

## Asymmetric transfer hydrogenation of prochiral cyclic 1,3-diketones

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Dedicated to Professor Jozef Drabowicz on the occasion of his 76<sup>th</sup> birthday

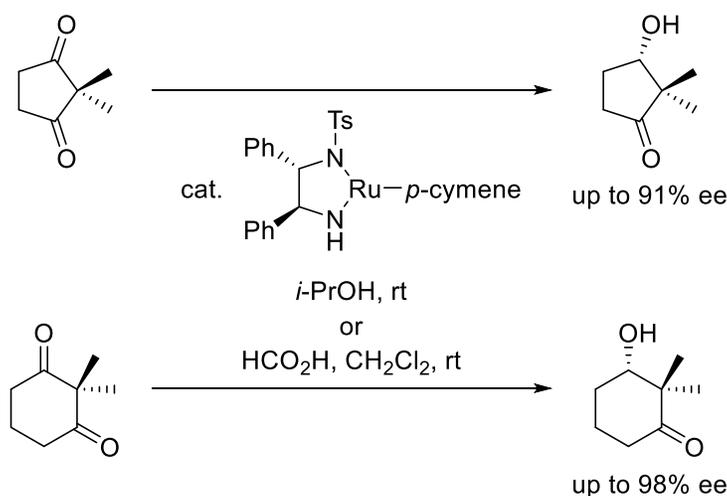
Received 10-25-2022

Accepted Manuscript 11-08-2022

Published on line 11-12-2022

### Abstract

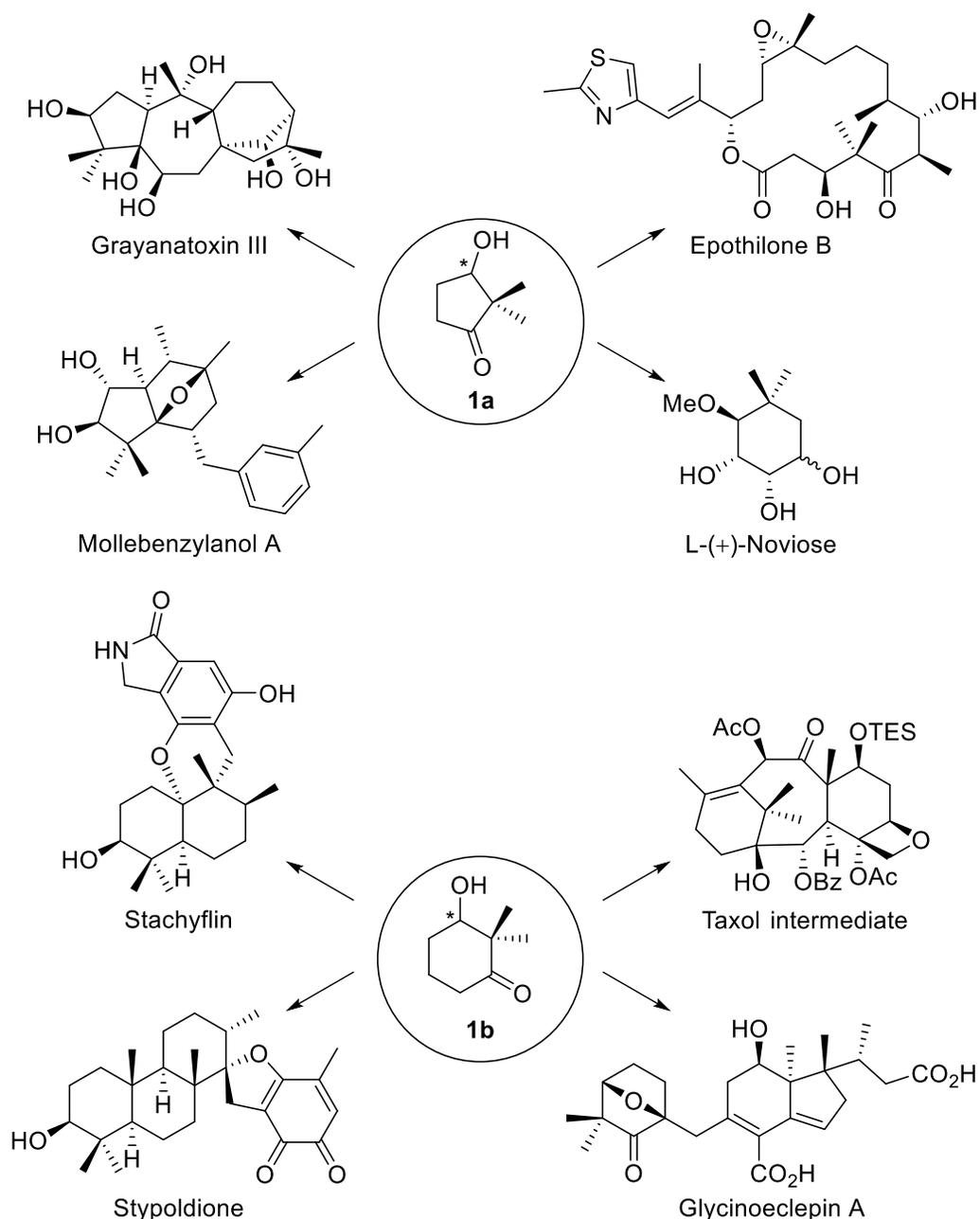
The enantioselective mono reduction of 2,2-dimethylcyclopentane-1,3-dione and 2,2-dimethylcyclohexane-1,3-dione was investigated. From the ruthenium, rhodium, and iridium TsDPEN complexes screened with isopropanol or formic acid as the hydrogen donor, the ruthenium complex performed best for both substrates. The resulting hydroxy ketones 3-hydroxy-2,2-dimethylcyclopentanone and 3-hydroxy-2,2-dimethylcyclohexanone, which are important building blocks for natural product synthesis, were obtained in excellent yield with high enantiomeric excess.



