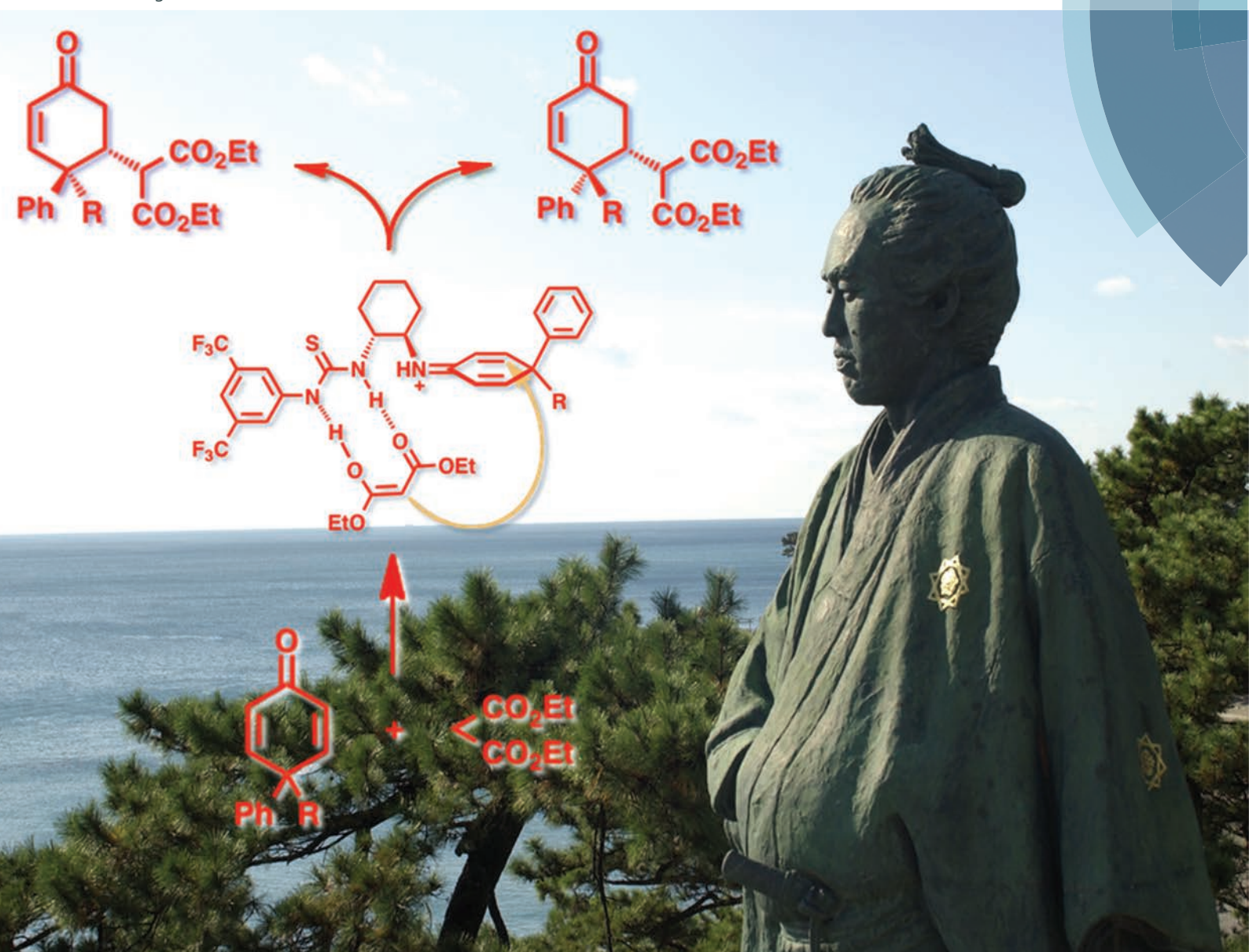


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## PAPER

Hiyoshizo Kotsuki *et al.*

Asymmetric organocatalytic desymmetrization of 4,4-disubstituted cyclohexadienones at high pressure: a new powerful strategy for the synthesis of highly congested chiral cyclohexenones

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## Asymmetric organocatalytic desymmetrization of 4,4-disubstituted cyclohexadienones at high pressure: a new powerful strategy for the synthesis of highly congested chiral cyclohexenones†

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A highly diastereoselective and enantioselective method for the asymmetric desymmetrization of 4,4-disubstituted cyclohexadienones using the Michael addition reaction of malonates under catalysis with the primary amine–thiourea conjugate catalyst and PPY at high pressure was developed.

### Introduction

Asymmetric desymmetrization can provide a powerful and highly expedient strategy for the construction of two or more new chiral stereogenic centers from prochiral compounds in a single-step operation. Accordingly, a variety of methods that use both enzymatic and non-enzymatic processes have been developed that show high to excellent enantioselectivity, and most involve the intrinsic nature of *meso*-anhydrides, epoxides and diols.<sup>2</sup> In addition to these precedents, recent efforts have been directed to explore the versatile utility of organocatalytic transformations.<sup>3</sup> These include, for example, functionalization of *meso*-diols and anhydrides,<sup>4</sup> aldol and related reactions,<sup>5</sup> discrimination of cyclohexadienes,<sup>2f,6</sup> Baeyer–Villiger oxidation of cyclobutanones,<sup>7</sup> and others.<sup>8</sup> Among these, we were particularly interested in devising an efficient method for differentiating between the two double bonds in 4,4-disubstituted cyclohexadienones based on organocatalytic asymmetric Michael addition reactions, since functionalized cyclohexenones or cyclohexanones are important key components in synthetic and natural products chemistry.<sup>9</sup>

Although there have been reports on intramolecular approaches to the desymmetrization of cyclohexadienones,<sup>6g,h,j–n</sup> to the best of our knowledge, very little information is available on intermolecular variants.<sup>6p,10</sup> Presumably, this might be the result of severe steric congestion at  $\beta$ -carbon atoms. Despite this fairly limited accessibility, we thought that the asymmetric discrimination of cyclohexadienones based on an intermolecular Michael addition strategy would be a great

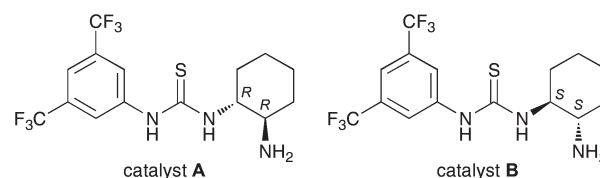


Fig. 1 Catalysts A and B.

challenge for the synthesis of cyclohexenone derivatives containing up to two stereocenters, in which an all-carbon quaternary stereogenic center was part of the stereoarray. In view of the great advances in the organocatalytic construction of quaternary stereogenic carbon centers,<sup>11</sup> this should contribute to progress in this field. Herein, we report a highly successful method for realizing this expectation by taking advantage of our recent findings on asymmetric Michael addition reactions using a dual catalyst system composed of the primary amine–thiourea conjugate catalyst **A** or **B** and 4-pyrrolidinopyridine (PPY) (Fig. 1).<sup>12</sup>

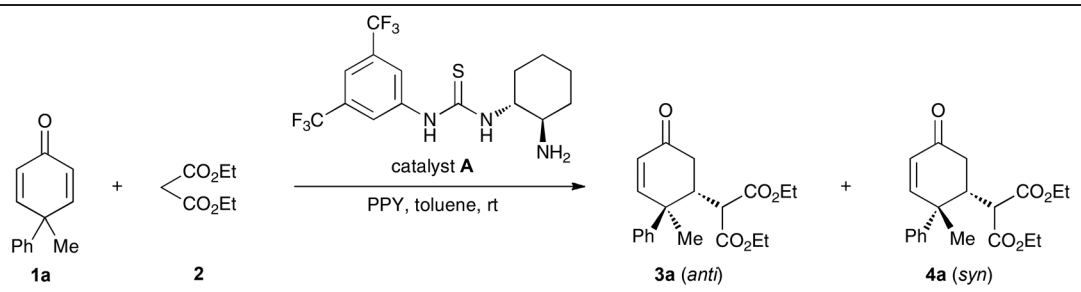
### Results and discussion

The starting 4,4-disubstituted cyclohexadienones **1a–f** used in this work were prepared by  $\alpha$ -selenylation followed by oxidative elimination of the corresponding cyclohexenone precursors,<sup>13</sup> which were readily accessible from  $\alpha,\alpha'$ -disubstituted acet-aldehydes and methyl vinyl ketone *via* Robinson-type annulation.<sup>14</sup> On the other hand, 4-methyl-4-trichloromethyl-2,2-cyclohexadienone (**1g**) was prepared from *p*-cresol by the Zincke–Suhl reaction, as described in the literature.<sup>15</sup>

