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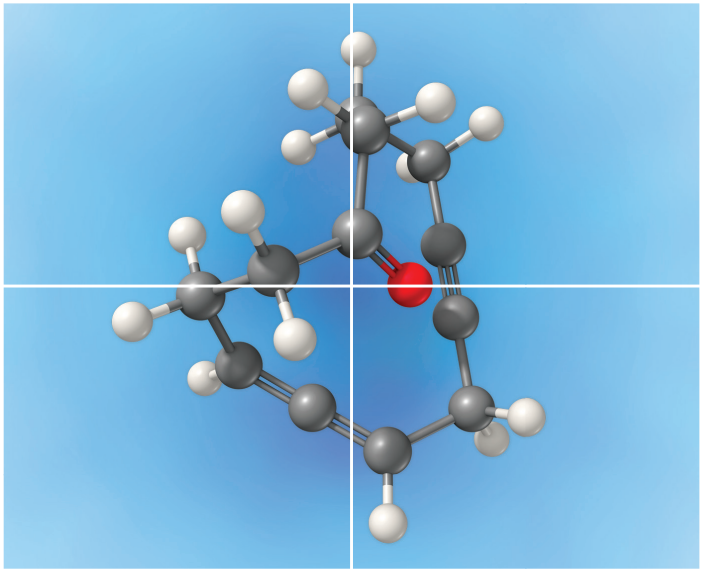

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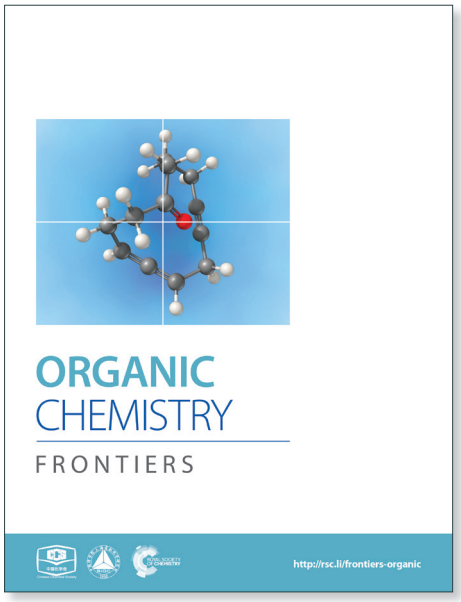


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# Chiral bicyclo[2.2.2]octa-2,5-diene ligand substituted with ferrocenyl group and its use for rhodium-catalyzed asymmetric 1,4-addition reactions

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A chiral diene, (*R*,*R*)-Fc,Ph-bod, which bears ferrocenyl (Fc) group and phenyl (Ph) group on the bicyclo[2.2.2]octa-2,5-diene skeleton has been synthesized, and its rhodium complex was examined as a catalyst for the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones. Its enantioselectivity was generally higher than that with (*R*,*R*)-Ph-bod, which is $C_2$ symmetric with two phenyl groups.

## Introduction

Chiral dienes have attracted considerable attention as chiral ligands for transition metal-catalyzed asymmetric reactions,[1] and structurally diverse array of chiral dienes have been developed for various types of the catalytic asymmetric reactions.[1] In the first report published in 2003, we have synthesized a $C_2$ symmetric chiral diene whose basic skeleton is bicyclo[2.2.1]hepta-2,5-diene and used it successfully for rhodium-catalyzed asymmetric conjugate addition reactions.[2] Carreira reported $C_1$ symmetric chiral diene ligands which are based on bicyclo[2.2.2]octa-2,5-diene skeleton.[3] Subsequently, there appeared chiral dienes based on bicyclo[3.3.1]nona-2,6-diene[4] and bicyclo[3.3.0]octa-2,5-diene.[5] Figure 1 illustrates some of the bicyclo[2.2.2]octa-2,5-diene (bod) which have been most commonly used.[6-10] Some of them are $C_2$ symmetric and some others are not.