**Keywords:** Enantioselective catalysis, transfer hydrogenation, 1,3-diketones, ruthenium

## Introduction

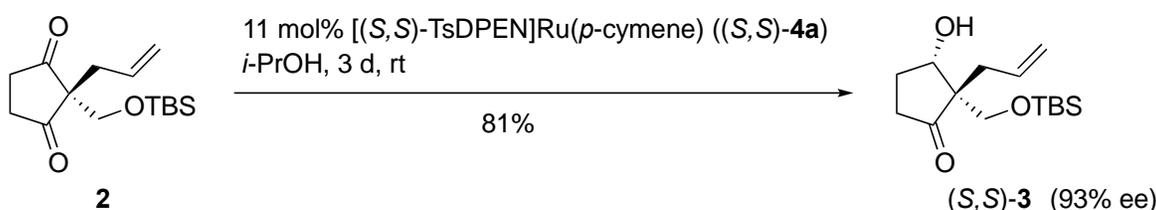
The hydroxy ketones **1a** and **1b** are important building blocks for natural product synthesis (Scheme 1). Both (*S*)-**1a** and (*R*)-**1a** can be prepared from the corresponding 1,3-diketone in 51-72% yield using a Corey-Bakshi-Shibata (CBS) reduction.<sup>1</sup> Thus, grayanotoxin III,<sup>2</sup> epothilone B,<sup>3</sup> and mollebenzylanol A<sup>4</sup> were derived by CBS reduction to produce (*S*)-**1a** with 83-96% ee, while L-(+)-noviose<sup>5</sup> was obtained from the (*R*) configured CBS product with 94% ee. Alternatively, (*R*)-**1a** was synthesized via catalytic asymmetric alkylation of 2-methyl-2-cyclopenten-1-one,<sup>6</sup> and (*S*)-**1a** was also accessed through lipase catalyzed desymmetrization in a multi-step sequence.<sup>7</sup> Interestingly, preparation of (*S*)-**1a** with 99% ee was reported by *Saccharomyces cerevisiae* reduction of the 1,3-diketone in 74% yield.<sup>8</sup> However, the latter process was never applied synthetically.



**Scheme 1.** Selected natural products prepared from chiral hydroxy ketones **1a** and **1b**.

The meroterpenoid stachyflin was derived from (*S*)-**1b** prepared by CBS reduction of the diketone with 83% ee,<sup>9</sup> and (*S*)-**1b** generated by reduction of the diketone with baker's yeast (>96% ee)<sup>10</sup> served as the pivotal intermediate for the synthesis of the depicted taxol intermediate,<sup>11</sup> stypoldione,<sup>12</sup> and glycinoclepin A.<sup>13-15</sup> (*R*)-**1b** is available as well by CBS reduction of the diketone<sup>1,16</sup> or by a multi-step route incorporating a lipase catalyzed desymmetrization that can also be utilized for production of (*S*)-**1b**.<sup>17</sup>

In 2009, we reported the first asymmetric transfer hydrogenation (ATH) of a prochiral cyclic 1,3-diketone using a Noyori-Ikariya metal-diamine catalyst to give a highly enantioenriched hydroxy ketone.<sup>18</sup> 1,3-Cyclopentanedione **2** was subjected to 11 mol% of catalyst (*S,S*)-**4a** in isopropanol at room temperature (Scheme 2). After a reaction time of three days, the product (*S,S*)-**3** was isolated with 93% enantiomeric purity in 81% yield after separation of the corresponding hydroxy ketone diastereomer (7%). Noteworthy, no conversion was noted upon treatment of **2** with baker's yeast.