First, we examined the asymmetric desymmetrization of 4-methyl-4-phenyl-2,5-cyclohexadienone (**1a**) through the Michael

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Table 1 Catalytic asymmetric desymmetrization: optimization<sup>a</sup>


Entry	1a : 2	Cat. A (mol%)	PPY (mol%)	Conditions	Yield <sup>b</sup> (%)	dr (3a/4a) <sup>c</sup>	ee (%) (3a/4a) <sup>d</sup>
1	1 : 1.5	10	10	4.5 days	11	90/10	92/82
2	1 : 1.5	10	10	0.8 GPa, 24 h	22	88/12	94/86
3 <sup>e</sup>	1 : 1.5	10	10	0.8 GPa, 24 h	Trace		
4 <sup>f</sup>	1 : 1.5	30	30	0.8 GPa, 2 days	54	87/13	88/82
5	1 : 3	30	30	0.8 GPa, 3 days	46 <sup>g</sup>	85/15	94/88
6	3 : 1	30	30	0.8 GPa, 2 days	82	84/16	92/86
7	3 : 1	30	30	0.6 GPa, 2 days	73	89/11	94/86
8	3 : 1	30	30	0.4 GPa, 2 days	54	89/11	92/76
9 <sup>h</sup>	3 : 1	30	30	0.8 GPa, 2 days	82	84/16	−92/−85

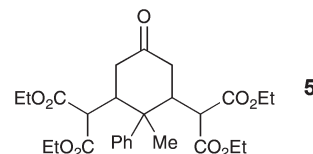
<sup>a</sup> Reactions performed at a concentration of 0.2 M in the solvent listed. <sup>b</sup> Combined yields of isolated products **3a** and **4a**. Yields based on the reacted **1a** (entries 1–5) or **2** (entries 6 and 7). <sup>c</sup> Determined by <sup>1</sup>H NMR (500 MHz). <sup>d</sup> Determined by chiral HPLC analysis using Chiralcel AD (hexane-*i*-PrOH = 90 : 10, flow rate 1.0 mL min<sup>−1</sup>, λ = 254 nm). <sup>e</sup> THF was used as a solvent. <sup>f</sup> 0.5 M in the solvent. <sup>g</sup> By-product **5** was isolated in 43% yield. <sup>h</sup> Catalyst **B** was used in place of catalyst **A**.

addition reaction of diethyl malonate (**2**). The results are summarized in Table 1.

Under our previously established standard conditions with 10 mol% of catalyst **A** and 10 mol% of PPY at atmospheric pressure,<sup>12a</sup> the desired reaction proceeded sluggishly to afford the desymmetrization products, the *anti*-adduct **3a** and the *syn*-adduct **4a**, with high diastereo- and enantioselectivity, but in only 11% yield (entry 1). We applied a high-pressure technique to accelerate this reaction,<sup>12b,16</sup> and observed that the pressure played an essential role in the present system (entry 2). Consistent with our previous observations,<sup>17</sup> when THF was used as a solvent, the reaction was completely suppressed, which indicated that a hydrogen-bonding interaction between the substrate and the catalyst may be inhibited in this HBD solvent (entry 3).<sup>18</sup> While an increase in the catalyst loading to 30 mol% improved the product yield (entry 4),<sup>19</sup> the use of 3 equiv. of **2** resulted in the formation of a large amount of the double-Michael adduct **5** due to the ease of the second-step reaction (entry 5) (Fig. 2).

After several experiments, we concluded that this problem could be easily solved using an excess of **1a**, and the products **3a** and **4a** were obtained in 82% combined yield with high diastereo- (**3a/4a** = 84 : 16) and enantioselectivity (**3a**, 92% ee; **4a**, 86% ee) (entry 6). In this case we also recognized the critical factor of pressure and yields decreased at lower pressures (entries 6–8).<sup>12b</sup> As expected, the use of catalyst **B** completely reversed this desymmetrization dictation (entry 9).

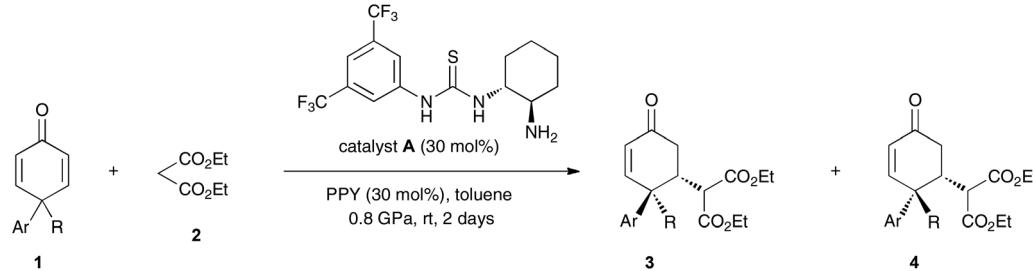
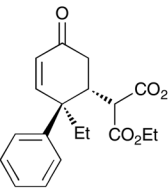
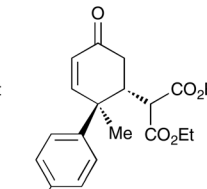
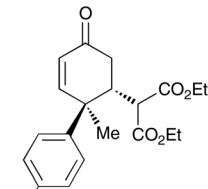
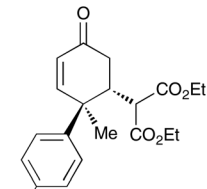
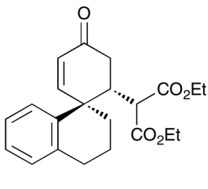
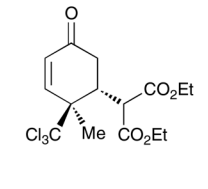
With our optimized reaction conditions in hand, we then explored the general scope of the reaction, and the results are summarized in Table 2.<sup>20</sup> All reactions were performed in

Fig. 2 By-product **5**.

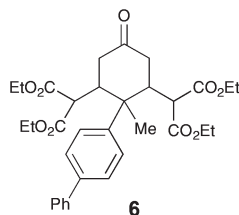
toluene at 0.8 GPa and rt for 2 days in the presence of 30 mol% of the respective catalyst **A** and PPY. Various 4-alkyl-4-aryl-disubstituted cyclohexadienones **1b–f** reacted smoothly with **2** to give the products in good yields (up to 99%) and with high diastereo- (up to 93 : 7) and enantioselectivity (up to 93% ee for **3** and 99% ee for **4**). When the size of the 4-alkyl group was increased from Me to Et (compare **3a** with **3b**), the diastereoselectivity significantly decreased, while the enantioselectivity remained roughly the same. Unexpectedly, cyclohexadienone **1g** could react only very slowly even with 1 equiv. of **2** at 0.8 GPa for 4 days and the product **3g** was obtained as an almost single diastereomer in 10% yield with 33% ee.

