LiOAc	**4ac**	4	91	81
9	$CH_2(COOBn)_2$ **3d**	LiOAc	**4ad**	4	94	86
10[d]	$CH_2(COOBn)_2$ **3d**	LiOAc	**4ad**	4	92	83
11[e]	$CH_2(COOBn)_2$ **3d**	LiOAc	**4ad**	48	54	91

[a] Absolute configuration of **4ad** was determined to be (*R*). See Scheme 1.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] Reaction was preformed in the presence of 20 mol % of LiOAc.
[e] Reaction was preformed at 4 °C.

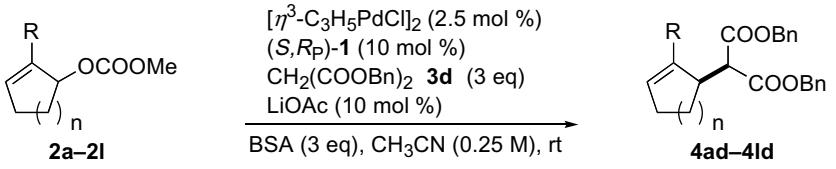
$[\eta^3\text{-}C_3H_5PdCl]_2$ (5 mol % of Pd catalyst) and 10 mol % of (*S*,R_P)-Ph-DIAPHOX **1**, the reaction proceeded slowly at room temperature to afford product **3a** in 43% yield and 68% ee.[9] The addition of an acetate salt often affects both the reactivity and enantioselectivity in the asymmetric allylic alkylation using transition metal-DIAPHOX catalyst systems. Thus, we investigated the effect of the additive in detail. Both reactivity and enantioselectivity were remarkably affected by the addition of acetate salts; LiOAc was the best additive for both reactivity and enantioselectivity (entry 2).[10] Further optimization of the ester substituents of a malonate nucleophile indicated that dibenzyl malonate resulted in the best enantioselectivity (entry 9). The increase in the amount of LiOAc did not affect reactivity (entry 10); although enantioselectivity was improved when the reaction was performed at 4 °C, the reactivity decreased remarkably (entry 11).

We next examined the scope and limitations of other 2-substituted cycloalkenyl carbonates using dibenzyl malonate as a nucleophile (Table 2). Using 5 mol % of Pd catalyst, 10 mol % of **1**, and 10 mol % of LiOAc, the asymmetric allylic alkylation of cyclohexenyl carbonates with a 2-naphthyl group proceeded at room temperature to provide the corresponding product in 86% yield and 92% ee (entry 2). Substrates bearing an aryl group with an electron-withdrawing functionality as well as an electron-donating functionality at the *para*- or *meta*-position were applicable to this reaction system, giving the products in excellent yield (93–99% yield) and with high enantioselectivity (85–91% ee) (entries 3–6). There was a remarkable decrease in reactivity when substrates with an *ortho*-substituted aromatic ring were used (entries 7–9). In particular, no reaction occurred at room temperature using 2-methoxyphenyl-substituted cyclohexenyl carbonate as the substrate. This reaction was sluggish even at 50 °C, affording the corresponding product in only 50% yield with 71% ee. 2-Phenyl-substituted cyclopentenyl carbonate was also applicable to this reaction, and the product was obtained in 92% yield with 89% ee (entry 10). In addition, substrates with an ester group or an amide group were examined using the same reaction conditions, providing the corresponding products in good yield with 71% ee and 79% ee, respectively (entries 11 and 12). Asymmetric allylic alkylation of simple cyclohexenyl carbonate gave a less satisfactory result using the present catalyst system (entry 13).

2.2. Determination of the absolute configuration of 4ad and 4id, and their synthetic applications

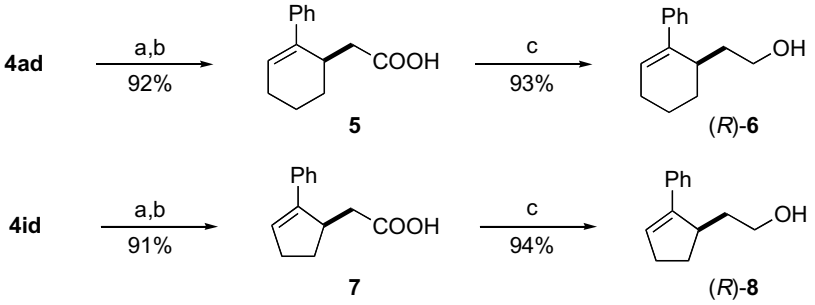
The absolute configuration of **4ad** and **4id** was determined by transforming them into known chiral alcohols (Scheme 1). Hydrolysis of the dibenzyl ester in **4ad**, followed by treatment with acetic acid, gave carboxylic acid **5** in 92% yield (2 steps). Reduction of the carboxylic acid moiety using $LiAlH_4$ afforded the known chiral alcohol **6** in 93% yield. Comparison of the measured specific rotation of **6** with the literature data revealed that the absolute stereochemistry of the allylic position was (*R*). {**6** from **4ad**: $[\alpha]_D^{23} = -118.6$ (*c* 0.84, CH_2Cl_2) 86% ee. Lit.[11] $[\alpha]_D^{25} = +107.2$ (*c* 0.05, CH_2Cl_2) 97% ee, (*S*)-isomer}. Similarly, **4id** was transformed into the corresponding chiral alcohol **8** in 86% yield (3 steps), and the absolute configuration of **8** was determined to be (*R*). {**8** from **4id**: $[\alpha]_D^{21} = -49.9$ (*c* 0.58, CH_2Cl_2) 89% ee. Lit.[11] $[\alpha]_D^{24} = +62.3$ (*c* 0.27, CH_2Cl_2) 98% ee, (*S*)-isomer}. Carboxylic acid **5** and alcohol **8** could be transformed into chiral heterocyclic compounds with a quaternary stereocenter (Scheme 2). The treatment of **5** with KI and I_2 in aqueous $NaHCO_3$ at room temperature induced iodolactonization and provided iodo-