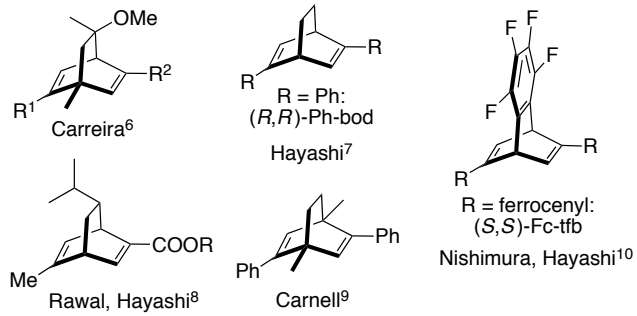
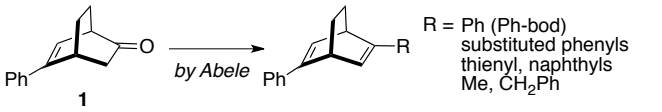



**Fig. 1** Some of the chiral diene ligands based on bicyclo[2.2.2]octa-2,5-diene skeleton.

One remarkable feature of the bod-type ligands is that Fc-tfb, which bears two ferrocenyl (Fc) groups on the tetrafluorobenzobarrelene (tfb) skeleton,[10a] has shown higher catalytic activity and higher enantioselectivity than other ligands in several types of rhodium-catalyzed asymmetric reactions.[10-15] Typically, they are asymmetric addition of organoboron reagents to unsaturated compounds, such as aldehydes,[10a] imines,[11] β-alkoxyacrylates,[12] α,β-unsaturated sulfonyl compounds,[13] and enynamides.[14]

On the other hand, Abele and coworkers recently reported[16] that enantiomerically pure 5-phenylbicyclo[2.2.2]oct-5-en-2-one **1** is readily available on a large scale through an organocatalytic one-pot Michael addition–aldol reaction and the ketone **1** is a suitable substrate for the synthesis of 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (Ph-bod) and its $C_1$-symmetric analogs substituted with aryl and alkyl groups (Scheme 1). These chiral dienes have been examined as chiral ligands for the rhodium-catalyzed asymmetric addition of arylboronic acids to enones and *N*-sulfonylimines.[17]



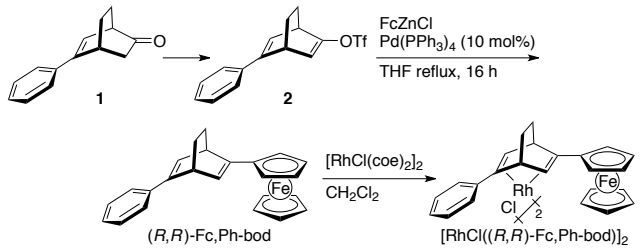

**Scheme 1** Synthesis of chiral bicyclo[2.2.2]octa-2,5-diene ligands by Abele

In this article, we report on the synthesis of a novel diene obtained by introducing the ferrocenyl group onto the bod skeleton based on the Abele's procedure,[16] and the diene ligand (Fc,Ph-bod) thus obtained which is substituted with ferrocenyl and phenyl groups is examined for its enantioselectivity in the rhodium-catalyzed asymmetric 1,4-addition of aryl- and alkenylboronic acids to α,β-unsaturated ketones.[18] The enantioselectivity is compared with that observed with Ph-bod and Fc-tfb to see the effects of the ferrocenyl group.

## Results and discussion

### Synthesis of 2-ferrocenyl-5-phenylbicyclo[2.2.2]octa-2,5-diene (Fc,Ph-bod)

According to the procedures reported by Abele,[16] the ketone **1** was converted into alkenyl triflate **2**, and it was subjected to the palladium-catalyzed cross-coupling with ferrocenylzinc reagent[7] (Scheme 2). An excess amount of FcZnCl, which is gererated by the reaction of ferrocene with *t*-BuLi followed by treatment of the resulting FcLi with $ZnCl_2$, was allowed to react with triflate **2** in the presence of 10 mol% $Pd(PPh_3)_4$ in refluxing THF for 16 h. Aqueous work-up followed by silica gel column chromatography gave the diene, (*R*,*R*)-Fc,Ph-bod, in 72% yield. This diene was used for the preparation of rhodium complex, $[RhCl((R,R)\text{-Fc,Ph-bod})]_2$, by the ligand exchange reaction with $[RhCl(coe)_2]_2$ in dichloromethane.