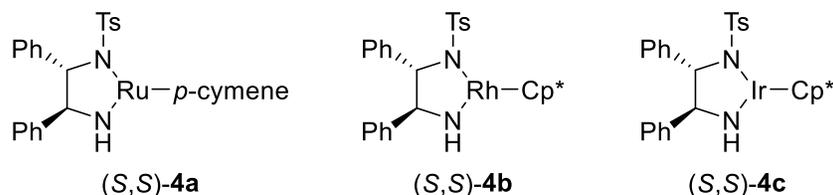


**Scheme 2.** ATH of prochiral diketone **2** catalyzed by ruthenium complex (*S,S*)-**4a**.

Since a catalyst loading of 10-40 mol % for CBS reductions to give **1a,b** was required, and baker's yeast reduction only gives rise to the (*S*) configured enantiomers of **1a,b**, we decided to explore the enantioselective preparation of **1a,b** by reduction using the Noyori-Ikariya catalyst (*S,S*)-**4a** and related metal complexes.

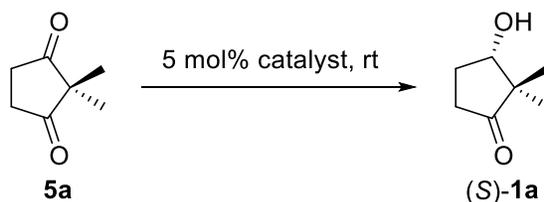
## Results and Discussion

As in our previous methodological studies on the enantioselective synthesis of flavanones<sup>19</sup> and isoflavanones<sup>20</sup> via ATH, we focused on the application of the ruthenium,<sup>21</sup> rhodium, and iridium TsDPEN complexes **4a-c** (Figure 1).<sup>22,23</sup>



**Figure 1.** Chiral metal TsDPEN complexes screened for mono reduction of the prochiral cyclic 1,3-diketones.

In a first set of experiments, we treated 1,3-diketone **5a**<sup>24</sup> in either isopropanol or with formic acid in dichloromethane as the hydrogen donor in the presence of 5 mol % of the metal complexes (*S,S*)-**4a**, (*S,S*)-**4b**, and (*S,S*)-**4c** at room temperature (Table 1).

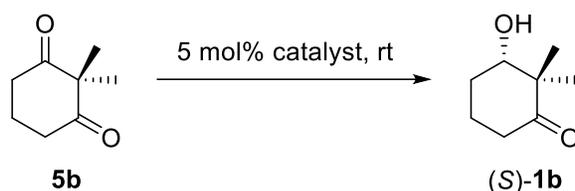
**Table 1.** ATH of prochiral diketone **5a** with ruthenium catalyst (*S,S*)-**4a**, rhodium catalyst (*S,S*)-**4b**, and iridium catalyst (*S,S*)-**4c**

Entry	Catalyst	H Donor	Time	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	( <i>S,S</i> )- <b>4a</b>	<i>i</i> -PrOH	3 d	<b>97</b>	<b>91</b>
2	( <i>S,S</i> )- <b>4a</b>	HCO <sub>2</sub> H	6 d	93	87
3	( <i>S,S</i> )- <b>4a</b>	<i>i</i> -PrOH	6 h <sup>c</sup>	98	89
4	( <i>S,S</i> )- <b>4b</b>	<i>i</i> -PrOH	3 d	36	73
5	( <i>S,S</i> )- <b>4b</b>	HCO <sub>2</sub> H	6 d	30	86
6	( <i>S,S</i> )- <b>4c</b>	<i>i</i> -PrOH	3 d	51	55
7	( <i>S,S</i> )- <b>4c</b>	HCO <sub>2</sub> H	6 d	94	51

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by chiral HPLC analysis of ester (*S*)-**7a**. <sup>c</sup> Reaction run at 60 °C.

The reactions were followed by TLC and stopped after three days for isopropanol as the hydrogen donor and after six days when formic acid in dichloromethane was used. For the rhodium catalyst (*S,S*)-**4b**, conversion was low and enantioselectivity moderate to good (entries 4,5). Application of the iridium catalyst (*S,S*)-**4c** led to higher conversion but with reduced enantioselectivity (entries 6,7). As in the reduction of diketone **2**, the ruthenium catalyst (*S,S*)-**4a** gave an excellent result (97% yield, 91% ee) with isopropanol as the hydrogen donor (entry 1), and formic acid performed nearly as well (entry 2). Additional experiments with (*S,S*)-**4a** showed that the reaction time in isopropanol could be reduced to 6 h by running the reaction at 60 °C without significant changes in yield or enantioselectivity (entry 3). Thus, further reduction of hydroxy ketone (*S*)-**1a** to give a 1,3-diol<sup>25</sup> did not take place at this elevated temperature.