Table 2. Scope and limitations

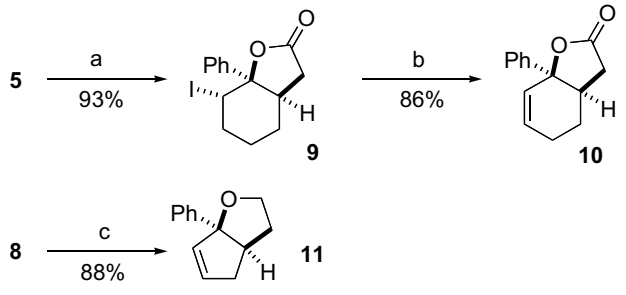


Entry	Substrate		Product	Time (h)	Yield[a] (%)	ee[b] (%)
1	**2a**	$n = 2$, R = C_6H_5	**4ad**	4	94	86 (*R*)
2	**2b**	$n = 2$, R = 2-Naphthyl	**4bd**	24	86	92
3	**2c**	$n = 2$, R = 4-F–C_6H_4	**4cd**	4	93	87
4	**2d**	$n = 2$, R = 4-MeO–C_6H_4	**4dd**	6	94	85
5	**2e**	$n = 2$, R = 3-F–C_6H_4	**4ed**	3	99	87
6	**2f**	$n = 2$, R = 3-MeO–C_6H_4	**4fd**	6	99	91
7	**2g**	$n = 2$, R = 2-F–C_6H_4	**4gd**	24	77	85
8	**2h**	$n = 2$, R = 2-MeO–C_6H_4	**4hd**	24	No reaction	—
9[c]	**2h**	$n = 2$, R = 2-MeO–C_6H_4	**4hd**	72	50	71
10	**2i**	$n = 1$, R = C_6H_5	**4id**	4	92	89 (*R*)[d]
11	**2j**	$n = 2$, R = COOMe	**4jd**	4	89	71
12	**2k**	$n = 2$, R = CONHBn	**4kd**	4	86	79
13[e]	**2l**	$n = 2$, R = H	**4ld**	24	97	53 (*S*)

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] Reaction was preformed at 50 °C.
[d] Absolute configuration of **4id** was determined to be R. See Scheme 1.
[e] Reaction was performed in CH_2Cl_2 in the absence of LiOAc.



Scheme 1. Determination of the absolute configuration of **4ad** and **4id**. Reagents and conditions: (a) NaOH, H_2O–MeOH, reflux, 8 h; (b) AcOH, reflux, 12 h; (c) $LiAlH_4$, THF, reflux, 16 h.



Scheme 2. Transformation of **5** and **8**. Reagents and conditions: (a) I_2, KI, $NaHCO_3$, H_2O, rt, 24 h; (b) DBU, toluene, reflux, 12 h; (c) $Pd(OAc)_2$ (5 mol %), O_2 (1 atm), DMSO, rt, 24 h.

lactone **9** (93% yield), which was converted into a bicyclic lactone **10** in 86% yield. In addition, oxidative cyclization of **8** proceeded in the presence of 5 mol % of $Pd(OAc)_2$ under an oxygen atmosphere, affording bicyclic furan **11** in 88% yield.[12]

3. Conclusion

In conclusion, we have achieved the Pd-catalyzed asymmetric allylic alkylation of 2-substituted cycloalkenyl carbonates using a chiral diaminophosphine oxide. Using the Pd-DIAPHOX catalyst system, the corresponding products were obtained in excellent yield with a high enantioselectivity. In addition, the reaction adducts were transformed into chiral heterocycles with a quaternary stereocenter.

4. Experimental

4.1. General

Infrared (IR) spectra were recorded on a JASCO FT/IR 230 Fourier transform infrared spectrophotometer, equipped with ATR (Smiths Detection, DuraSample IR

II). NMR spectra were recorded on a JEOL ecp 400 spectrometer, operating at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR. Chemical shifts in $CDCl_3$ were reported downfield from TMS (=0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported downfield from TMS (=0 ppm) or on a scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. Optical rotations were measured on a JASCO P-1020 polarimeter. EI mass spectra were measured on JEOL GC-mate. FAB mass spectra were measured on JMX-AX500. The enantiomeric excess (ee) was determined by HPLC analysis. HPLC was performed on JASCO HPLC systems consisting of the following: pump, PU-980; detector, UV-970, measured at 254 nm; column, DAICEL CHIRALPAK AD, DAICEL CHIRALPAK AD-H, DAICEL CHIRALPAK AS-H, DAICEL CHIRALCEL OD–H; mobile phase, 2-propanol/hexane. Reactions were carried out in dry solvent under an argon atmosphere. Other reagents were purified by the usual methods.

4.2. Experimental procedure for the Pd-catalyzed asymmetric allylic alkylation and compound characterization

Reaction products **4aa**–**4ld** were prepared according to the general procedure. Cycloalkenyl carbonates **2a**–**2l** were prepared from the corresponding allylic alcohols using a usual procedure (methyl chloroformate, pyridine, $CHCl_3$, rt). For the spectral data of these cycloalkenyl carbonates, see Ref. 5.

4.2.1. General procedure for asymmetric allylic alkylation using the Pd-DIAPHOX catalyst system. (1*R*)-2-Phenyl-2-cyclohexen-1-yl malonic acid dibenzyl ester (*R*)-4ad. To a stirred mixture of $[\eta^3\text{-}C_3H_5PdCl]_2$ (2.0 mg, 0.0055 mmol), (S,R_P)-**1** (8.6 mg, 0.022 mmol), LiOAc (1.5 mg, 0.022 mmol), and **2a** (51.1 mg, 0.22 mmol) in CH_3CN (0.9 mL) at room temperature was added BSA (163 μL, 0.66 mmol), and the solution stirred for 5 min at the same temperature. Dibenzyl malonate (165 μL, 0.66 mmol) was added and the resulting mixture was stirred for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue obtained was purified by flash column chromatography (SiO_2, hexane/ethyl acetate: 40/1 to 20/1) to give (*R*)-**4ad** as a colorless oil (91.2 mg, 94%, 86% ee). IR (ATR): ν 3032, 2937, 1747, 1732, 1454, 1334, 1271, 1215, 1149, 746, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.50–1.65 (m, 2H), 1.80–1.96 (m, 2H), 2.06–2.11 (m, 2H), 3.65 (d, J = 6.8 Hz, 1H), 3.55–3.65 (m, 1H), 4.60 (dd, J = 2.0 Hz, 12.8 Hz, 1H), 4.70 (dd, J = 2.0 Hz, 12.8 Hz, 1H), 4.99 (dd, J = 2.0 Hz, 12.4 Hz, 1H), 5.06 (dd, J = 2.0 Hz, 12.4 Hz, 1H), 5.84–5.88 (m, 1H), 7.14–7.30 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 19.0, 25.5, 25.6, 36.2, 54.4, 66.5, 66.6, 126.6, 126.8 (×2), 127.8 (×2), 127.9, 128.0 (×2), 128.1, 128.1 (×2), 128.3 (×2), 128.3 (×2), 128.4, 129.8, 135.2, 138.3, 141.8, 167.9, 168.3; FAB-LRMS m/z 441 (MH^+); FAB-HRMS. Calcd for $C_{29}H_{29}O_4$ (MH^+): 441.2066. Found: 441.2049; $[\alpha]_D^{22} = -35.4$ (c 0.32, $CHCl_3$, 86% ee). The enantiomeric excess of **4ad** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 5/95, flow rate 0.5 mL/min, t_R 19.7 min [(*S*)-isomer] and 21.7 min [(*R*)-isomer], detection at 254 nm).