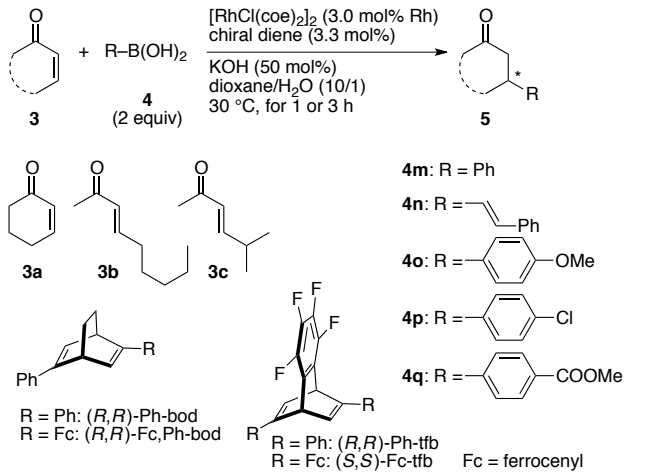



**Scheme 2** Synthesis of 2-ferrocenyl-5-phenylbicyclo[2.2.2]octa-2,5-diene (Fc,Ph-bod).

### Asymmetric 1,4-addition catalyzed by rhodium complexes coordinated with (*R*,*R*)-Fc,Ph-bod and its related chiral dienes

Table 1 summarizes the results of the asymmetric 1,4-addition of organoboronic acids to α,β-unsaturated cyclic ketones in the presence of a rhodium catalyst coordinated with (*R*,*R*)-Fc,Ph-bod obtained above. For comparison, this Table also contains the results of reactions in the presence of other related chiral diene/rhodium complexes, which have been previously reported as effective catalysts for the asymmetric 1,4-addition. First, (*R*,*R*)-Fc,Ph-bod was examined for the addition of phenylboronic acid to 2-cyclohexenone, which is one of the benchmark reactions to demonstrate high efficiency of newly developed chiral rhodium catalysts.[1] Thus, the reaction of 2-cyclohexenone **3a** with phenylboronic acid **4m** (2 equiv) was carried out in the presence of $[RhCl((R,R)\text{-Fc,Ph-bod})]_2$ (3 mol% Rh) and KOH (50 mol%) in dioxane/$H_2O$ (10/1) at 30 °C for 1 h to give a high yield (99%) of (*R*)-3-phenylcyclohexanone **5am** with 98% ee (entry 1). In situ generation of the chiral diene/rhodium catalyst from $[RhCl(coe)_2]_2$ and (*R*,*R*)-Fc,Ph-bod gave the addition product **5am** of the same 98% ee (entry 2). This enantioselectivity is slightly higher than that observed with (*R*,*R*)-Ph-bod under the same condition (entries 3 and 4). The higher enantioselectivity of (*R*,*R*)-Fc,Ph-bod (95% ee) than (*R*,*R*)-Ph-bod (93% ee) was also observed in the addition of alkenylboronic acid **4n** to **3a** (entries 5 and 6). For comparison, (*R*,*R*)-Ph-tfb and (*S*,*S*)-Fc-tfb gave the product **5an** with 93% and 98% ee, respectively (entries 7 and 8). In the addition of phenylboronic acid **4m** to acyclic enone, (*E*)-non-3-en-2-one **3b**, which is known to be a difficult substrate to achieve high enantioselectivity in the rhodium-catalyzed conjugate addition, Fc,Ph-bod gave the product **3bm** of 90% ee (entry 9). Although this enantioselectivity is lower than that obtained with Fc-tfb (98% ee, entry 12), it is higher than that with Ph-bod (83% ee, entry 10) and Ph-tfb (85% ee, entry 11). The higher enantioselectivity of Fc,Ph-bod than Ph-bod was also observed in the reaction of enone **3b** with phenylboronic acids substituted with 4-methoxy **4o**, 4-chloro **4p**, and 4-methoxycarbonyl **4q** groups (entries 13-18). Similarly, the reaction of another acyclic enone, (*E*)-5-methylhex-3-en-2-one (**3c**), with arylboronic acids, **4m**, **4o**, **4p**, and **4q**, proceeded with higher enantioselectivity in the presence of Fc,Ph-bod than Ph-bod (entries 19-26).