The absolute configurations of the products **3a** and **4a** were determined unambiguously by conversion to the corresponding cyclohexanone derivatives **7** and **10**, and by comparison of their optical rotations with those of the authentic samples prepared independently from optically pure (*R*)-cyclohexenone **8**<sup>14</sup> (Scheme 1). Thus, catalytic hydrogenation of **3a** in EtOH as a solvent at rt in the presence of a catalytic amount of Pd/C afforded **7**, [ $\alpha$ ]<sub>D</sub><sup>27</sup> +5.4 (*c* = 0.49, EtOH, 92% ee), in 36% yield<sup>21</sup> without the loss of diastereomeric and enantiomeric

Table 2 Catalytic asymmetric desymmetrization: generality<sup>a</sup>

	
 <b>3b</b> , 68% yield <sup>b</sup> <b>3b/4b</b> = 68 : 32 <sup>d</sup> <b>3b</b> , 92% ee <sup>e</sup> <b>4b</b> , 86% ee <sup>e</sup>	 <b>3c</b> , 99% yield <sup>b</sup> <b>3c/4c</b> = 87 : 13 <sup>d</sup> <b>3c</b> , 92% ee <sup>e</sup> <b>4c</b> , 89% ee <sup>e</sup>
 <b>3d</b> , 85% yield <sup>b</sup> <b>3d/4d</b> = 84 : 16 <sup>d</sup> <b>3d</b> , 93% ee <sup>e</sup> <b>4d</b> , 90% ee <sup>e</sup>	 <b>3e</b> , 75% yield <sup>b,c</sup> <b>3e/4e</b> = 87 : 13 <sup>d</sup> <b>3e</b> , 92% ee <sup>e</sup> <b>4e</b> , 87% ee <sup>e</sup>
 <b>3f</b> , 60% yield <sup>b</sup> <b>3f/4f</b> = 93 : 7 <sup>d</sup> <b>3f</b> , 82% ee <sup>e</sup> <b>4f</b> , >99% ee <sup>e</sup>	 <b>3g</b> , 10% yield (4 days) <b>3g/4g</b> = >99 : 1 <b>3g</b> , 33% ee <sup>e</sup> <b>4g</b> , ---

<sup>a</sup> Reactions performed at a concentration of 0.2 M in toluene. <sup>b</sup> The combined yield of isolated products **3** and **4**, and based on the reacted **2**. The absolute configuration of the products was surmised in analogy with **3a**. <sup>c</sup> By-product **6** was formed in 8% yield. <sup>d</sup> Determined by <sup>1</sup>H NMR (500 MHz). <sup>e</sup> Determined by chiral HPLC analysis using Chiralcel AD (hexane-*i*-PrOH = 90 : 10, flow rate 1.0 mL min<sup>-1</sup>, λ = 254 nm) except for **3b**, **3e** (hexane-*i*-PrOH = 95 : 5, flow rate 0.5 mL min<sup>-1</sup>), and **3f** (hexane-*i*-PrOH = 99 : 1, flow rate 0.5 mL min<sup>-1</sup>).

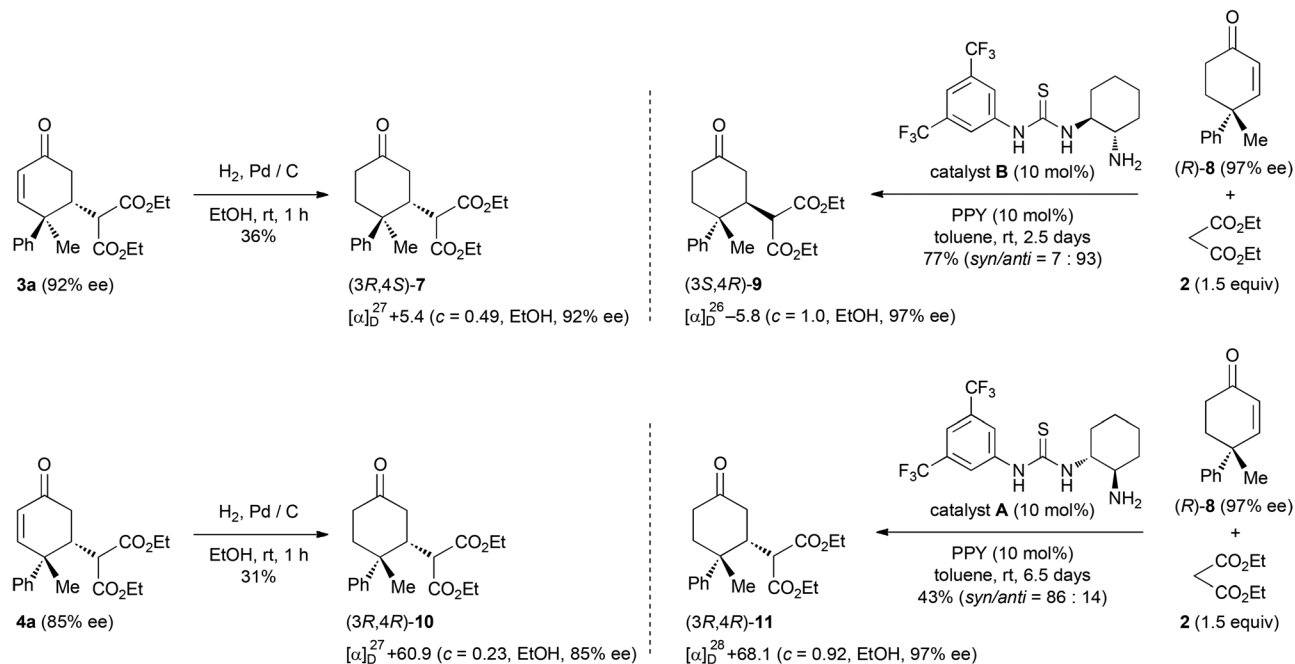


excess. On the other hand, the authentic sample of (3*S*,4*R*)-**9**, [ $\alpha$ ]<sub>D</sub><sup>26</sup> −5.8 (*c* = 1.0, EtOH, 97% ee), was prepared from **8** and **2** in 77% yield with high *anti*-selectivity (*syn/anti* = 7 : 93) via the diastereoselective Michael addition reaction using catalyst **B** at atmospheric pressure and rt for 2.5 days. The results of optical rotation revealed that **7** and **9** are enantiomers of each other, and hence **7** has a (3*R*,4*S*)-configuration for the all-carbon substituted quaternary stereogenic center and the adjacent tertiary stereogenic center, and therefore also for the corresponding moieties in **3a**. In a similar manner, the absolute configuration of **4a** was determined to be (3*R*,4*R*) after it was reduced to **10**; this compound was in good agreement with (3*R*,4*R*)-**11** derived from (*R*)-**8** with the assistance of catalyst **A**. The latter reaction proceeded fairly slowly due to steric congestion at the C3 position, but with good *syn*-selectivity (*syn/anti* = 86 : 14) as a result of the so-called catalyst control. Meanwhile, the relative stereochemistry of *syn*- and *anti*-adducts, *i.e.*, (3*S*,4*R*)-**9** and (3*R*,4*R*)-**11**, was confirmed by NOESY experiments (Fig. 3). Thus, (3*S*,4*R*)-**9** revealed an NOE interaction between the C4 methyl and the malonate proton, indicating that a phenyl ring has a

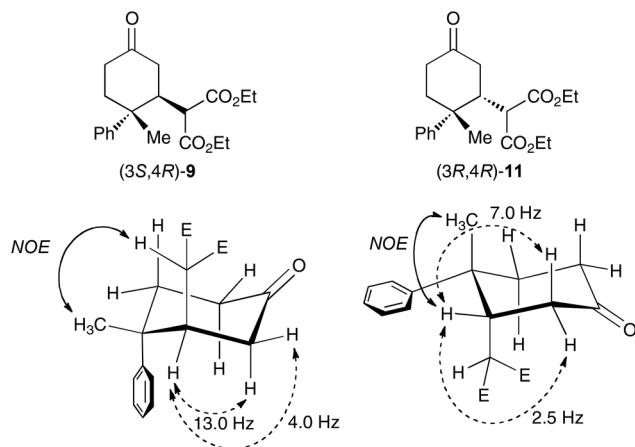
favorable axial position.<sup>22</sup> On the other hand, the interaction between the C4 methyl and the C3 methine in (3*R*,4*R*)-**11** reflected the existence of a severe steric repulsion between the equatorial phenyl ring and the axial malonate substituent.