4.2.2. 2-Phenyl-2-cyclohexen-1-yl malonic acid dimethyl ester 4aa. Colorless oil. IR (ATR): ν 2950, 1739, 1730, 1492, 1434, 1274, 1159, 1029, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.62–1.68 (m, 2H), 1.86–1.92 (m, 2H), 2.18–2.22 (m, 2H), 3.21 (s, 3H), 3.54 (d, J = 8.0 Hz, 1H), 3.52–3.60 (m, 1H), 3.64 (s, 3H), 3.74 (s, 3H), 5.90–5.93 (m, 1H), 7.18–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 18.5, 25.6, 25.9, 36.0, 51.8, 52.0, 54.6, 126.7, 126.8 (×2), 128.0 (×2), 129.9, 138.4, 141.9, 168.8, 168.9; FAB-LRMS m/z 289 (MH^+); FAB-HRMS. Calcd for $C_{17}H_{21}O_4$ (MH^+): 289.1440. Found: 289.1434; $[\alpha]_D^{17} = -114.2$ (c 1.37, $CHCl_3$, 80% ee). The enantiomeric excess of **4aa** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 5/95, flow rate 0.4 mL/min, t_R 14.6 min (major isomer) and 20.2 min (minor isomer), detection at 254 nm).

4.2.3. 2-Phenyl-2-cyclohexen-1-yl malonic acid diethyl ester 4ab. Colorless oil. IR (ATR): ν 2983, 2937, 1750, 1732, 1444, 1369, 1331, 1265, 1151, 1033, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.06–1.10 (m, 3H), 1.17–1.21 (m, 3H), 1.64–1.69 (m, 2H), 1.87–1.95 (m, 2H), 2.17–2.22 (m, 2H), 3.50 (d, J = 7.2 Hz, 1H), 3.52–3.60 (m, 1H), 4.08–4.13 (m, 2H), 4.17–4.24 (m, 2H), 5.90–5.92 (m, 1H), 7.18–7.28 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 13.7, 13.9, 18.9, 25.6, 25.7, 36.0, 54.6, 60.9, 61.4, 126.6, 126.8 (×2), 128.0 (×2), 129.9, 138.6, 142.0, 168.3, 168.7; FAB-LRMS m/z 317 (MH^+); FAB-HRMS. Calcd for $C_{19}H_{25}O_4$ (MH^+): 317.1753. Found: 317.1739; $[\alpha]_D^{20} = -86.9$ (c 0.48, $CHCl_3$, 85% ee). The enantiomeric excess of **4ab** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 5/95, flow rate 0.4 mL/min, t_R 11.7 min (major isomer) and 13.7 min (minor isomer), detection at 254 nm).

4.2.4. 2-Phenyl-2-cyclohexen-1-yl malonic acid di-*tert*-butyl ester 4ac. Colorless oil. IR (ATR): ν 2978, 2931, 1722, 1366, 1254, 1133, 849, 758, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 9H), 1.38 (s, 9H), 1.56–1.66 (m, 1H), 1.72–1.82 (m, 1H), 1.88–2.21 (m, 4H), 3.37 (d, J = 5.6 Hz, 1H), 3.39–3.44 (m, 1H), 5.88–5.91 (m, 1H), 7.19–7.30 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 20.3, 25.1, 25.7, 27.8 (×3), 27.9 (×3), 36.3, 55.6, 80.8, 81.3, 126.6, 126.9 (×2), 128.1 (×2), 129.4, 139.3, 142.3, 167.7, 168.6; FAB-LRMS m/z 373 (MH^+); FAB-HRMS. Calcd for $C_{23}H_{33}O_4$ (MH^+): 373.2379. Found: 373.2358; $[\alpha]_D^{22} = -41.5$ (c 1.15, $CHCl_3$, 82% ee). The enantiomeric excess of **4ac** was determined by HPLC analysis (DAICEL CHIRALPAK AD, 2-propanol/hexane 1/100, flow rate 0.5 mL/min, t_R 9.4 min (minor isomer) and 10.0 min (major-isomer), detection at 254 nm).

4.2.5. 2-(2-Naphthyl)-2-cyclohexen-1-yl malonic acid dibenzyl ester 4bd. Colorless oil. IR (ATR): ν 3032, 2947, 1748, 1732, 1331, 1269, 1215, 1147, 1003, 746, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.62–1.72 (m, 2H), 1.89–2.03 (m, 2H), 2.16–2.23 (m, 2H), 3.68 (d, J = 7.2 Hz, 1H), 3.68–3.75 (m, 1H), 4.48 (d, J = 12.4 Hz, 1H), 4.62 (d, J = 12.4 Hz, 1H), 4.98 (d, J = 12.4 Hz, 1H), 5.05 (d, J = 12.4 Hz, 1H), 5.99–6.02 (m, 1H), 7.01–7.03 (m, 2H), 7.14–7.43 (m, 11H), 7.62 (s, 1H), 7.69–7.78 (m, 3H); ^{13}C NMR ($CDCl_3$): δ 19.2, 25.8, 25.8, 36.4, 54.5, 66.7, 66.8, 125.3, 125.5, 125.6, 126.0, 127.5, 127.6, 127.8, 128.0 (×2), 128.0, 128.2, 128.3 (×2), 128.3 (×2), 128.4 (×2), 130.6, 132.4, 133.3, 135.2,

135.2, 138.4, 139.3, 168.1, 168.5; FAB-LRMS *m/z* 491 (MH^+); FAB-HRMS. Calcd for $C_{33}H_{31}O_4$ (MH^+): 491.2222. Found: 491.2237; $[\alpha]_D^{21} = -35.2$ (*c* 0.47, $CHCl_3$, 92% ee). The enantiomeric excess of **4ad** was determined by HPLC analysis (DAICEL CHIRALPAK AS-H, 2-propanol/hexane 1/9, flow rate 0.5 mL/min, t_R 14.6 min (major-isomer) and 17.0 min (minor isomer), detection at 254 nm).