Table 2 lists the results of the corresponding experiments with 1,3-cyclohexanedione **5b**.<sup>10</sup> Again, conversion was low with the rhodium catalyst (*S,S*)-**4b**, while the enantioselectivity was rather good (entries 3,4). Utilization of the iridium catalyst (*S,S*)-**4c** improved the conversion, and provided a satisfactory result in isopropanol (entry 5), whereas formic acid caused partial over-reduction to give a significant amount of diol **6** combined with erosion of enantioselectivity (entry 6). Gratifyingly, ruthenium catalyst (*S,S*)-**4a** in isopropanol (entry 1) gave an excellent result already after one day at room temperature (97% yield, 96% ee). Formic acid turned out to be more reactive for this substrate, but suffered from some over-reduction with formation of diol **6** while maintaining high enantiocontrol (entry 2). In contrast to the reaction of 1,3-cyclopentanedione **5a**, attempted acceleration of the reaction of 1,3-cyclohexanedione **5b** with (*S,S*)-**4a** in isopropanol by increasing the temperature to 60 °C for 6 h caused mostly over-reduction to give the diol **6**.

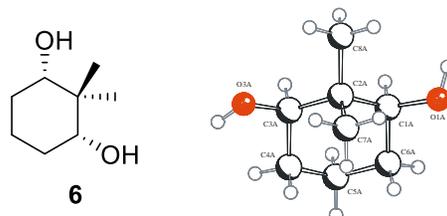
**Table 2.** ATH of prochiral diketone **5b** with ruthenium catalyst (*S,S*)-**4a**, rhodium catalyst (*S,S*)-**4b**, and iridium catalyst (*S,S*)-**4c**

Entry	Catalyst	H Donor	Time	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	( <i>S,S</i> )- <b>4a</b>	<i>i</i> -PrOH	1 d	<b>97</b>	<b>96</b>
2	( <i>S,S</i> )- <b>4a</b>	HCO <sub>2</sub> H	4 h	87 <sup>c</sup>	96
3	( <i>S,S</i> )- <b>4b</b>	<i>i</i> -PrOH	3 d	33	86
4	( <i>S,S</i> )- <b>4b</b>	HCO <sub>2</sub> H	6 d	31	94
5	( <i>S,S</i> )- <b>4c</b>	<i>i</i> -PrOH	3 d	94	90
6	( <i>S,S</i> )- <b>4c</b>	HCO <sub>2</sub> H	6 d	79 <sup>d</sup>	59

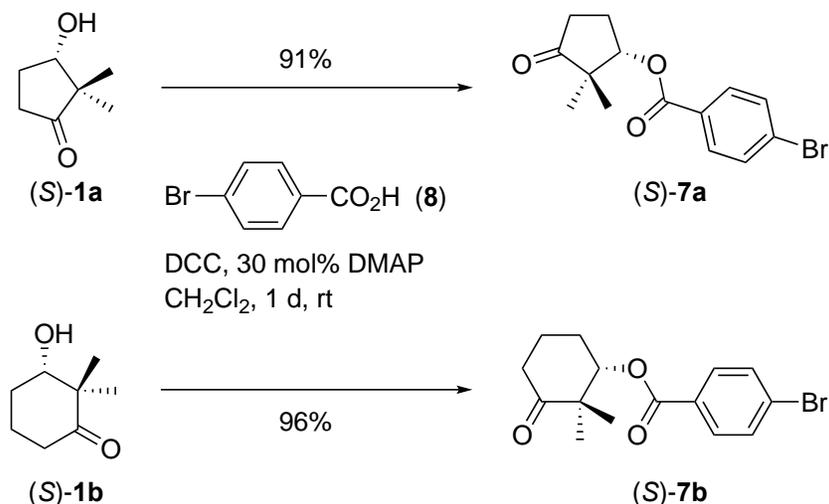
<sup>a</sup> Isolated yield. <sup>b</sup> Determined by chiral HPLC analysis of ester (*S*)-**7b**. <sup>c</sup> 12% of 1,3-diol **6** additionally isolated.

<sup>d</sup> 21% of 1,3-diol **6** additionally isolated.

Only the *cis* 1,3-diol **6** was isolated as the product of over-reduction of 1,3-cyclohexanedione **5b** as proven by comparison of the NMR data of **6** with literature data.<sup>26</sup> This assignment was confirmed by diffraction analysis of **6** (Figure 2).<sup>27</sup>

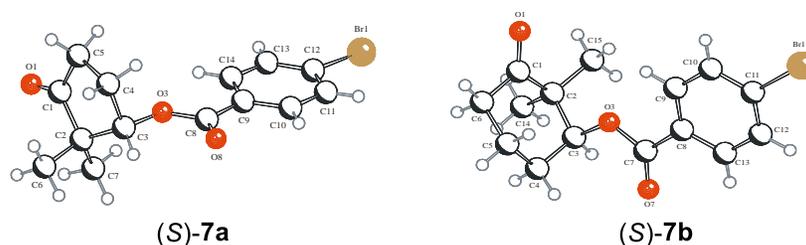
**Figure 2.** Structure and X-ray crystal structure of 1,3-diol **6**.

While the absolute configuration of hydroxy ketones (*S*)-**1a** and (*S*)-**1b** was readily inferred from their specific rotation data,<sup>1</sup> accurate determination of their enantiomeric purity was possible by chiral HPLC analysis of the *p*-bromobenzoate derivatives (*S*)-**7a** and (*S*)-**7b** easily prepared by Steglich esterification<sup>28</sup> of the hydroxy ketones with *p*-bromobenzoic acid (Scheme 3).