Based on the experimental results described above and our recent studies, we propose a mechanism to account for the present high level of asymmetric desymmetrization of cyclohexadienones (Fig. 4).<sup>12,16</sup> First, the dual catalyst system composed of catalyst **A** and PPY can activate both **2** as a Michael donor *via* double hydrogen bonding with a thiourea part of catalyst **A** and **1a** as a Michael acceptor by anchoring to form the ketiminium ion intermediate with a free amine part of catalyst **A** (**I**). After proton abstraction by PPY, the resulting malonate anion then attacks one of the two enantiotopic double bonds from the less-hindered side opposite a rather bulky phenyl ring in an intramolecular fashion (**II**). As a result of the main control from the cyclohexanediamine chiral motif of catalyst **A**, high discrimination would be enforced to give the desired chiral adduct (**III**), **3a** after hydrolysis, which is consistent with the experimental results.





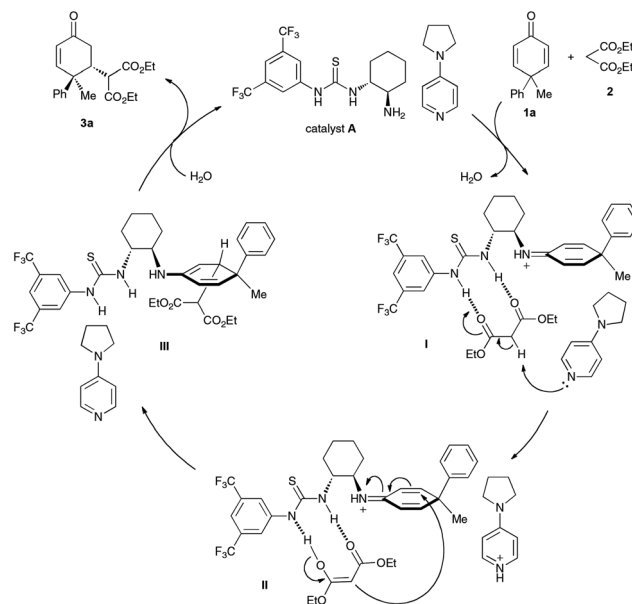
**Scheme 1** Determination of the absolute configurations of the products **3a** and **4a**.



**Fig. 3** NOESY experiments on **(3S,4R)-9** and **(3R,4R)-11** (500 MHz,  $\text{CDCl}_3$ ). Characteristic correlations are shown. Important vicinal coupling constants are indicated by dashed arrows.

## Conclusions

In conclusion, we have developed a highly diastereoselective and enantioselective method for the asymmetric desymmetrization of 4,4-disubstituted cyclohexadienones using the Michael addition reaction of malonates under catalysis with the primary amine–thiourea conjugate catalyst **A** or **B** and PPY at high pressure. This method is particularly useful for constructing highly functionalized cyclohexenones containing a quaternary carbon stereogenic center and two contiguous stereocenters in only one step. Further studies on the application of this method to natural product synthesis are now in progress in our laboratory.



**Fig. 4** Plausible mechanism.

## Experimental section

### Typical procedure for the asymmetric desymmetrization of **1a** (Table 1, entry 6)

A mixture of **1a** (166 mg, 0.9 mmol) and diethyl malonate (**2**, 48 mg, 0.3 mmol) in the presence of catalyst **A** (34.7 mg, 30 mol%) and PPY (13.3 mg, 30 mol%) in toluene (1.4 mL) was placed in a Teflon reaction vessel and the mixture was allowed to react at 0.8 GPa and rt for 2 days. After the pressure was released, the mixture was concentrated and purified by

column chromatography on alumina (eluted with hexane–AcOEt) to give **3a** (71.4 mg, 69%) and **4a** (13.4 mg, 13%) along with the recovered **1a** (103 mg).

**Diethyl 2-((1*S*,2*R*)-1-methyl-4-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)malonate (**3a**)**

Colorless oil;  $R_f$  0.26 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{25} +91.6$  ( $c$  = 0.93, EtOH, 92% ee); FTIR (KBr)  $\nu$  1754, 1730, 1683  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.10 (3H, t,  $J$  = 7.5 Hz), 1.28 (3H, t,  $J$  = 7.5 Hz), 1.52 (3H, s), 2.59 (1H, dd,  $J$  = 17.0, 4.0 Hz), 2.71 (1H, dd,  $J$  = 17.0, 12.0 Hz), 3.27 (1H, ddd,  $J$  = 12.0, 5.5, 4.0 Hz), 3.35 (1H, d,  $J$  = 5.5 Hz), 3.80–3.92 (2H, m), 4.19 (2H, q,  $J$  = 7.5 Hz), 6.07 (1H, d,  $J$  = 10.0 Hz), 6.72 (1H, d,  $J$  = 10.0 Hz), 7.25–7.38 (5H, m);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  13.77, 13.96, 18.04, 37.64, 44.23, 44.52, 52.11, 61.54, 61.60, 126.96 ( $\times 2$ ), 127.04, 127.31, 128.62 ( $\times 2$ ), 144.31, 158.00, 167.80, 168.37, 198.11; HRMS calcd for  $\text{C}_{20}\text{H}_{24}\text{O}_5$  344.1624, found 344.1623.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane–i-PrOH = 90 : 10,  $1.0 \text{ cm}^3 \text{ min}^{-1}$ ):  $R_t$  (major) = 12.6 min;  $R_t$  (minor) = 14.1 min.

**Diethyl 2-((1*R*,2*R*)-1-methyl-4-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)malonate (**4a**)**

Colorless oil;  $R_f$  0.19 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{25} -71.7$  ( $c$  = 0.09, EtOH, 86% ee); FTIR (KBr)  $\nu$  1756, 1730, 1683  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.09 (3H, t,  $J$  = 8.5 Hz), 1.20 (3H, t,  $J$  = 8.5 Hz), 1.67 (3H, s), 2.55 (1H, dd,  $J$  = 22.0, 6.0 Hz), 2.88 (1H, dd,  $J$  = 22.0, 14.0 Hz), 3.11 (1H, dt,  $J$  = 14.0, 6.0 Hz), 3.46 (1H, d,  $J$  = 6.0 Hz), 3.67–3.81 (2H, m), 4.03–4.16 (2H, m), 6.18 (1H, d,  $J$  = 12.0 Hz), 6.78 (1H, d,  $J$  = 12.0 Hz), 7.28–7.38 (5H, m);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  13.72, 13.94, 26.51, 36.92, 43.91, 44.16, 51.91, 61.13, 61.89, 127.58, 127.89, 128.03 ( $\times 2$ ), 128.45 ( $\times 2$ ), 138.50, 155.80 ( $\times 2$ ), 167.43, 168.64, 198.71; HRMS calcd for  $\text{C}_{20}\text{H}_{24}\text{O}_5$  344.1624, found 344.1622.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane–i-PrOH = 90 : 10,  $1.0 \text{ cm}^3 \text{ min}^{-1}$ ):  $R_t$  (major) = 10.7 min;  $R_t$  (minor) = 17.6 min.

**Tetraethyl 2,2'-(2-methyl-5-oxo-2-phenylcyclohexane-1,3-diyl)-dimalonate (by-product 5; Table 1, entry 5)**

Colorless oil;  $R_f$  0.15 (hexane–AcOEt = 5 : 1); FTIR (KBr)  $\nu$  1028, 1148, 1304, 1729  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.07–1.26 (12H, m), 1.62 (3H, s), 2.64 (2H, dd,  $J$  = 5.3 Hz), 2.72–2.85 (3H, m), 3.17 (1H, d,  $J$  = 4.0 Hz), 3.40 (1H, d,  $J$  = 3.5 Hz), 3.64 (1H, dt,  $J$  = 3.9, 13.0 Hz), 3.85–4.06 (6H, m), 4.09–4.19 (2H, m), 7.24–7.27 (1H, m), 7.33–7.39 (4H, m);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  13.71, 13.78, 13.85, 13.92, 38.69, 39.10, 39.57, 43.58, 46.31, 52.10, 52.36, 61.39, 61.48, 61.68, 61.75, 127.23, 127.47 ( $\times 2$ ), 128.59 ( $\times 2$ ), 142.69, 168.39, 168.45, 168.49, 168.55, 208.41; HRMS calcd for  $\text{C}_{27}\text{H}_{36}\text{O}_9$  + H 505.2438, found 505.2437.