4.2.6. 2-(4-Fluorophenyl)-2-cyclohexen-1-yl malonic acid dibenzyl ester 4cd. Colorless oil. IR (ATR): *v* 3033, 2935, 1746, 1731, 1601, 1510, 1454, 1234, 1161, 1005, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.57–1.64 (m, 2H), 1.85–1.96 (m, 2H), 2.10–2.16 (m, 2H), 3.52–3.55 (m, 1H), 3.60 (d, $J = 7.2$ Hz, 1H), 4.67 (d, $J = 12.4$ Hz, 1H), 4.76 (d, $J = 12.4$ Hz, 1H), 5.01 (d, $J = 12.4$ Hz, 1H), 5.09 (d, $J = 12.4$ Hz, 1H), 5.81–5.83 (m, 1H), 6.87–6.91 (m, 2H), 7.11–7.30 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 19.0, 25.6, 25.7, 36.5, 54.5, 66.8, 66.9, 114.9 (d, $J = 21.4$ Hz) (×2), 127.9 (×2), 128.2 (×2), 128.3, 128.3 (×2), 128.4, 128.4 (×2), 128.4, 128.5, 130.1, 135.2 (d, $J = 4.9$ Hz) (×2), 137.5, 138.0, 161.7 (d, $J = 244.3$ Hz), 168.0, 168.4; FAB-LRMS *m/z* 459 (MH^+); FAB-HRMS. Calcd for $C_{29}H_{28}FO_4$ (MH^+): 459.1972. Found: 459.1997; $[\alpha]_D^{17} = -46.2$ (*c* 1.25, $CHCl_3$, 87% ee). The enantiomeric excess of **4cd** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/200, flow rate 0.5 mL/min, t_R 47.7 min (minor isomer) and 52.2 min (major isomer), detection at 254 nm).

4.2.7. 2-(4-Methoxyphenyl)-2-cyclohexen-1-yl malonic acid dibenzyl ester 4dd. Colorless oil. IR (ATR): *v* 3033, 2949, 1747, 1732, 1456, 1331, 1265, 1215, 1149, 1003, 750, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.54–1.65 (m, 2H), 1.84–1.99 (m, 2H), 2.11–2.15 (m, 2H), 3.52–3.55 (m, 1H), 3.67 (d, $J = 6.8$ Hz, 1H), 3.74 (s, 3H), 4.68 (d, $J = 12.4$ Hz, 1H), 4.76 (d, $J = 12.4$ Hz, 1H), 5.02 (d, $J = 12.4$ Hz, 1H), 5.10 (d, $J = 12.4$ Hz, 1H), 5.80–5.84 (m, 1H), 6.74–6.78 (m, 2H), 7.11–7.36 (m, 12H); ^{13}C NMR ($CDCl_3$): δ 19.0, 25.6, 25.8, 36.4, 54.5, 66.7, 66.8, 113.5, 127.8, 127.9, 128.0, 128.2, 128.3 (×2), 128.3 (×2), 128.4 (×2), 128.6 (×2), 128.8, 134.7, 135.2, 135.4, 137.8, 161.7, 168.1, 168.5; FAB-LRMS *m/z* 471 (MH^+); FAB-HRMS. Calcd for $C_{30}H_{31}O_5$ (MH^+): 471.2171. Found: 471.2147; $[\alpha]_D^{20} = -18.1$ (*c* 1.29, $CHCl_3$, 85% ee). The enantiomeric excess of **4dd** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow rate 0.5 mL/min, t_R 50.9 min (minor isomer) and 58.6 min (major isomer), detection at 254 nm).

4.2.8. 2-(3-Fluorophenyl)-2-cyclohexen-1-yl malonic acid dibenzyl ester 4ed. Colorless oil. IR (ATR): *v* 3035, 2933, 1741, 1731, 1581, 1456, 1271, 1220, 1157, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.57–1.66 (m, 2H), 1.83–1.99 (m, 2H), 2.11–2.15 (m, 2H), 3.52–3.56 (m, 1H), 3.62 (d, $J = 6.4$ Hz, 1H), 4.71 (d, $J = 12.4$ Hz, 1H), 4.79 (d, $J = 12.4$ Hz, 1H), 5.01 (d, $J = 12.0$ Hz, 1H), 5.09 (d, $J = 12.0$ Hz, 1H), 5.88–5.91 (m, 1H), 6.85–6.98 (m, 3H), 7.16–7.31 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 19.0, 25.6, 25.6, 36.2, 54.2, 66.8, 66.8, 113.5 (d, $J = 21.0$ Hz), 113.7 (d, $J = 21.4$ Hz), 122.4 (d, $J = 2.7$ Hz), 127.9 (×2), 128.1, 128.2, 128.3 (×2), 128.4 (×2), 128.4 (×2), 129.5, 129.5, 130.9, 135.2 (d, $J = 4.6$ Hz), 137.5 (d, $J = 1.9$ Hz), 144.3 (d, $J = 7.3$ Hz), 162.6 (d, $J = 244.3$ Hz), 167.9, 168.3; FAB-LRMS *m/z* 459 (MH^+); FAB-HRMS. Calcd for $C_{29}H_{28}FO_4$ (MH^+): 459.1972. Found: 459.1954; $[\alpha]_D^{24} = -47.4$ (*c* 0.65, $CHCl_3$, 87% ee). The enantiomeric excess of **4ed** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/200, flow rate 0.5 mL/min, t_R 74.8 min (minor isomer) and 84.6 min (major isomer), detection at 254 nm).

4.2.9. 2-(3-Methoxyphenyl)-2-cyclohexen-1-yl malonic acid dibenzyl ester 4fd. Colorless oil. IR (ATR): *v* 3032, 2935, 1750, 1732, 1599, 1577, 1456, 1217, 1165, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.57–1.64 (m, 2H), 1.83–1.99 (m, 2H), 2.10–2.16 (m, 2H), 3.52–3.58 (m, 1H), 3.66 (d, $J = 6.8$ Hz, 1H), 3.70 (s, 3H), 4.70 (d, $J = 12.4$ Hz, 1H), 4.78 (d, $J = 12.4$ Hz, 1H), 5.02 (d, $J = 12.4$ Hz, 1H), 5.09 (d, $J = 12.4$ Hz, 1H), 5.91 (dd, $J = 2.8$ Hz, 4.0 Hz, 1H), 6.72–6.81 (m, 3H), 7.14–7.33 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 19.2, 25.6, 25.6, 36.4, 54.3, 55.0, 66.7, 66.8, 112.4, 112.4, 119.3, 127.9 (×2), 128.1, 128.2, 128.2 (×2), 128.3, 128.4 (×2), 128.4 (×2), 129.1, 130.0, 135.3, 138.4, 143.4, 159.4, 168.1, 168.5; FAB-LRMS *m/z* 471 (MH^+); FAB-HRMS. Calcd for $C_{30}H_{31}O_5$ (MH^+): 471.2171. Found: 471.2155; $[\alpha]_D^{24} = -37.4$ (*c* 0.45, $CHCl_3$, 91% ee). The enantiomeric excess of **4fd** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 1/99, flow rate 0.15 mL/min, t_R 176.5 min (major isomer) and 192.3 min (minor isomer), detection at 254 nm).