Table **1** Rhodium-catalyzed asymmetric 1,4-addition of organoboronic acids to α,β-unsaturated carbonyl compounds[a]




| entry | 3 | 4 | time (h) | ligand | product 5 | yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1[d] | **3a** | **4m** | 1 | (*R*,*R*)-Fc,Ph-bod | **5am** | 99 | 98 (*R*) |
| 2 | | | 1 | (*R*,*R*)-Fc,Ph-bod | **5am** | 93 | 98 (*R*) |
| 3[d] | | | 1 | (*R*,*R*)-Ph-bod | **5am** | 93 | 97 (*R*) |
| 4 | | | 1 | (*R*,*R*)-Ph-bod | **5am** | 95 | 97 (*R*) |
| 5 | **3a** | **4n** | 3 | (*R*,*R*)-Fc,Ph-bod | **5an** | 89 | 95 (*R*) |
| 6 | | | 3 | (*R*,*R*)-Ph-bod | **5an** | 90 | 93 (*R*) |
| 7[d] | | | 3 | (*R*,*R*)-Ph-tfb[e] | **5an** | 87 | 93 (*R*) |
| 8[d] | | | 3 | (*S*,*S*)-Fc-tfb | **5an** | 99 | 98 (*R*) |
| 9 | **3b** | **4m** | 1 | (*R*,*R*)-Fc,Ph-bod | **5bm** | 90 | 90 (*S*) |
| 10 | | | 1 | (*R*,*R*)-Ph-bod | **5bm** | 97 | 83 (*S*) |
| 11[d] | | | 1 | (*R*,*R*)-Ph-tfb[e] | **5bm** | 85 | 85 (*S*) |
| 12[d] | | | 1 | (*S*,*S*)-Fc-tfb[e] | **5bm** | 92 | 98 (*S*) |
| 13 | **3b** | **4o** | 1 | (*R*,*R*)-Fc,Ph-bod | **5bo** | 95 | 95 (*S*) |
| 14 | | | 1 | (*R*,*R*)-Ph-bod | **5bo** | 96 | 89 (*S*) |
| 15 | **3b** | **4p** | 2 | (*R*,*R*)-Fc,Ph-bod | **5bp** | 81 | 92 (*S*) |
| 16 | | | 2 | (*R*,*R*)-Ph-bod | **5bp** | 76 | 89 (*S*) |
| 17 | **3b** | **4q** | 2 | (*R*,*R*)-Fc,Ph-bod | **5bq** | 99 | 93 (*S*) |
| 18 | | | 2 | (*R*,*R*)-Ph-bod | **5bq** | 96 | 87 (*S*) |
| 19 | **3c** | **4m** | 1 | (*R*,*R*)-Fc,Ph-bod | **5cm** | 91 | 88 (*R*) |
| 20 | | | 1 | (*R*,*R*)-Ph-bod | **5cm** | 84 | 84 (*R*) |
| 21 | **3c** | **4o** | 1 | (*R*,*R*)-Fc,Ph-bod | **5co** | 96 | 92 (*R*) |
| 22 | | | 1 | (*R*,*R*)-Ph-bod | **5co** | 98 | 89 (*R*) |
| 23 | **3c** | **4p** | 1 | (*R*,*R*)-Fc,Ph-bod | **5cp** | 88 | 94 (*R*) |
| 24 | | | 1 | (*R*,*R*)-Ph-bod | **5cp** | 93 | 92 (*R*) |
| 25 | **3c** | **4o** | 1 | (*R*,*R*)-Fc,Ph-bod | **5co** | 99 | 92 (*R*) |
| 26 | | | 1 | (*R*,*R*)-Ph-bod | **5co** | 99 | 90 (*R*) |