**Diethyl 2-((1*S*,2*R*)-1-ethyl-4-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)malonate (**3b**)**

Colorless oil;  $R_f$  0.33 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{26} +67.9$  ( $c$  = 1.0, EtOH, 91% ee); FTIR (KBr)  $\nu$  1754, 1730, 1684  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.84 (3H, t,  $J$  = 7.5 Hz), 1.14 (3H, t,  $J$  = 7.5 Hz), 1.28 (3H, t,  $J$  = 7.5 Hz), 1.87 (1H, dq,  $J$  = 13.5, 7.5 Hz), 2.18 (1H, dq,  $J$  = 13.5, 7.5 Hz), 2.49 (1H, dd,  $J$  = 17.5, 5.0 Hz), 2.74 (1H, dd,  $J$  = 17.5, 10.5 Hz), 3.18 (1H, dt,  $J$  = 10.5, 5.0 Hz), 3.47 (1H, d,  $J$  = 5.0 Hz), 3.98 (2H, q,  $J$  = 7.5 Hz), 4.13–4.23 (2H, m), 6.22 (1H, d,  $J$  = 10.0 Hz), 6.97 (1H, d,  $J$  = 10.0 Hz), 7.25–7.38 (5H, m);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  8.90, 13.83, 13.93, 25.11, 37.35, 46.12, 48.00, 51.45, 61.52, 61.67, 127.09, 127.58 ( $\times 2$ ), 128.67 ( $\times 2$ ), 128.98, 142.38, 155.67, 168.14, 168.66, 197.83; HRMS calcd for  $\text{C}_{21}\text{H}_{26}\text{O}_5$  358.1780, found 358.1777.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane–i-PrOH = 95 : 5,  $0.5 \text{ cm}^3 \text{ min}^{-1}$ ):  $R_t$  (major) = 33.8 min;  $R_t$  (minor) = 36.7 min.

**Diethyl 2-((1*R*,2*R*)-1-ethyl-4-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)malonate (**4b**)**

Colorless oil;  $R_f$  0.26 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{25} -29.9$  ( $c$  = 0.48, EtOH, 86% ee); FTIR (KBr)  $\nu$  1759, 1730, 1683  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  0.90 (3H, t,  $J$  = 7.5 Hz), 1.10 (3H, t,  $J$  = 7.5 Hz), 1.19 (3H, t,  $J$  = 7.5 Hz), 2.11 (1H, dq,  $J$  = 14.5, 7.5 Hz), 2.20 (1H, dq,  $J$  = 14.5, 7.5 Hz), 2.62 (1H, dd,  $J$  = 18.0, 5.0 Hz), 2.84 (1H, dd,  $J$  = 18.0, 9.5 Hz), 3.22 (1H, dt,  $J$  = 9.5, 5.0 Hz), 3.38 (1H, d,  $J$  = 5.0 Hz), 3.79 (2H, q,  $J$  = 7.5 Hz), 4.01–4.14 (2H, m), 6.25 (1H, d,  $J$  = 10.5 Hz), 6.93 (1H, d,  $J$  = 10.5 Hz), 7.27–7.37 (5H, m);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  8.98, 13.69, 13.90, 31.66, 36.76, 41.83, 47.66, 51.97, 61.11, 61.78, 127.44, 128.21 ( $\times 2$ ), 128.52 ( $\times 2$ ), 129.49, 138.21, 154.21, 167.63, 168.68, 198.25; HRMS calcd for  $\text{C}_{21}\text{H}_{26}\text{O}_5$  358.1780, found 358.1778.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane–i-PrOH = 95 : 5,  $0.5 \text{ cm}^3 \text{ min}^{-1}$ ):  $R_t$  (major) = 28.2 min;  $R_t$  (minor) = 49.4 min.

**Diethyl 2-((1*S*,2*R*)-4'-methoxy-1-methyl-4-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)malonate (**3c**)**

Colorless oil;  $R_f$  0.15 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{26} +105.8$  ( $c$  = 0.97, EtOH, 92% ee); FTIR (KBr)  $\nu$  1754, 1729, 1683, 1609, 1514  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.12 (3H, t,  $J$  = 7.0 Hz), 1.28 (3H, t,  $J$  = 7.0 Hz), 1.49 (3H, s), 2.60 (1H, dd,  $J$  = 17.5, 5.0 Hz), 2.71 (1H, dd,  $J$  = 17.5, 12.5 Hz), 3.22 (1H, dt,  $J$  = 12.5, 5.0 Hz), 3.35 (1H, d,  $J$  = 5.0 Hz), 3.81 (3H, s), 3.84–3.95 (2H, m), 4.20 (2H, q,  $J$  = 7.0 Hz), 6.05 (1H, d,  $J$  = 10.0 Hz), 6.70 (1H, d,  $J$  = 10.0 Hz), 6.89 (2H, m), 7.24 (2H, m);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  13.80, 13.98, 18.07, 37.67, 43.63, 44.68, 52.10, 55.27, 61.53, 61.65, 113.93 ( $\times 2$ ), 126.87, 128.09 ( $\times 2$ ), 136.29, 158.45, 158.63, 167.90, 168.47, 198.31; HRMS calcd for  $\text{C}_{21}\text{H}_{26}\text{O}_6$  374.1729, found 374.1727.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane–i-PrOH =

90:10, 1.0 cm<sup>3</sup> min<sup>-1</sup>):  $R_t$  (major) = 15.9 min;  $R_t$  (minor) = 18.8 min.

**Diethyl 2-((1*R*,2*R*)-4'-methoxy-1-methyl-4-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)malonate (4c)**

Colorless oil;  $R_f$  0.13 (hexane-AcOEt = 5:1);  $[\alpha]_D^{25}$  -68.7 ( $c$  = 0.31, EtOH, 89% ee); FTIR (KBr)  $\nu$  1756, 1729, 1683, 1609, 1513 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.11 (3H, t,  $J$  = 7.5 Hz), 1.22 (3H, t,  $J$  = 7.5 Hz), 1.64 (3H, s), 2.53 (1H, dd,  $J$  = 17.5, 4.5 Hz), 2.85 (1H, dd,  $J$  = 17.5, 11.5 Hz), 3.08 (1H, dt,  $J$  = 11.5, 4.5 Hz), 3.45 (1H, d,  $J$  = 4.5 Hz), 3.72–3.85 (2H, m), 3.80 (3H, s), 4.06–4.17 (2H, m), 6.15 (1H, d,  $J$  = 10.0 Hz), 6.74 (1H, d,  $J$  = 10.0 Hz), 6.87 (2H, d,  $J$  = 9.0 Hz), 7.23 (2H, d,  $J$  = 9.0 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>)  $\delta$  8.99, 13.70, 13.91, 31.66, 36.76, 41.83, 47.66, 51.96, 61.12, 61.78, 127.44, 128.20 ( $\times 2$ ), 128.53 ( $\times 2$ ), 129.49, 138.21, 154.23, 167.64, 168.69, 198.27; HRMS calcd for C<sub>21</sub>H<sub>26</sub>O<sub>6</sub> 374.1729, found 374.1737.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, 0.46  $\times$  25 cm, hexane-*i*-PrOH = 90:10, 1.0 cm<sup>3</sup> min<sup>-1</sup>):  $R_t$  (major) = 14.0 min;  $R_t$  (minor) = 23.6 min.