4.2.10. 2-(2-Fluorophenyl)-2-cyclohexen-1-yl malonic acid dibenzyl ester 4gd. Colorless oil. IR (ATR): *v* 3033, 2935, 1754, 1732, 1487, 1450, 1257, 1219, 1140, 758, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55–1.74 (m, 2H), 1.83–1.93 (m, 2H), 2.12–2.18 (m, 2H), 3.53–3.58 (m, 2H), 4.78 (d, $J = 12.4$ Hz, 1H), 4.88 (d, $J = 12.4$ Hz, 1H), 4.99 (d, $J = 12.4$ Hz, 1H), 5.03 (d, $J = 12.4$ Hz, 1H), 5.83–5.85 (m, 1H), 6.92–7.32 (m, 14H); ^{13}C NMR ($CDCl_3$): δ 19.9, 25.4, 25.6, 37.3, 54.3, 66.7, 66.7, 115.3 (d, $J = 22.6$ Hz), 123.9 (d, $J = 3.4$ Hz), 127.9 (×2), 128.2, 128.3, 128.3 (×2), 128.4 (×2), 128.4 (×2), 128.4, 128.5, 129.4 (d, $J = 14.5$ Hz), 130.8 (d, $J = 4.6$ Hz), 132.1, 134.5, 135.3, 158.8 (d, $J = 419.9$ Hz), 167.8, 168.4; FAB-LRMS *m/z* 459 (MH^+); FAB-HRMS. Calcd for $C_{29}H_{28}FO_4$ (MH^+): 459.1972. Found: 459.1954; $[\alpha]_D^{24} = -28.0$ (*c* 0.58, $CHCl_3$, 85% ee). The enantiomeric excess of **4gd** was determined by HPLC analysis (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 5/95, flow rate 0.5 mL/min, t_R 26.9 min (minor isomer) and 39.8 min (major isomer), detection at 254 nm).

4.2.11. 2-(2-Methoxyphenyl)-2-cyclohexen-1-yl malonic acid dibenzyl ester 4hd. Colorless oil. IR (ATR): *v* 2930, 1749, 1729, 1242, 1136, 1118, 1025, 749, 695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.55–1.92 (m, 4H), 2.10–2.20 (m, 2H), 3.51 (d, $J = 6.0$ Hz, 1H), 3.72 (s, 3H), 4.80 (d, $J = 12.4$ Hz, 1H), 4.93 (d, $J = 12.4$ Hz, 1H), 4.96 (d, $J = 12.4$ Hz, 1H), 5.02 (d, $J = 12.4$ Hz, 1H), 5.71–5.76 (m, 1H), 6.74–6.83 (m, 2H), 6.96–6.99 (m, 1H), 7.16–7.30 (m, 11H); ^{13}C NMR ($CDCl_3$): δ 20.6, 25.3, 25.7, 37.3, 54.3, 55.2, 66.6, 66.6, 110.1, 120.6, 127.9 (×2), 128.1, 128.1, 128.3, 128.3 (×2), 128.4 (×2), 128.4 (×2), 129.9, 131.0, 131.1, 135.4, 135.5,

138.4, 156.5, 168.2, 169.0; FAB-LRMS m/z 471 (MH^+); FAB-HRMS. Calcd for $C_{30}H_{31}O_5$ (MH^+): 471.2171. Found: 471.2155; $[\alpha]_D^{19} = +3.0$ (c 0.79, $CHCl_3$, 71% ee). The enantiomeric excess of **4hd** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 3/97, flow rate 0.5 mL/min, t_R 23.7 min (minor isomer) and 28.0 min (major isomer), detection at 254 nm).

4.2.12. (1*R*)-2-Phenyl-2-cyclopenten-1-yl malonic acid dibenzyl ester 4id. Colorless oil. IR (ATR): ν 2947, 1745, 1728, 1236, 1213, 1180, 1140, 1021, 982, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.13–2.34 (m, 2H), 2.38–2.47 (m, 2H), 3.72 (d, $J = 6.0$ Hz, 1H), 3.92–3.98 (m, 1H), 4.84 (d, $J = 12.4$ Hz, 1H), 4.94 (d, $J = 12.4$ Hz, 1H), 5.01 (d, $J = 12.4$ Hz, 1H), 5.08 (d, $J = 12.4$ Hz, 1H), 5.95–5.99 (m, 1H), 7.18–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 27.5, 31.6, 45.5, 53.6, 66.7, 66.8, 126.4 (×2), 127.2, 128.0 (×2), 128.1, 128.2, 128.2 (×2), 128.3 (×2), 128.3, 128.4 (×2), 128.4 (×2), 130.1, 135.3, 135.7, 142.9, 168.2, 168.8; FAB-LRMS m/z 427 (MH^+); FAB-HRMS. Calcd for $C_{28}H_{27}O_4$ (MH^+): 427.1909. Found: 427.1890; $[\alpha]_D^{19} = -43.2$ (c 0.87, $CHCl_3$, 89% ee). The enantiomeric excess of **4id** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 5/95, flow rate 0.5 mL/min, t_R 16.2 min [(*S*)-isomer] and 19.2 min [(*R*)-isomer], detection at 254 nm).

4.2.13. 2-Methoxycarbonyl-2-cyclohexen-1-yl malonic acid dibenzyl ester 4jd. Colorless oil. IR (ATR): ν 3032, 2951, 1747, 1732, 1716, 1456, 1257, 1147, 752, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.45–1.60 (m, 2H), 1.74–1.85 (m, 2H), 2.08–2.16 (m, 2H), 3.38–3.46 (m, 1H), 3.64 (s, 3H), 4.00 (d, $J = 6.4$ Hz, 1H), 5.09 (d, $J = 12.0$ Hz, 2H), 5.14 (d, $J = 12.0$ Hz, 2H), 7.05 (dt, $J = 1.6$ Hz, 4.0 Hz, 1H), 7.24–7.34 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 18.2, 25.2, 25.4, 33.4, 51.4, 53.9, 66.8, 66.9, 128.0 (×2), 128.1, 128.2 (×2), 128.3 (×2), 128.4 (×2), 128.4, 130.3, 135.2, 135.3, 142.7, 167.2, 168.2, 168.4; FAB-LRMS m/z 423 (MH^+); FAB-HRMS. Calcd for $C_{25}H_{27}O_6$ (MH^+): 423.1808. Found: 423.1797; $[\alpha]_D^{17} = -9.3$ (c 1.32, $CHCl_3$, 71% ee). The enantiomeric excess of **4jd** was determined by HPLC analysis (DAICEL CHIRALCEL OD-H, 2-propanol/hexane 5/95, flow rate 0.4 mL/min, t_R 29.7 min (major isomer) and 34.3 min (minor isomer), detection at 254 nm).