[a] Enone **3** (0.30 mmol), boronic acid **4** (0.60 mmol), $[RhCl(coe)_2]_2$ (9.0 mmol of Rh), diene ligand (9.9 mmol), and KOH (0.15 mmol) in dioxane/$H_2O$ (1.0/0.1 mL). [b] Isolated yield. [c] The % ee was determined by chiral HPLC. The absolute configurations of known compounds were determined by comparison of their optical rotations with those reported, and the absolute configurations of new compounds, **5bq**, **5cp**, and **5cq**, are estimated by similarity of the stereochemical pathway. [d] Isolated rhodium complex $[RhCl(diene)]_2$ was used in place of in situ generation from $[RhCl(coe)_2]_2$ and diene ligand. [e] In the experiment of entries 7 and 11, (*S*,*S*) isomer of Ph-tfb ligand was used. For easier understanding of the stereochemical outcome, it is shown as if (*R*,*R*) isomer is used. In entry 12, (*R*,*R*)-Fc-tfb was used in the experiment.

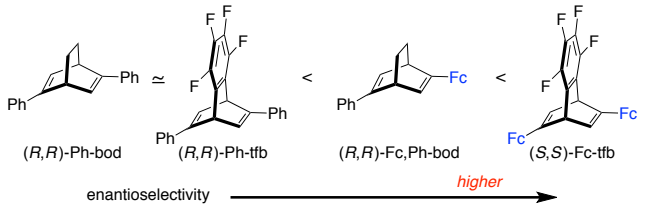



**Fig. 2** Higher enantioselectivity with Fc (ferrocenyl) group introduction

In all the reactions shown in Table 1, Fc,Ph-bod ligand showed higher enantioselectivity than Ph-bod and Ph-tfb, but it was less enantioselective than Fc-tfb. It follows that Fc (ferrocenyl) group brings about higher enantioselectivity than Ph group and two Fc groups are more enantioselective than one Fc group in the present 1,4-addition reactions.

## Conclusions

We have synthesized a chiral diene, (*R*,*R*)-Fc,Ph-bod, which is $C_1$ symmetric substituted with ferrocenyl group and phenyl group. Its rhodium complex, $[RhCl((R,R)\text{-Fc,Ph-bod})]_2$ was used as a catalyst for the asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones to show higher enantioselectivity than the Ph-bod catalyst. Through these studies, it has been demonstrated that the ferrocenyl (Fc) group on the bod ligand contributes to the higher enantioselectivity.

## Experimental

### General

All air- and moisture-sensitive manipulations were carried out with standard Schlenk techniques under argon. The starting materials were obtained from commercial sources and used without further purification. THF and dioxane were distilled over benzophenone ketyl under argon. $CH_2Cl_2$ was distilled over $CaH_2$ under argon. $[RhCl(coe)_2]_2$ was prepared following the literature procedures.[19]

### Preparation of (*R*,*R*)-Fc,Ph-bod and $[RhCl((R,R)\text{-Fc,Ph-bod})]_2$

The alkenyl triflate **2** was prepared from enantiomerically pure ketone, 5-phenylbicyclo[2.2.2]oct-5-en-2-one (**1**), according to the reported procedures.[16]