**Diethyl 2-((1*S*,2*R*)-4'-bromo-1-methyl-4-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)malonate (3d)**

Colorless oil;  $R_f$  0.20 (hexane-AcOEt = 5:1);  $[\alpha]_D^{25}$  +94.0 ( $c$  = 0.87, EtOH, 93% ee); FTIR (KBr)  $\nu$  1755, 1729, 1684 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.12 (3H, t,  $J$  = 7.5 Hz), 1.28 (3H, t,  $J$  = 7.5 Hz), 1.50 (3H, s), 2.59 (1H, dd,  $J$  = 17.0, 5.0 Hz), 2.69 (1H, dd,  $J$  = 17.0, 12.5 Hz), 3.21 (1H, dt,  $J$  = 12.5, 5.0 Hz), 3.31 (1H, d,  $J$  = 5.0 Hz), 3.83–3.95 (2H, m), 4.20 (2H, q,  $J$  = 7.5 Hz), 6.08 (1H, d,  $J$  = 10.0 Hz), 6.66 (1H, d,  $J$  = 10.0 Hz), 7.21 (2H, d,  $J$  = 9.0 Hz), 7.49 (2H, d,  $J$  = 9.0 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>)  $\delta$  13.78, 13.97, 18.06, 37.58, 44.03, 44.41, 52.09, 61.64, 61.77, 121.48, 127.36, 128.80 ( $\times 2$ ), 131.72 ( $\times 2$ ), 143.44, 157.08, 167.69, 168.20, 197.72; HRMS calcd for C<sub>20</sub>H<sub>23</sub>BrO<sub>5</sub> 422.0729, found 422.0735.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, 0.46  $\times$  25 cm, hexane-*i*-PrOH = 90:10, 1.0 cm<sup>3</sup> min<sup>-1</sup>):  $R_t$  (major) = 21.6 min;  $R_t$  (minor) = 25.6 min.

**Diethyl 2-((1*R*,2*R*)-4'-bromo-1-methyl-4-oxo-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)malonate (4d)**

White solid, mp 102–106 °C;  $R_f$  0.18 (hexane-AcOEt = 5:1);  $[\alpha]_D^{25}$  -87.2 ( $c$  = 0.24, EtOH, 90% ee); FTIR (KBr)  $\nu$  1743, 1719, 1682 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.12 (3H, t,  $J$  = 7.0 Hz), 1.21 (3H, t,  $J$  = 7.0 Hz), 1.65 (3H, s), 2.58 (1H, dd,  $J$  = 17.5, 4.5 Hz), 2.83 (1H, dd,  $J$  = 17.5, 10.5 Hz), 3.10 (1H, dt,  $J$  = 10.5, 4.5 Hz), 3.41 (1H, d,  $J$  = 4.5 Hz), 3.72–3.86 (2H, m), 4.04–4.16 (2H, m), 6.17 (1H, d,  $J$  = 10.0 Hz), 6.74 (1H, d,  $J$  = 10.0 Hz), 7.20 (2H, d,  $J$  = 8.5 Hz), 7.47 (2H, d,  $J$  = 8.5 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>)  $\delta$  13.73, 13.93, 26.54, 36.83, 43.61, 44.10, 51.87, 61.32, 62.00, 121.91, 128.19, 129.81 ( $\times 2$ ), 131.52 ( $\times 2$ ), 137.90, 154.87, 167.37, 168.44, 198.13; HRMS calcd for C<sub>20</sub>H<sub>23</sub>BrO<sub>5</sub> 422.0729, found 422.0747.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column, 0.46  $\times$  25 cm, hexane-*i*-PrOH = 90:10, 1.0 cm<sup>3</sup> min<sup>-1</sup>):  $R_t$  (major) = 19.3 min;  $R_t$  (minor) = 27.0 min.

**Diethyl 2-((1*S*,2*R*)-1-methyl-4-oxo-1,2,3,4-tetrahydro-[1,1':4',1''-terphenyl]-2-yl)malonate (3e)**

Colorless oil;  $R_f$  0.23 (hexane-AcOEt = 5:1);  $[\alpha]_D^{26}$  +152.8 ( $c$  = 1.0, EtOH, 92% ee); FTIR (KBr)  $\nu$  1754, 1729, 1683 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.10 (3H, t,  $J$  = 7.5 Hz), 1.30 (3H, t,  $J$  = 7.5 Hz), 1.56 (3H, s), 2.64 (1H, dd,  $J$  = 17.5, 5.0 Hz), 2.74 (1H, dd,  $J$  = 17.5, 12.0 Hz), 3.32 (1H, dt,  $J$  = 12.0, 5.0 Hz), 3.41 (1H, d,  $J$  = 5.0 Hz), 3.80–3.94 (2H, m), 4.22 (2H, q,  $J$  = 7.5 Hz), 6.10 (1H, d,  $J$  = 10.0 Hz), 6.76 (1H, d,  $J$  = 10.0 Hz), 7.34–7.46 (5H, m), 7.58–7.61 (4H, m); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>)  $\delta$  13.79, 13.98, 18.08, 37.70, 44.07, 44.50, 52.26, 61.58, 61.68, 126.92 ( $\times 2$ ), 127.11, 127.25 ( $\times 2$ ), 127.47 ( $\times 3$ ), 128.81 ( $\times 2$ ), 140.14, 140.22, 143.32, 157.92, 167.83, 168.39, 198.09; HRMS calcd for C<sub>26</sub>H<sub>28</sub>O<sub>5</sub> 420.1937, found 420.1936.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46  $\times$  25 cm, hexane-*i*-PrOH = 95:5, 0.5 cm<sup>3</sup> min<sup>-1</sup>):  $R_t$  (major) = 71.7 min;  $R_t$  (minor) = 86.6 min.

**Diethyl 2-((1*R*,2*R*)-1-methyl-4-oxo-1,2,3,4-tetrahydro-[1,1':4',1''-terphenyl]-2-yl)malonate (4e)**

White solid, mp 74–79 °C;  $R_f$  0.14 (hexane-AcOEt = 5:1);  $[\alpha]_D^{25}$  -88.5 ( $c$  = 0.06, EtOH, 87% ee); FTIR (KBr)  $\nu$  1759, 1725, 1683 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.07 (3H, t,  $J$  = 7.5 Hz), 1.20 (3H, t,  $J$  = 7.5 Hz), 1.71 (3H, s), 2.59 (1H, dd,  $J$  = 17.5, 5.0 Hz), 2.91 (1H, dd,  $J$  = 17.5, 11.5 Hz), 3.15 (1H, dt,  $J$  = 11.5, 5.0 Hz), 3.51 (1H, d,  $J$  = 5.0 Hz), 3.67–3.81 (2H, m), 4.03–4.16 (2H, m), 6.20 (1H, d,  $J$  = 10.0 Hz), 6.81 (1H, d,  $J$  = 10.0 Hz), 7.31–7.46 (5H, m), 7.56–7.58 (4H, m); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>)  $\delta$  13.72, 13.94, 26.58, 36.98, 43.73, 44.26, 52.02, 61.18, 61.92, 126.90 ( $\times 2$ ), 127.00 ( $\times 2$ ), 127.54, 127.94, 128.55 ( $\times 2$ ), 128.85 ( $\times 2$ ), 137.57, 140.14, 140.35, 155.69, 167.50, 168.62, 198.61; HRMS calcd for C<sub>26</sub>H<sub>28</sub>O<sub>5</sub> 420.1937, found 420.1938.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column, 0.46  $\times$  25 cm, hexane-*i*-PrOH = 95:5, 0.5 cm<sup>3</sup> min<sup>-1</sup>):  $R_t$  (major) = 67.5 min;  $R_t$  (minor) = 124.0 min.