4.2.14. 2-Benzylcarbamoyl-2-cyclohexen-1-yl malonic acid dibenzyl ester 4kd. Colorless oil. IR (ATR): ν 3406, 3032, 2935, 1747, 1731, 1660, 1622, 1520, 1281, 1147, 696 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.46–1.80 (m, 3H), 1.85–2.15 (m, 3H), 3.42–3.51 (m, 1H), 3.95 (d, $J = 4.8$ Hz, 1H), 4.26 (dd, $J = 5.6$ Hz, 14.8 Hz, 1H), 4.40 (dd, $J = 6.0$ Hz, 14.8 Hz, 1H), 4.97 (d, $J = 12.0$ Hz, 1H), 5.11 (s, 2H), 5.15 (d, $J = 12.0$ Hz, 2H), 5.76 (dd, $J = 5.6$ Hz, 6.0 Hz, 1H), 6.22–6.25 (m, 1H), 7.20–7.35 (m, 15H); ^{13}C NMR ($CDCl_3$): δ 19.5, 24.9, 25.1, 34.3, 43.5, 53.4, 66.9, 67.0, 127.4, 127.8 (×2), 128.2 (×2), 128.4, 128.4, 128.5 (×2), 128.5 (×2), 128.5 (×2), 128.6 (×2), 133.7, 135.4, 135.4, 136.3, 138.3, 168.4, 168.4, 169.1; FAB-LRMS m/z 498 (MH^+); FAB-HRMS. Calcd for $C_{31}H_{32}NO_5$ (MH^+): 498.2280. Found: 498.2267; $[\alpha]_D^{17} = +11.7$ (c 1.00, $CHCl_3$, 79% ee). The enantiomeric excess of **4kd** was determined by HPLC analysis (DAICEL CHIRALPAK AD-H, 2-propanol/hexane 20/80, flow rate 0.5 mL/min, t_R 54.2 min (minor isomer) and 66.1 min (major isomer), detection at 254 nm).

4.2.15. (1*S*)-2-Cyclohexen-1-yl malonic acid dibenzyl ester 4ld. Colorless oil. IR (ATR): ν 2930, 1752, 1729, 1261, 1213, 1135, 1002, 734, 694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.32–1.42 (m, 1H), 1.48–1.58 (m, 1H), 1.64–1.80 (m, 2H), 1.93–1.98 (m, 2H), 2.92–2.97 (m, 1H), 3.38 (d, $J = 9.2$ Hz, 1H), 5.14 (s, 2H), 5.15 (s, 2H), 5.51–5.54 (m, 1H), 5.71–5.76 (m, 1H), 7.26–7.35 (m, 10H); ^{13}C NMR ($CDCl_3$): δ 20.9, 24.9, 26.5, 35.4, 57.0, 66.9, 66.9, 127.3, 128.1 (×2), 128.1 (×2), 128.2, 128.3, 128.5 (×2), 128.5 (×2), 129.6, 135.4, 135.4, 168.1, 168.2; FAB-LRMS m/z 365 (MH^+); FAB-HRMS. Calcd for $C_{23}H_{25}O_4$ (MH^+): 365.1753. Found: 365.1740; $[\alpha]_D^{17} = -21.4$ (c 0.85, $CHCl_3$, 53% ee). The enantiomeric excess of **4ld** was determined by HPLC analysis (DAICEL CHIRALPAK AD, 2-propanol/hexane 5/95, flow rate 0.4 mL/min, t_R 31.2 min [(*S*)-isomer] and 35.7 min [(*R*)-isomer], detection at 254 nm). The absolute configuration of **4ld** was determined after converting into the known carboxylic acid [Reaction conditions: (1) NaOH, MeOH–H_2O. (2) AcOH, reflux.]. $[\alpha]_D^{19} = -31.3$ (c 1.08, $CHCl_3$, 53% ee), Lit.[13] $[\alpha]_D^{20} = -59.5$ (c 2.6, $CHCl_3$, 94% ee).

4.3. Determination of the absolute configuration of 4ad and 4id

4.3.1. (1*R*)-2-Phenyl-2-cyclohexen-1-yl acetic acid 5. To a stirred solution of **4ad** (404.3 mg, 0.918 mmol) in MeOH (9.18 mL) was added 3.3 N NaOH (1.53 mL), and the reaction mixture was heated in oil bath and refluxed for 8 h. After cooling down to room temperature, the reaction mixture was evaporated. The obtained residue was dissolved in AcOH (4.59 mL) and the solution was refluxed for 12 h. After cooling down to room temperature, the reaction mixture was evaporated. After the addition of H_2O to the residue, the mixture was extracted with ethyl acetate (×3), washed with H_2O and brine, and then dried over Na_2SO_4. After concentration under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate: 10/1 to 4/1) to give **5** (182.8 mg, 92%) as a white solid. Mp: 99–101 °C; IR (ATR): ν 2926, 1692, 1404, 1280, 1196, 916, 878, 756, 693 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.60–1.78 (m, 4H), 1.84–1.93 (m, 1H), 2.15–2.22 (m, 2H), 2.22 (dd, $J = 10.8$ Hz, 16.0 Hz, 1H), 2.41 (dd, $J = 2.8$ Hz, 16.0 Hz, 1H), 3.20–3.30 (m, 1H), 5.98–6.00 (m, 1H), 7.22–7.32 (m, 5H), a carboxylic acid proton could not be detected in ^1H NMR ($CDCl_3$ and C_6D_6); ^{13}C NMR ($CDCl_3$): δ 18.2, 26.0, 27.5, 32.4, 38.1, 126.2 (×2), 126.9, 127.5, 128.4 (×2), 139.8, 141.4, 179.5; EI-LRMS m/z 216 (M^+); EI-HRMS. Calcd for $C_{14}H_{16}O_2$ (M^+): 216.1150. Found: 216.1135; $[\alpha]_D^{24} = -135.2$ (c 1.03, $CHCl_3$, 86% ee).

4.3.2. (1*R*)-2-Phenyl-2-cyclohexen-1-yl ethanol 6. To a stirred suspension of $LiAlH_4$ (41.2 mg, 1.086 mmol) in THF (7.24 mL) at 0 °C was added **5** (156.6 mg, 0.724 mmol). The resulting suspension was heated on an oil bath and refluxed for 16 h. After cooling down to room temperature, the reaction was quenched by the addition of water and 1 M NaOH. The obtained white solid was

filtered, and refluxed in THF (7.24 mL) for 3 h. After filtration, the combined organic layers were washed with brine, dried over Na_2SO_4, and then evaporated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate: 20/1 to 10/1) to give **6** as a colorless oil (136.1 mg, 93%). IR (ATR): ν 3309, 2927, 2859, 1492, 1444, 1055, 1013, 756, 695 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.26 (broad peak (O*H*), 1H), 1.42–1.87 (m, 6H), 2.12–2.20 (m, 2H), 2.82–2.91 (m, 1H), 3.55–3.61 (m, 2H), 5.90–5.92 (m, 1H), 7.20–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 18.5, 26.0, 27.3, 32.0, 36.4, 61.1, 126.2 (×2), 126.4, 126.5, 128.2 (×2), 141.7, 142.6; EI-LRMS *m*/*z* 202 (M^+); EI-HRMS. Calcd for $C_{14}H_{18}O$ (M^+): 202.1358. Found: 202.1360; $[\alpha]_D^{23} = -118.6$ (*c* 0.84, CH_2Cl_2, 86% ee).