To a solution of ferrocene (259 mg, 1.39 mmol) in THF (2.5 mL), *t*-BuLi (1.5 M in pentane, 0.85 mL, 1.27 mmol) was slowly added at -78 °C, and the mixture was allowed to warm to room temperature and stirred for 2 h. $ZnCl_2$ (173 mg, 1.27 mmol) in THF (1.5 mL) was added and the mixture was stirred at room temperature for 0.5 h to form FcZnCl solution. The FcZnCl solution was added dropwise to a solution of **2** (100 mg, 0.30 mmol) and $Pd(PPh_3)_4$ (35 mg, 0.030 mmol) in THF (1.0 mL), and the mixture was refluxed for 16 h. Water was added to quench the reaction, and the mixture was extracted with $Et_2O$. The organic layer was washed with brine, dried over $Na_2SO_4$, and evaporated under vacuum. The residue was subjected to column chromatography on silica gel with hexane/ethyl acetate (49/1) to give the orange solid (*R*,*R*)-Fc,Ph-bod (79.5 mg, 0.22 mmol, 72% yield). The diene ligand was allowed to react with $[RhCl(coe)_2]_2$ (95 mg, 0.26 mmol) in $CH_2Cl_2$ (5 mL) at room temperature for 2 h to give dark-red solid $[RhCl((R,R)\text{-Fc,Ph-bod})]_2$ (100 mg, 0.20 mmol, 91% yield). The NMR spectrum of $[RhCl((R,R)\text{-Fc,Ph-bod})]_2$ is hard to be analyzed due to the stereoisomers.

**(*R*,*R*)-Fc,Ph-bod.** $[\alpha]^{22}_D$ +71 (*c* 0.99, $CHCl_3$). $^1H$ NMR ($CDCl_3$): δ 7.46 (dd, *J* = 8.4,1.3 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.23 (tt, *J* = 7.4, 1.1 Hz, 1H), 6.67 (dd, *J* = 6.4, 2.0 Hz, 1H), 6.30 (dd, *J* = 6.4, 2.0 Hz, 1H), 4.36-4.37 (m, 1H), 4.34-4.35 (m, 1H), 4.20-4.22 (m, 2H), 4.13 (s, 5H), 4.08-4.10 (m, 1H), 3.93-3.94 (m, 1H), 1.52-1.56 (m, 4H). $^{13}C$ NMR ($CDCl_3$): δ 146.8, 144.6, 138.3, 129.1, 128.4, 126.7, 125.1, 124.7, 83.7, 68.6, 68.5, 68.4, 65.5, 64.5, 40.8, 39.6, 26.4, 25.8. HRMS (ESI) *m/z* calcd for $C_{24}H_{22}Fe$ $M^+$ 366.1065, found 366.1060.

### General procedure for asymmetric 1,4-addition catalyzed by a rhodium complex in situ generated from $[RhCl(coe)_2]_2$ and chiral diene

A solution of $[RhCl(coe)_2]_2$ (9.0 μmol Rh), chiral diene ligand (9.9 μmol), and boronic acid **4** (0.60 mmol) in 1.0 mL of dioxane was stirred at room temperature for 5 min. To this mixture was added aqueous KOH (0.10 mL, 1.5 M, 0.15 mmol), and the mixture was stirred at room temperature for another 5 min. Enone **3** (0.30 mmol) was added, and the mixture was stirred at 30 °C for 1 h or 3 h. The mixture was passed through a short silica gel column (eluent: diethyl ether) and the solvent was removed under vacuum. The residue was subjected to column chromatography on silica gel with EtOAc/hexane to give the 1,4-addition product.

### General procedure for asymmetric 1,4-addition catalyzed by an isolated rhodium complex $[RhCl(diene)]_2$

To a solution of $[RhCl(diene)]_2$ complex (9.0 μmol Rh) and boronic acid **4** (0.60 mmol) in 1.0 mL of dioxane was added aqueous KOH (0.10 mL, 1.5 M, 0.15 mmol), and the mixture was stirred at room temperature for 5 min. Enone **3** (0.30 mmol) was added, and the mixture was stirred at 30 °C for 1 h or 3 h. The same work up as above gave the 1,4-addition product.