**Tetraethyl 2,2'-(2-([1,1'-biphenyl]-4-yl)-2-methyl-5-oxocyclohexane-1,3-diyl)dimalonate (6) (Table 2, footnote c)**

Colorless oil;  $R_f$  0.08 (hexane-AcOEt = 5:1); FTIR (KBr)  $\nu$  1728, 1313, 1148, 1028 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>)  $\delta$  1.09 (3H, t,  $J$  = 7.3 Hz), 1.15 (5H, dt,  $J$  = 4.3, 7.1 Hz), 1.24 (4H, t,  $J$  = 7.0 Hz), 1.66 (3H, s), 2.67 (2H, dd,  $J$  = 5.5, 17.0 Hz), 2.76–2.91 (3H, m), 3.24 (1H, d,  $J$  = 4.0 Hz), 3.44 (1H, d,  $J$  = 3.5 Hz), 3.66 (1H, dt,  $J$  = 4.0, 12.5 Hz), 3.84–4.07 (6H, m), 4.11–4.21 (2H, m), 7.36 (1H, t,  $J$  = 7.5 Hz), 7.44–7.47 (4H, m), 7.59 (4H, d,  $J$  = 8.5 Hz); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>)  $\delta$  13.74, 13.81, 13.88, 13.96, 21.85, 38.86, 39.12, 39.58, 43.44, 46.30, 52.18, 52.30, 61.46, 61.52, 61.76, 61.82, 126.76 ( $\times 2$ ), 127.02 ( $\times 2$ ), 127.52,

128.06 ( $\times 2$ ), 128.88 ( $\times 2$ ), 139.79, 140.00, 141.68, 168.40, 168.49 ( $\times 2$ ), 168.56, 208.48; HRMS calcd for  $C_{33}H_{40}O_9 + H$  581.2751, found 581.2743.

**Diethyl 2-((1*S*,6*R*)-4-oxo-3',4'-dihydro-2'*H*-spiro[cyclohex[2]ene-1,1'-naphthalen]-6-yl)malonate (3f)**

Colorless oil;  $R_f$  0.20 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{26} +107.3$  ( $c = 1.0$ , EtOH, 78% ee); FTIR (KBr)  $\nu$  1754, 1729, 1682  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  1.06 (3H, t,  $J = 7.5$  Hz), 1.25 (3H, t,  $J = 7.5$  Hz), 1.67–1.76 (1H, m), 1.93–2.03 (2H, m), 2.26 (1H, dt,  $J = 12.5, 2.5$  Hz), 2.65 (1H, dd,  $J = 17.0, 5.0$  Hz), 2.69 (1H, dd,  $J = 17.0, 12.5$  Hz), 2.76–2.81 (1H, m), 2.86 (1H, ddd,  $J = 16.0, 11.5, 5.0$  Hz), 3.35 (1H, d,  $J = 5.5$  Hz), 3.58–3.64 (2H, m), 3.73 (1H, ddd,  $J = 14.5, 11.0, 7.0$  Hz), 4.15–4.21 (2H, m), 5.92 (1H, d,  $J = 10.0$  Hz), 6.93 (1H, d,  $J = 10.0$  Hz), 7.10–7.22 (4H, m);  $^{13}C$  NMR (125.8 MHz,  $CDCl_3$ )  $\delta$  13.74, 14.00, 19.94, 30.15, 30.33, 37.73, 43.36, 43.46, 53.07, 61.48, 61.55, 125.25, 126.56, 126.99, 128.11, 129.63, 138.36 ( $\times 2$ ), 159.64, 167.68, 168.26, 197.94; HRMS calcd for  $C_{22}H_{26}O_5 + H$  371.1859, found 371.1834.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column,  $0.46 \times 25$  cm, hexane–i-PrOH = 99 : 1,  $0.5$   $cm^3$   $min^{-1}$ ):  $R_t$  (*minor*) = 103.7 min;  $R_t$  (*major*) = 111.6 min.

**Diethyl 2-((1*R*,6*R*)-4-oxo-3',4'-dihydro-2'*H*-spiro[cyclohex[2]ene-1,1'-naphthalen]-6-yl)malonate (4f)**

White solid, mp 163–165  $^{\circ}C$ ;  $R_f$  0.21 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{25} +7.70$  ( $c = 0.13$ , EtOH, >99% ee); FTIR (KBr)  $\nu$  1743, 1718, 1682  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  1.06 (3H, t,  $J = 7.5$  Hz), 1.19 (3H, t,  $J = 7.5$  Hz), 1.76–1.82 (1H, m), 1.89–1.96 (1H, m), 2.09–2.20 (2H, m), 2.64 (1H, dd,  $J = 17.5, 5.0$  Hz), 2.82 (1H, dd,  $J = 17.5, 8.0$  Hz), 2.84 (1H, dd,  $J = 17.5, 6.0$  Hz), 2.96 (1H, ddd,  $J = 17.0, 7.0, 5.0$  Hz), 3.38 (1H, q,  $J = 6.0$  Hz), 3.57 (1H, d,  $J = 7.5$  Hz), 3.62–3.68 (1H, m), 3.78–3.85 (1H, m), 3.92–4.04 (2H, m), 6.10 (1H, d,  $J = 10.5$  Hz), 6.82 (1H, dd,  $J = 10.5, 1.0$  Hz), 7.09–7.18 (4H, m);  $^{13}C$  NMR (125.8 MHz,  $CDCl_3$ )  $\delta$  13.77 ( $\times 2$ ), 18.71, 28.36, 33.37, 37.18, 40.61, 43.10, 52.60, 61.41, 61.57, 125.44, 127.39, 127.51, 129.55, 129.59, 137.38, 138.31, 156.27, 167.89, 168.54, 196.97; HRMS calcd for  $C_{22}H_{26}O_5 + H$  371.1859, found 371.1856.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD-H column,  $0.46 \times 25$  cm, hexane–i-PrOH = 95 : 5,  $0.5$   $cm^3$   $min^{-1}$ ):  $R_t$  (*major*) = 85.4 min.

**Diethyl 2-((1*S*,2*R*)-1-methyl-1-trichloromethyl-4-oxo-1,2,3,4-tetrahydrophenyl)malonate (3g)**

Colorless oil;  $R_f$  0.30 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{25} -10.5$  ( $c = 0.50$ , EtOH, 33% ee); FTIR (KBr)  $\nu$  1747, 1731, 1691  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  1.26 (3H, t,  $J = 7.5$  Hz), 1.27 (3H, t,  $J = 7.5$  Hz), 1.65 (3H, s), 2.83 (1H, dd,  $J = 17.5, 6.0$  Hz), 2.88 (1H, dd,  $J = 17.5, 9.0$  Hz), 3.78 (1H, ddd,  $J = 9.0, 6.0, 2.5$  Hz), 4.11–4.27 (4H, m), 4.26 (1H, d,  $J = 2.5$  Hz), 6.16 (1H, d,  $J = 11.0$  Hz), 6.94 (1H, d,  $J = 11.0$  Hz);  $^{13}C$  NMR (125.8 MHz,  $CDCl_3$ )  $\delta$  13.92, 14.02, 19.62, 37.87, 38.31, 53.04, 56.10, 61.70,

62.15, 107.73, 130.47, 148.76, 168.12, 168.23, 196.45; HRMS calcd for  $C_{15}H_{19}Cl_3O_5 + H$  385.0376, found 385.0381.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane–i-PrOH = 99 : 1,  $1.0$   $cm^3$   $min^{-1}$ ):  $R_t$  (*minor*) = 24.0 min;  $R_t$  (*major*) = 30.9 min.

**Diastereoselective Michael addition reaction of (R)-8 using catalyst B**

A mixture of (R)-8 (140 mg, 0.75 mmol; 97% ee)<sup>14</sup> and diethyl malonate (2, 180 mg, 1.125 mmol) in the presence of catalyst B (29 mg, 10 mol%) and PPY (11 mg, 10 mol%) in toluene (0.75 mL) was reacted at rt for 2.5 days (a small amount of unreacted (R)-8 remained in the mixture). Then, the mixture was concentrated and purified by column chromatography on silica gel (eluted with hexane–AcOEt) to give (3*S*,4*R*)-9 (187 mg, 72%) as a colorless oil and its diastereomer (13 mg, 5%).