4.3.3. (1*R*)-2-Phenyl-2-cyclopenten-1-yl acetic acid 7. Compound **7** was prepared using the same procedure for the transformation of **4ad** to **5**. White solid. Mp: 68 °C; IR (ATR): ν 2935, 2843, 1686, 1403, 1285, 1203, 936, 754, 691 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.82–1.89 (m, 1H), 2.18 (dd, $J = 10.8$ Hz, 16.0 Hz, 1H), 2.27–2.35 (m, 1H), 2.48–2.60 (m, 2H), 2.67 (dd, $J = 2.8$ Hz, 16.0 Hz, 1H), 3.56–3.65 (m, 1H), 6.10–6.12 (m, 1H), 7.22–7.41 (m, 5H), a carboxylic acid proton could not be detected in ^1H NMR ($CDCl_3$ and C_6D_6); ^{13}C NMR ($CDCl_3$): δ 30.0, 31.2, 38.2, 41.6, 126.1 (×2), 127.2, 127.6, 128.5 (×2), 135.4, 144.8, 179.5; EI-LRMS *m*/*z* 202 (M^+); EI-HRMS. Calcd for $C_{13}H_{14}O_2$ (M^+): 202.0994. Found: 202.0994; $[\alpha]_D^{23} = -57.2$ (*c* 0.82, $CHCl_3$, 89% ee).

4.3.4. (1*R*)-2-Phenyl-2-cyclopenten-1-yl ethanol 8. Compound **8** was prepared using the same procedure for the transformation of **5** to **6**. Colorless oil. IR (ATR): ν 3311, 2932, 2843, 1494, 1444, 1054, 752, 692 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.31 (broad peak (O*H*), 1H), 1.41–1.54 (m, 1H), 1.74–1.93 (m, 2H), 2.15–2.25 (m, 1H), 2.40–2.56 (m, 2H), 3.22–3.32 (m, 1H), 3.63–3.77 (m, 1H), 6.06 (dd, $J = 2.4$ Hz, 4.0 Hz, 1H), 7.20–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 29.8, 31.5, 36.4, 41.5, 61.6, 126.1 (×2), 126.7, 126.8, 128.3 (×2), 136.2, 146.2; EI-LRMS *m*/*z* 188 (M^+); EI-HRMS. Calcd for $C_{13}H_{16}O$ (M^+): 188.1201. Found: 188.1203; $[\alpha]_D^{21} = -51.0$ (*c* 0.58, CH_2Cl_2, 89% ee).

4.4. Experimental procedure for the transformation of 5 and 8

4.4.1. (3a*R*,7*S*,7a*R*)-7-Iodo-7a-phenyl-hexahydrobenzofuran-2-one 9. Compound **5** (50.0 mg, 0.231 mmol) was added to a solution of $NaHCO_3$ (58.2 mg, 0.693 mmol) in water (0.58 mL), and the resulting mixture was stirred until it became homogeneous. The flask was then protected from light, and the mixture was treated with a solution of KI (230.1 mg, 1.386 mmol) and iodine (30.8 mg, 0.243 mmol) in water (0.58 mL) in one portion. The reaction mixture was stirred at room temperature for 24 h and then extracted with $CHCl_3$ (×3). The organic extracts were combined, washed with 10% aqueous $Na_2S_2O_3$, 10% aqueous $NaHCO_3$, and water, and then dried Na_2SO_4. After concentration under reduced pressure, the residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate: 20/1 to 5/1) to give **9** (73.6 mg, 93%) as a white solid. Mp 76 °C; IR (ATR): ν 2924, 1771, 1233, 1155, 1131, 932, 902, 769, 747, 699 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.50–1.58 (m, 1H), 1.71–1.77 (m, 1H), 1.88–1.97 (m, 1H), 2.06–2.14 (m, 1H), 2.12–2.25 (m, 2H), 2.35 (dd, $J = 4.4$ Hz, 17.2 Hz, 1H), 2.54 (dd, $J = 6.8$ Hz, 17.2 Hz, 1H), 3.14–3.21 (m, 1H), 4.66–4.69 (m, 1H), 7.32–7.48 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.2, 27.0, 32.7, 36.3, 37.2, 37.3, 88.0, 126.0 (×2), 128.1 (×2), 128.5, 142.4, 175.3; EI-LRMS *m*/*z* 342 (M^+); EI-HRMS. Calcd for $C_{14}H_{15}IO_2$ (M^+): 342.0117. Found: 342.0110; $[\alpha]_D^{21} = +26.1$ (*c* 0.28, $CHCl_3$, 86% ee).

4.4.2. (3a*R*,7a*S*)-7a-Phenyl-3a,4,5,7-tetrahydro-3*H*-benzofuran-2-one 10. Iodolactone **9** (71.8 mg, 0.210 mmol) was dissolved in dry toluene (2.10 mL) containing freshly distilled 1,8-diazabicyclo[5.4.0]-7-undecene (DBU) (48.0 mg, 0.315 mmol), and the mixture was refluxed for 12 h, cooled to room temperature, and then filtered. After the filtrate was concentrated under reduced pressure, the obtained residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate: 10/1 to 5/1) to give **8** as a colorless oil (38.8 mg, 86%). IR (ATR): ν 2926, 1769, 1243, 1213, 1171, 1007, 981, 944, 903, 757, 698 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.62–1.72 (m, 1H), 1.82–1.90 (m, 1H), 2.17–2.30 (m, 2H), 2.42–2.51 (m, 1H), 2.59–2.68 (m, 2H), 5.77 (dt, $J = 10.0$ Hz, 2 Hz, 1H), 6.17 (dt, $J = 10.0$ Hz, 4 Hz, 1H), 7.26–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 21.0, 22.1, 33.5, 42.0, 85.6, 125.2 (×2), 127.3, 127.8, 128.4 (×2), 131.2, 142.4, 176.2; EI-LRMS *m*/*z* 214 (M^+); EI-HRMS. Calcd for $C_{14}H_{14}O_2$ (M^+): 214.0994. Found: 214.0983; $[\alpha]_D^{24} = +98.2$ (*c* 1.59, $CHCl_3$, 86% ee).