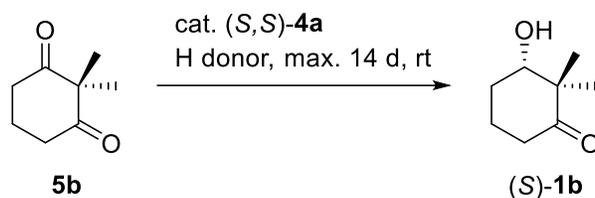
**Scheme 3.** Esterification of hydroxy ketones (S)-1a and (S)-1b to give *p*-bromobenzoate derivatives (S)-7a and (S)-7b.

As an additional benefit of this derivatization, both esters (S)-7a and (S)-7b provided suitable crystals for an independent direct determination of their absolute configuration by anomalous X-ray scattering (Figure 3).<sup>27</sup>



**Figure 3.** X-ray crystal structures of esters (S)-7a and (S)-7b.

In another series of experiments, we investigated to what extent the (S,S)-4a loading could be lowered for the ATH of diketone 5b with isopropanol or formic acid as the hydrogen donor (Table 3). The reactions were stopped after a maximum time of 14 d, even if the conversion was not yet complete. Whereas a quantitative yield of (S)-1b with 96% ee was achieved with 3 mol % (S,S)-4a after three days at room temperature in isopropanol (entry 1), a further decrease in catalyst loading to 1 mol % was insufficient for complete conversion within the specified time frame (entry 2). On the other hand, using formic acid in dichloromethane, the catalyst loading could be reduced to 0.1 mol % to give a nearly quantitative yield of (S)-1b with 97% ee after three days at room temperature (entries 3-5). However, attempted further lowering to 0.01 mol % catalyst loading showed the limits of this method (entry 6).

**Table 3.** ATH of prochiral diketone **5b** with decreased loadings of ruthenium catalyst (*S,S*)-**4a**

Entry	Catalyst loading (mol %)	H Donor	Time	Yield (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	3	<i>i</i> -PrOH	3 d	<b>100</b>	<b>96</b>
2	1	<i>i</i> -PrOH	14 d	60	95
3	3	HCO <sub>2</sub> H	2 h	95	98
4	0.5	HCO <sub>2</sub> H	20 h	98	97
5	0.1	HCO <sub>2</sub> H	3 d	<b>99</b>	<b>97</b>
6	0.01	HCO <sub>2</sub> H	14 d	5	– <sup>c</sup>

<sup>a</sup> Isolated yield. <sup>b</sup> Determined by chiral HPLC analysis of ester (*S*)-**7b**. <sup>c</sup> Not determined.

## Conclusions

In summary, the hydroxy ketones (*S*)-3-hydroxy-2,2-dimethylcyclopentanone ((*S*)-**1a**) and (*S*)-3-hydroxy-2,2-dimethylcyclohexanone ((*S*)-**1b**) were obtained in excellent yield and high enantiomeric purity by enantioselective mono reduction of 2,2-dimethylcyclopentane-1,3-dione and 2,2-dimethylcyclohexane-1,3-dione, respectively, using low loadings of the ruthenium TsDPEN complex (*S,S*)-**4a** either in isopropanol or with formic acid in dichloromethane. As both enantiomers of the ruthenium catalyst **4a** are readily available, both enantiomers of **1a** and **1b** can be prepared by this methodology, e.g. for future applications in natural product synthesis.

## Experimental Section

**General.** CH<sub>2</sub>Cl<sub>2</sub> was dried and purified by passage through a MB-SPS-800 device using molecular sieves. Isopropanol was dried over molecular sieves (4 Å). Triethylamine was freshly distilled over CaH<sub>2</sub> before use. All other commercially available reagents were used as received. Reactions were performed under an argon atmosphere. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F<sub>254</sub> 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm and 366 nm and subsequently colorized with potassium permanganate and a heat gun. Flash column chromatography was carried out using silica gel (Merck, particle size 40-63 microns). Melting points were measured on an IA 9100 Electrothermal Engineering LTD. apparatus and are uncorrected. Infrared spectra were recorded on a Thermo Nicolet Avatar 360 instrument using ATR. NMR spectra were recorded on a Bruker DRX 500 P (500.13 MHz <sup>1</sup>H, 125.77 MHz <sup>13</sup>C) or on a Bruker Avance III-600 (600.16 MHz <sup>1</sup>H, 150.92 MHz <sup>13</sup>C). Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual proton-containing solvent as internal standard (CDCl<sub>3</sub> at 7.26 ppm (<sup>1</sup>H) and 77.00 ppm (<sup>13</sup>C)). Abbreviations used in the description of resonances are: s (singlet), d