### Characterization data for the addition products

**(*R*)-3-Phenylcyclohexanone (5am):** (CAS 34993-51-6) Colorless oil. 99% yield. The ee was determined on a Daicel Chiralpak AD-H column with hexane/2-propanol = 100/1, flow = 1.0 mL/min. Retention times: 10.0 min [minor enantiomer], 12.3 min [major enantiomer]. 98% ee, $[\alpha]^{25}_D$ +20 (*c* 1.00, $CHCl_3$), *R* configuration. $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.33 (t, *J* = 7.5 Hz, 2H), 7.25-7.21 (m, 3H), 3.01 (tt, *J* = 11.9 and 3.9 Hz, 1H), 2.60 (ddt, *J* = 14.0, 4.4, and 1.9 Hz, 1H), 2.53 (ddd, *J* = 13.8, 12.5, and 0.9 Hz, 1H), 2.50-2.43 (m, 1H), 2.38 (dddd, *J* = 14.3, 12.6, 6.1, and 0.9 Hz, 1H), 2.15 (ddt, *J*= 13.0, 6.6, and 3.2Hz, 1H), 2.12-2.06 (m, 1H), 1.91-1.73 (m, 2H).

**(*R*)-3-((*E*)-2-Phenylethenyl)cyclohexanone (5an):** (CAS 1063949-45-0) Colorless oil. 89% yield. The ee was determined on a Daicel Chiralcel OD-H column with hexane/2-propanol = 100/2, flow = 1.0 mL/min. Retention times: 15.1 min [minor enantiomer], 17.2 min [major enantiomer]. 95% ee, $[\alpha]^{25}_{D}$ –8.9 (*c* 1.01, $CHCl_3$), *R* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 6.16 (dd, *J* = 15.9 and 6.9 Hz, 1H), 2.73-2.62 (m, 1H), 2.57-2.48 (m, 1H), 2.44-2.37 (m, 1H), 2.36-2.27 (m, 2H), 2.15-2.06 (m, 1H), 2.05-1.98 (m, 1H), 1.81-1.69 (m, 1H), 1.67-1.57 (m, 1H).

**(*S*)-4-Phenyl-2-nonanone (5bm):** (CAS 501919-45-5) Colorless oil. 90% yield. The ee was determined on a Daicel Chiralcel OB-H column with hexane/2-propanol = 100/1, flow = 0.5 mL/min. Retention times: 12.0 min [major enantiomer], 15.8 min [minor enantiomer]. 90% ee, $[\alpha]^{25}_{D}$ +18 (*c* 1.00, $CHCl_3$), *S* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.21-7.15 (m, 3H), 3.15-3.06 (m, 1H), 2.73 (dd, *J* = 16.1, and 7.4 Hz, 1H), 2.69 (dd, *J* = 16.1, and 7.0 Hz, 1H), 2.00 (s, 3H), 1.65-1.50 (m, 2H), 1.30-1.06 (m, 6H), 0.82 (t, *J* = 6.9 Hz, 3H).

**(*S*)-4-(4-Methoxyphenyl)nonan-2-one (5bo):** (CAS 850409-87-9) Colorless oil. 95% yield. The ee was determined on two Daicel Chiralcel OJ-H columns with hexane/2-propanol = 100/1, flow = 0.5 mL/min. Retention times: 36.2 min [major enantiomer], 39.9 min [minor enantiomer]. 95% ee, $[\alpha]^{25}_{D}$ +18 (*c* 1.02, $CHCl_3$), *S* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.6 Hz, 2H), 3.78 (s, 3H), 3.10-2.99 (m, 1H), 2.71-2.63 (m, 2H), 2.00 (s, 3H), 1.62-1.45 (m, 2H), 1.29-1.05 (m, 6H), 0.82 (t, *J* =6.9 Hz, 3H).