**Diethyl 2-((1*S*,2*R*)-2-methyl-5-oxo-2-phenylcyclohexyl)-malonate ((3*S*,4*R*)-9)**

Colorless oil;  $R_f$  0.20 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{26} -5.8$  ( $c = 1.0$ , EtOH, >97% ee); FTIR (KBr)  $\nu$  1751, 1720  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  1.12 (3H, t,  $J = 7.5$  Hz), 1.26 (3H, t,  $J = 7.5$  Hz), 1.54 (3H, s), 1.82 (1H, ddd,  $J = 14.0, 6.0, 3.0$  Hz), 2.23 (1H, dt,  $J = 14.0, 5.0$  Hz), 2.42 (1H, m), 2.53–2.59 (2H, m), 2.79 (1H, dd,  $J = 15.5, 13.0$  Hz), 3.17 (1H, d,  $J = 4.0$  Hz), 3.30 (1H, dt,  $J = 13.0, 4.0$  Hz), 3.85–3.94 (2H, m), 4.12–4.23 (2H, m), 7.24 (1H, t,  $J = 7.5$  Hz), 7.35 (2H, t,  $J = 7.5$  Hz), 7.42 (2H, d,  $J = 7.5$  Hz);  $^{13}C$  NMR (125.8 MHz,  $CDCl_3$ )  $\delta$  13.82, 13.96, 17.54, 38.18, 40.49, 40.81, 40.90, 44.52, 52.46, 61.33, 61.56, 125.94 ( $\times 2$ ), 126.76, 128.62 ( $\times 2$ ), 145.84, 168.19, 168.53, 209.52; HRMS calcd for  $C_{20}H_{26}O_5$  346.1780, found 346.1789.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane–i-PrOH = 90 : 10,  $1.0$   $cm^3$   $min^{-1}$ ):  $R_t$  (*major*) = 15.2 min.

**Catalytic hydrogenation of 3a**

To a solution of 3a (50 mg, 0.145 mmol) in EtOH (0.7 mL) was added 10% Pd/C (5 mg), and the mixture was stirred under hydrogen at rt. After consumption of the starting material (1 h), the mixture was filtered and concentrated. The crude sample was purified by column chromatography on silica gel (eluted with hexane–AcOEt) to give (3*R*,4*S*)-7 (18 mg, 36%) as a colorless oil.<sup>21</sup>

**Diethyl 2-((1*R*,2*S*)-2-methyl-5-oxo-2-phenylcyclohexyl)-malonate ((3*R*,4*S*)-7)**

Colorless oil;  $R_f$  0.20 (hexane–AcOEt = 5 : 1);  $[\alpha]_D^{27} +5.4$  ( $c = 0.49$ , EtOH, 92% ee); FTIR (KBr)  $\nu$  1754, 1718  $cm^{-1}$ ;  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  1.12 (3H, t,  $J = 7.0$  Hz), 1.26 (3H, t,  $J = 7.0$  Hz), 1.54 (3H, s), 1.83 (1H, ddd,  $J = 14.0, 6.0, 3.0$  Hz), 2.24 (1H, dt,  $J = 14.0, 5.0$  Hz), 2.43 (1H, m), 2.53–2.60 (2H, m), 2.80 (1H, dd,  $J = 15.0, 13.0$  Hz), 3.18 (1H, d,  $J = 4.5$  Hz), 3.30 (1H, dt,  $J = 13.0, 4.5$  Hz), 3.86–3.95 (2H, m), 4.12–4.22 (2H, m), 7.24 (1H, t,  $J = 7.5$  Hz), 7.36 (2H, t,  $J = 7.5$  Hz), 7.43 (2H, d,  $J = 7.5$  Hz);  $^{13}C$  NMR (125.8 MHz,  $CDCl_3$ )  $\delta$  14.01, 14.15, 17.70,



38.38, 40.68, 40.98, 41.08, 44.72, 52.64, 61.53, 61.76, 126.13 ( $\times 2$ ), 126.95, 128.81 ( $\times 2$ ), 146.01, 168.38, 168.74, 209.75; HRMS calcd for  $C_{20}H_{26}O_5$  346.1780, found 346.1786.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane-*i*-PrOH = 95 : 5,  $1.0 \text{ cm}^3 \text{ min}^{-1}$ ):  $R_t$  (major) = 15.4 min;  $R_t$  (minor) = 14.5 min.

#### Diastereoselective Michael addition reaction of (*R*)-8 using catalyst A

A mixture of (*R*)-8 (140 mg, 0.75 mmol; 97% ee)<sup>14</sup> and diethyl malonate (2, 180 mg, 1.125 mmol) in the presence of catalyst A (29 mg, 10 mol%) and PPY (11 mg, 10 mol%) in toluene (0.75 mL) was reacted at rt for 6.5 days (a considerable amount of unreacted (*R*)-8 remained in the mixture). Then, the mixture was concentrated and purified by column chromatography on silica gel (eluted with hexane-AcOEt) to give (3*R*,4*R*)-11 (96 mg, 37%) as a colorless oil and its diastereomer (16 mg, 6%). The latter compound was indistinguishable from (3*S*,4*R*)-9 prepared as above.

#### Diethyl 2-((1*R*,2*R*)-2-methyl-5-oxo-2-phenylcyclohexyl)-malonate ((3*R*,4*R*)-11)

Colorless oil;  $R_f$  0.15 (hexane-AcOEt = 5 : 1);  $[\alpha]_D^{28} +68.1$  ( $c = 0.92$ , EtOH, >97% ee); FTIR (KBr)  $\nu$  1751, 1731, 1713, 1279  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  1.10 (3H, t,  $J = 7.5$  Hz), 1.21 (3H, t,  $J = 7.5$  Hz), 1.56 (3H, s), 2.03–2.07 (1H, m), 2.44–2.55 (3H, m), 2.63 (1H, dd,  $J = 17.5, 2.5$  Hz), 2.78 (1H, dd,  $J = 17.5, 7.0$  Hz), 3.09 (1H, d,  $J = 3.5$  Hz), 3.23 (1H, m), 3.90–4.01 (2H, m), 4.03–4.14 (2H, m), 7.21–7.25 (1H, m), 7.33–7.35 (4H, m);  $^{13}\text{C}$  NMR (125.8 MHz,  $\text{CDCl}_3$ )  $\delta$  13.77, 13.83, 27.30, 30.17, 36.70, 39.40, 39.72, 44.18, 52.84, 61.38, 61.53, 125.86 ( $\times 2$ ), 126.61, 128.59 ( $\times 2$ ), 146.30, 168.94, 168.98, 208.51; HRMS calcd for  $C_{20}H_{26}O_5$  346.1780, found 346.1779.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane-*i*-PrOH = 90 : 10,  $1.0 \text{ cm}^3 \text{ min}^{-1}$ ):  $R_t$  (major) = 8.4 min.

#### Catalytic hydrogenation of 4a

Following the previous procedure for the preparation of (3*R*,4*S*)-7, (3*R*,4*R*)-10 was obtained in 31% yield and found to be indistinguishable from (3*R*,4*R*)-11 prepared as above except for the chiral behavior.

#### (3*R*,4*R*)-10

Colorless oil;  $R_f$  0.15 (hexane-AcOEt = 5 : 1);  $[\alpha]_D^{27} +60.9$  ( $c = 0.23$ , EtOH, 85% ee); HRMS calcd for  $C_{20}H_{26}O_5$  346.1780, found 346.1785.

The ee of the product was determined by chiral HPLC analysis (Chiralpak AD column,  $0.46 \times 25$  cm, hexane-*i*-PrOH = 90 : 10,  $1.0 \text{ cm}^3 \text{ min}^{-1}$ ):  $R_t$  (major) = 8.3 min;  $R_t$  (minor) = 9.8 min.

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