(doublet), t (triplet), q (quartet), br (broad). Coupling constants ( $J$ ) are quoted to the nearest 0.1 Hz. Mass spectra (GC/MS, 70 eV) were recorded on an Agilent 5973N detector coupled with an Agilent 6890N GC. Optical rotations were measured on a Perkin Elmer 341 LC polarimeter. Enantiomeric excess values were determined by chiral HPLC on a Hewlett Packard LC 1090 with photodiode array detector (DAD, 280 nm) using a Daicel Chiralpak IA column (250 mm length, inner diameter 4.6 mm, particle size 5 microns). All chiral HPLC measurements were carried out using *i*-PrOH/hexane (1:99) at ambient temperature with a flow of 0.8 mL/min. Elemental analysis was performed on a Hekatech EA 3000. X-ray diffraction analyses were carried out with a Bruker Kappa CCD diffractometer.

### Typical preparation of the catalyst for ATH in isopropanol

A solution of the ruthenium catalyst for 4 ATH runs with 5 mol % catalyst loading was prepared as follows: In a 10 mL round-bottom flask, dichloro(*p*-cymene)ruthenium(II) dimer (35.8 mg, 58.5  $\mu$ mol) and (*S,S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine ((*S,S*)-TsDPEN of 98% purity, 43.8 mg, 117  $\mu$ mol) were dissolved in dry dichloromethane (1 mL). After addition of freshly ground KOH (46.0 mg, 820  $\mu$ mol), the mixture was stirred for 5 min at rt followed by addition of water (1 mL). The layers were separated, the aqueous layer was extracted with dry CH<sub>2</sub>Cl<sub>2</sub> (2 mL), and the combined organic layers were dried over calcium hydride. After filtering off the drying agent (elution with dry CH<sub>2</sub>Cl<sub>2</sub>), the solvent was first cautiously removed on a rotary evaporator and then completely removed under high vacuum for about 30 min. The residue was dissolved in dry Me<sub>2</sub>CHOH (10.0 mL). Formation of the catalyst was estimated to proceed in ca. 85% yield.

### Typical procedure for ATH in isopropanol

A part (2.5 mL, 25.0  $\mu$ mol, 5 mol %) of the catalyst solution prepared as described above was added to a solution of the 1,3-diketone **5** (500  $\mu$ mol) in dry Me<sub>2</sub>CHOH (5 mL). The reaction mixture was stirred at rt for the time listed in the Tables. Then the solvent was completely removed on a rotary evaporator, and the residue was purified by flash chromatography (Et<sub>2</sub>O/pentane 1:1) to give the hydroxy ketones (*S*)-**1** with the yields listed in the Tables.

### Typical preparation of the catalyst for ATH with formic acid

A solution of the ruthenium catalyst for 4 ATH runs with 5 mol % catalyst loading was prepared as follows: In a 25 mL round-bottom flask, dichloro(*p*-cymene)ruthenium(II) dimer (30.6 mg, 50.0  $\mu$ mol) and (*S,S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine ((*S,S*)-TsDPEN of 98% purity, 37.4 mg, 100  $\mu$ mol) were dissolved in dry CH<sub>2</sub>Cl<sub>2</sub> (8 mL). After addition of a triethylamine/formic acid mixture (3:1 v/v, 0.51 mL, 3.38 mmol), the mixture was stirred for 1 h at rt.

### Typical procedure for ATH with formic acid

A part (2.0 mL, 25.0  $\mu$ mol, 5 mol %) of the catalyst solution prepared as described above was added to a solution of the 1,3-diketone **5** (500  $\mu$ mol) in dry CH<sub>2</sub>Cl<sub>2</sub> (5 mL). The reaction mixture was stirred at rt for the time listed in the Tables. Then the solvent was completely removed on a rotary evaporator, and the residue was purified by flash chromatography (Et<sub>2</sub>O/pentane 1:1) to give the hydroxy ketones (*S*)-**1** and the 1,3-diol **6** with the yields listed in the Tables.

**(S)-3-Hydroxy-2,2-dimethylcyclopentanone ((S)-1a)**.  $R_f$  = 0.11 (Et<sub>2</sub>O/pentane 1:1).  $[\alpha]_D^{25}$  = +11.7 ( $c$  = 1, CHCl<sub>3</sub>), 91% ee by HPLC of (*S*)-**7a**. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 1.03 (2 $\times$  s, 3 H each), 1.73 (br s, 1 H, OH), 1.86 - 1.95 (m, 1 H), 2.20 - 2.30 (m, 2 H), 2.42 - 2.51 (m, 1 H), 4.05 (dd like t with  $J$  = 5.2 Hz, 1 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 16.8 (CH<sub>3</sub>), 22.1 (CH<sub>3</sub>), 27.7 (CH<sub>2</sub>), 34.1 (CH<sub>2</sub>), 50.0 (C), 78.2 (CH), 221.0 (C). IR (ATR):  $\nu$  [cm<sup>-1</sup>] = 3435, 2967, 2926, 2866, 1917, 1869, 1844, 1770, 1725, 1684, 1651, 1635, 1463, 1404, 1381, 1332, 1254, 1214, 1170, 1102, 1077, 1061, 1017, 967, 935, 888, 798. MS (GC-MS, EI):  $m/z$  (%) = 128 (38) [M]<sup>+</sup>, 110 (10) [M-H<sub>2</sub>O]<sup>+</sup>,

95 (15), 85 (10), 83 (11), 82 (26), 72 (18), 71 (24), 70 (11), 69 (100), 68 (19), 67 (29), 57 (54), 56 (27), 55 (19), 43 (36), 42 (15), 41 (52), 39 (24).