4.4.3. (3a*R*,6a*S*)-6a-Phenyl-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan 11. Compound **8** (24.4 mg, 0.130 mmol) was dissolved in DMSO (0.52 mL) and the vessel was purged with O_2. Next 5 mol % of $Pd(OAc)_2$ was added and the vessel was sealed, evacuated and filled with oxygen twice. After the reaction mixture was stirred for 24 h at room temperature, the reaction was quenched with 5 mL of water. The aqueous phase was extracted four times with ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent was carefully distilled off. The crude residue was purified by flash column chromatography (SiO_2, hexane/ethyl acetate: 30/1 to 10/1) to give **13** as a colorless oil (21.2 mg, 88%). IR (ATR): ν 2961, 2923, 2851, 1446, 1269, 1058, 1030, 752, 728, 697 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.65–1.72 (m, 1H), 2.17–2.28 (m, 2H), 2.71–2.76 (m, 1H), 2.80–2.86 (m, 1H), 3.80 (ddd, $J = 5.6$ Hz, 8.4 Hz, 8.8 Hz, 1H), 4.05 (ddd, $J = 3.6$ Hz, 6.8 Hz, 8.4 Hz, 1H), 5.66 (dt, $J = 5.6$ Hz, 2.0 Hz, 1H), 6.03 (dt, $J = 5.6$ Hz, 2.4 Hz, 1H), 7.20–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 35.6, 39.9, 48.6, 66.9, 98.9, 124.9 (×2), 126.7, 128.1 (×2), 133.6, 133.8, 145.6; EI-LRMS *m*/*z* 186 (M^+); EI-HRMS. Calcd for $C_{13}H_{14}O$ (M^+): 186.1045. Found: 186.1026; $[\alpha]_D^{23} = +65.4$ (*c* 0.55, $CHCl_3$, 89% ee).

Acknowledgments

This work was supported by Grant-in-aid for Scientific Research on Priority Areas, Chemistry of Concerto Catalysis, and Grant-in Aid for Encouragement of Young

Scientist (A), from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

References

1. For reviews on Pd-catalyzed asymmetric allylic substitution, see: (a) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395; (b) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1; (c) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921; (d) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.
2. For examples using carbon nucleophiles, see: (a) Hamada, Y.; Sakaguchi, K.; Hatano, K.; Hara, O. *Tetrahedron Lett.* **2001**, *42*, 1297; (b) Stang, A. Q.; Helmchen, G. *Helv. Chim. Acta* **2005**, *88*, 2738.
3. For examples using nitrogen nucleophiles, see: (a) Mori, M.; Kuroda, S.; Zhang, C.-S.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263; (b) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057; (c) Mori, M.; Nishimata, T.; Nagasawa, Y.; Sato, Y. *Adv. Synth. Catal.* **2001**, *343*, 34; (d) Mori, M.; Nakanishi, D.; Kajishima, D.; Sato, Y. *J. Am. Chem. Soc.* **2003**, *125*, 9801.
4. For examples using oxygen nucleophiles, see: (a) Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014; (b) Trost, B. M.; Tang, W.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 14785.
5. (a) Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, *7*, 4447; (b) Nemoto, T.; Fukuyama, T.; Yamamoto, E.; Tamura, S.; Fukuda, T.; Matsumoto, T.; Akimoto, Y.; Hamada, Y. *Org. Lett.* **2007**, *9*, 927.
6. For recent representative examples of Pd-catalyzed asymmetric allylic substitution of cycloalkenyl alcohol derivatives using malonate nucleophiles, see: (a) Zhao, D.; Ding, K. *Org. Lett.* **2003**, *5*, 1249; (b) Greenfield, S.; Agarkov, A.; Gilbertson, S. R. *Org. Lett.* **2003**, *5*, 3069; (c) Seemann, M.; Schöller, M.; Kudis, S.; Helmchen, G. *Eur. J. Org. Chem.* **2003**, 2122; (d) Diéguez, M.; Pàmies, O.; Claver, C. *J. Org. Chem.* **2005**, *70*, 3363; (e) Pàmies, O.; Diéguez, M.; Claver, C. *J. Am. Chem. Soc.* **2005**, *127*, 3646; (f) Okuyama, Y.; Nakano, H.; Saito, Y.; Takahashi, K.; Hongo, H. *Tetrahedron: Asymmetry* **2005**, *16*, 2551; (g) Hilgraf, R.; Pfaltz, A. *Adv. Synth. Catal.* **2005**, *347*, 61; (h) Chapsal, B. D.; Ojima, I. *Org. Lett.* **2006**, *8*, 1395; (i) Pei, Y.; Brulé, E.; Moberg, C. *Org. Biomol. Chem.* **2006**, *4*, 544; (j) Raluy, E.; Claver, C.; Diéguez, M. *Org. Lett.* **2007**, *9*, 49; (k) Liu, D.; Xie, F.; Zhang, W. *J. Org. Chem.* **2007**, *72*, 6992.
7. For other asymmetric reactions using the transition metal-DIAPHOX catalyst systems, see: (a) Nemoto, T.; Matsumoto, T.; Masuda, T.; Hitomi, T.; Hatano, K.; Hamada, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3690; (b) Nemoto, T.; Masuda, T.; Matsumoto, T.; Hamada, Y. *J. Org. Chem.* **2005**, *70*, 7172; (c) Nemoto, T.; Fukuda, T.; Matsumoto, T.; Hitomi, T.; Hamada, Y. *Adv. Synth. Catal.* **2005**, *347*, 1504; (d) Nemoto, T.; Jin, L.; Nakamura, H.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 6577; (e) Nemoto, T.; Sakamoto, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2006**, *47*, 8737; (f) Nemoto, T.; Sakamoto, T.; Fukuyama, T.; Hamada, Y. *Tetrahedron Lett.* **2007**, *48*, 4977; (g) Nemoto, T.; Harada, T.; Matsumoto, T.; Hamada, Y. *Tetrahedron Lett.* **2007**, *48*, 6304.
8. For reviews on phosphine oxide preligands in transition metal catalysis, see: (a) Dubrovina, N. V.; Börner, A. *Angew. Chem., Int. Ed.* **2004**, *43*, 5883; (b) Ackermann, L. *Synthesis* **2006**, 1557; (c) Ackermann, L. *Synlett* **2007**, 507; (d) Nemoto, T.; Hamada, Y. *Chem. Rec.* **2007**, *7*, 150.
9. When this reaction was performed in other solvents, the product was obtained with lower enantiomeric excess. CH_2Cl_2: 65% yield, 60% ee; toluene: 5% yield, 55% ee; THF: 53% yield, 56% ee.
10. When a lithium enolate prepared from dibenzyl malonate and LiH was used as the nucleophile, **4ad** was obtained in 99% yield with 86% ee. This result indicates that LiOAc is likely related to the generation of lithium enolate in situ, resulting in increased enantioselectivity.
11. Ebner, D. C.; Novák, Z.; Stoltz, B. M. *Synlett* **2006**, 3533.
12. (a) Rönn, M.; Bäckvall, J.-E.; Anderson, P. G. *Tetrahedron Lett.* **1995**, *36*, 7749; (b) Trend, R. M.; Ramtohul, Y. K.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2892.
13. Fuchs, S.; Berl, V.; Lepoittevin, J.-P. *Eur. J. Org. Chem.* **2007**, 1145.