**(S)-3-Hydroxy-2,2-dimethylcyclohexanone ((S)-1b).**  $R_f = 0.12$  (Et<sub>2</sub>O/pentane 1:1).  $[\alpha]_D^{25} = +23.1$  ( $c = 1$ , CHCl<sub>3</sub>) 96% ee by HPLC of (S)-7b. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 1.13 (s, 3 H), 1.17 (s, 3 H), 1.62 - 1.74 (m, 2 H), 1.78 - 1.87 (m, 1 H), 1.98 - 2.08 (m, 2 H), 2.35 - 2.45 (m, 2 H), 3.72 (dd,  $J = 7.9, 3.2$  Hz, 1 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 19.5 (CH<sub>3</sub>), 20.5 (CH<sub>2</sub>), 22.7 (CH<sub>3</sub>), 28.8 (CH<sub>2</sub>), 37.1 (CH<sub>2</sub>), 51.1 (C), 77.7 (CH), 214.6 (C). IR (ATR):  $\nu$  [cm<sup>-1</sup>] = 3436, 2969, 2941, 2872, 2138, 2056, 2030, 2009, 1917, 1870, 1844, 1771, 1751, 1734, 1699, 1652, 1636, 1454, 1383, 1315, 1266, 1242, 1142, 1119, 1055, 984, 964, 902, 859, 835, 718, 663. MS (GC-MS, EI):  $m/z$  (%) = 142 (31) [M]<sup>+</sup>, 124 (31) [M-H<sub>2</sub>O]<sup>+</sup>, 98 (37), 86 (32), 83 (29), 82 (100), 81 (19), 71 (87), 69 (52), 67 (69), 57 (37), 55 (32), 53 (15), 43 (60), 42 (39), 41 (68), 39 (39).

**cis-2,2-Dimethylcyclohexane-1,3-diol (6).**  $R_f = 0.09$  (Et<sub>2</sub>O/pentane 1:1). **M.p.** = 109.8 °C. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 1.00 (s, 3 H), 1.03 (s, 3 H), 1.30 - 1.40 (m, 1 H), 1.53 - 1.58 (m, 2 H), 1.72 - 1.81 (m, 3 H), 1.81 - 1.88 (br s, 2 H), 3.41 (br dd like t with  $J = 2.5$  Hz, 2 H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 17.1 (CH<sub>2</sub>), 24.6 (CH<sub>3</sub>), 29.3 (CH<sub>2</sub>), 39.7 (C), 76.3 (CH). IR (ATR):  $\nu$  [cm<sup>-1</sup>] = 3290, 2934, 2859, 1447, 1361, 1334, 1299, 1253, 1213, 1140, 1073, 1013, 981, 908, 845, 668, 606. MS (GC-MS, EI):  $m/z$  (%) = 126 (11) [M-H<sub>2</sub>O]<sup>+</sup>, 111 (90) [M-H<sub>2</sub>O-CH<sub>3</sub>]<sup>+</sup>, 83 (19), 82 (100), 73 (13), 70 (21), 69 (19), 67 (31), 57 (35), 55 (32), 44 (13), 43 (39), 41 (32), 39 (19). **Anal.** Calcd (%) for C<sub>8</sub>H<sub>16</sub>O<sub>2</sub>: C, 66.63; H, 11.18. Found: C, 66.52; H, 11.13.

#### Esterification of the hydroxy ketones (S)-1a and (S)-1b with *p*-bromobenzoic acid (8)

A solution of the hydroxy ketone (S)-1a (13.1 mg, 102  $\mu$ mol) or (S)-1b (14.1 mg, 99.2  $\mu$ mol) was added dropwise to a suspension of *p*-bromobenzoic acid (8, 1.6 equiv.), *N,N'*-dicyclohexylcarbodiimide (DCC, 1.7 equiv.), and 4-dimethylaminopyridine (DMAP, 30 mol %) previously stirred for 5 min in dry CH<sub>2</sub>Cl<sub>2</sub> (1 mL). After stirring at rt for 1 d, the white solid was filtered off, washed with a small amount of Et<sub>2</sub>O, and the solvents were removed under vacuum. Purification by flash chromatography (Et<sub>2</sub>O/pentane 1:3) yielded the *p*-bromobenzoates (S)-7a (29.0 mg, 91%) and (S)-7b (30.8 mg, 96%), respectively.

**(S)-2,2-Dimethyl-3-oxocyclopentyl 4-bromobenzoate ((S)-7a).**  $R_f = 0.24$  (Et<sub>2</sub>O/pentane 1:3). **Chiral HPLC:** major enantiomer 19.8 min, minor enantiomer 18.2 min. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 1.12 (s, 3 H), 1.14 (s, 3 H), 2.09 - 2.16 (m, 1 H), 2.38 - 2.46 (m, 2 H), 2.46 - 2.56 (m, 1 H), 5.35 - 5.38 (m, 1 H), 7.57 - 7.61 (m, 2 H), 7.84 - 7.88 (m, 2 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 17.7 (CH<sub>3</sub>), 22.6 (CH<sub>3</sub>), 25.4 (CH<sub>2</sub>), 34.1 (CH<sub>2</sub>), 49.4 (C), 80.6 (CH), 128.4 (C), 128.8 (C), 131.1 (CH), 131.9 (CH), 165.1 (C), 219.4 (C). IR (ATR):  $\nu$  [cm<sup>-1</sup>] = 2974, 2929, 2873, 2108, 1734, 1713, 1652, 1588, 1481, 1396, 1271, 1228, 1171, 1128, 1100, 1071, 1044, 1009, 944, 878, 844, 752, 725, 681. MS (GC-MS, EI):  $m/z$  (%) = 312 (1) [<sup>81</sup>BrM]<sup>+</sup>, 310 (1) [<sup>79</sup>BrM]<sup>+</sup>, 185 (97) [COC<sub>6</sub>H<sub>4</sub><sup>81</sup>Br]<sup>+</sup>, 183 (100) [COC<sub>6</sub>H<sub>4</sub><sup>79</sup>Br]<sup>+</sup>, 157 (17), 155 (18), 110 (11) [M-HOCOC<sub>6</sub>H<sub>4</sub>Br]<sup>+</sup>, 82 (60), 76 (13), 75 (10), 41 (11). **Anal.** Calcd (%) for C<sub>14</sub>H<sub>15</sub>BrO<sub>3</sub>: C, 54.04; H, 4.86. Found: C, 54.39; H, 4.99.

**(S)-2,2-Dimethyl-3-oxocyclohexyl 4-bromobenzoate ((S)-7b).**  $R_f = 0.24$  (Et<sub>2</sub>O/pentane 1:3). **Chiral HPLC:** major enantiomer 20.5 min, minor enantiomer 17.4 min. **M.p.** = 70.3 °C. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 1.17 (s, 3 H), 1.26 (s, 3 H), 1.82 - 1.90 (m, 1 H), 1.98 - 2.06 (m, 2 H), 2.17 - 2.24 (m, 1 H), 2.44 - 2.49 (m, 1 H), 2.54 - 2.61 (m, 1 H), 5.19 (dd,  $J = 6.1, 2.7$  Hz, 1 H), 7.56 - 7.60 (m, 2 H), 7.83 - 7.87 (m, 2 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  [ppm]: 20.5 (CH<sub>3</sub>), 21.0 (CH<sub>2</sub>), 23.5 (CH<sub>3</sub>), 25.8 (CH<sub>2</sub>), 37.2 (CH<sub>2</sub>), 49.6 (C), 80.3 (CH), 128.3 (C), 128.9 (C), 131.1 (CH), 131.8 (CH), 164.8 (C), 213.1 (C). IR (ATR):  $\nu$  [cm<sup>-1</sup>] = 2949, 2873, 1917, 1844, 1771, 1709, 1685, 1653, 1635, 1589, 1510, 1458, 1395, 1335, 1262, 1172, 1099, 1068, 1042, 1010, 977, 930, 847, 755, 682, 626. MS (GC-MS, EI):  $m/z$  (%) = 326 (4) [<sup>81</sup>BrM]<sup>+</sup>, 324 (4) [<sup>79</sup>BrM]<sup>+</sup>, 185 (98) [COC<sub>6</sub>H<sub>4</sub><sup>81</sup>Br]<sup>+</sup>, 183 (100) [COC<sub>6</sub>H<sub>4</sub><sup>79</sup>Br]<sup>+</sup>, 157 (16), 155 (17), 124 (49) [M-HOCOC<sub>6</sub>H<sub>4</sub>Br]<sup>+</sup>, 82 (20), 76 (10), 55 (11), 41 (10). **Anal.** Calcd (%) for C<sub>15</sub>H<sub>17</sub>BrO<sub>3</sub>: C, 55.40; H, 5.27. Found: C, 55.73; H, 5.53.

## Acknowledgements

We thank Dr. Margit Gruner (TU Dresden), Dr. Tilo Lübken (TU Dresden), and Dr. Ingmar Bauer (TU Dresden) for analytical support.

## Supplementary Material

Copies of  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectra as well as Crystallographic Information Files (CIF) are given in the Supplementary Material associated with the manuscript.

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