**(*S*)-4-(4-Chlorophenyl)nonan-2-one (5bp):** (CAS 1346758-81-3) Colorless oil. 81% yield. The ee was determined on two Daicel Chiralcel OJ-H columns with hexane/2-propanol = 100/1, flow = 0.5 mL/min. Retention times: 21.4 min [major enantiomer], 22.6 min [minor enantiomer]. 92% ee, $[\alpha]^{25}_{D}$ +13 (*c* 0.73, $CHCl_3$), *S* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 3.14-3.05 (m, 1H), 2.68 (d, *J* = 7.2 Hz, 2H), 2.02 (s, 3H), 1.62-1.45 (m, 2H), 1.27-1.03 (m, 6H), 0.82 (t, *J* = 6.8 Hz, 3H).

**(*S*)-Methyl 4-(2-oxononan-4-yl)benzoate (5bq):** Colorless oil. 99% yield. The ee was determined on two Daicel Chiralcel OJ-H columns with hexane/2-propanol = 100/2, flow = 1.0 mL/min. Retention times: 23.2 min [major enantiomer], 24.8 min [minor enantiomer]. 93% ee, $[\alpha]^{25}_{D}$ +11 (*c* 0.87, $CHCl_3$), *S* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.24 (d, *J* = 8.3 Hz, 2H), 3.89 (s, 3H), 3.21-3.16 (m, 1H), 2.73 (d, *J* = 7.1 Hz, 2H), 2.02 (s, 3H), 1.65-1.50 (m, 2H), 1.27-1.01 (m, 6H), 0.82 (t, *J*= 6.9 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 207.3, 167.0, 150.2, 129.8, 128.3, 127.5, 52.0, 50.5, 41.1, 36.2, 31.6, 30.6, 26.9, 22.4, 14.0. HRMS (ESI) *m/z* calcd for $C_{17}H_{24}O_3Na$ ($M+Na^+$) 299.1618, found 299.1628.

**(*R*)-5-Methyl-4-phenylhexan-2-one (5cm):** (CAS 162239-77-2) Colorless oil. 91% yield. The ee was determined on Daicel Chiralcel OD-H + Daicel Chiralpak ID columns with hexane/2-propanol = 100/1, flow = 1.0 mL/min. Retention times: 12.6 min [major enantiomer], 13.9 min [minor enantiomer]. 88% ee, $[\alpha]^{25}_{D}$ +23 (*c* 0.88, $CHCl_3$), *R* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.27 (t, *J* = 7.5 Hz, 2H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.14 (d, *J* = 7.4 Hz, 2H), 2.94-2.88 (m, 1H), 2.84-2.7 (m, 2H), 1.97 (s, 3H), 1.83 (octet, *J* = 6.8 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 6.7 Hz, 3H).

**(*R*)-4-(4-Methoxyphenyl)-5-methylhexan-2-one (5co):** (CAS 1346758-78-8) Colorless oil. 96% yield. The ee was determined on a Daicel Chiralpak IF column with hexane/2-propanol = 100/1, flow = 1.0 mL/min. Retention times: 10.2 min [major enantiomer], 11.1 min [minor enantiomer]. 92% ee, $[\alpha]^{25}_{D}$ +29 (*c* 1.00, $CHCl_3$), *R* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.06 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 3.77 (s, 3H), 2.88-2.84 (m, 1H), 2.80-2.71 (m, 2H), 1.97 (s, 3H), 1.78 (octet, *J* = 6.8 Hz, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.72 (d, *J* = 6.7 Hz, 3H).

**(*R*)-4-(4-Chlorophenyl)-5-methylhexan-2-one (5cp):** Colorless oil. 88% yield. The ee was determined on two Daicel Chiralcel OJ-H columns with hexane/2-propanol = 100/0.5, flow = 1.0 mL/min. Retention times: 14.9 min [major enantiomer], 17.4 min [minor enantiomer]. 94% ee, $[\alpha]^{25}_{D}$ +23 (*c* 0.85, $CHCl_3$), *R* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, *J* = 8.6 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 2.93-2.88 (m, 1H), 2.80 (dd, *J* =16.2 and 5.0 Hz, 1H), 2.74 (dd, *J* =16.2 and 9.5 Hz, 1H), 1.99 (s, 3H), 1.84-1.74 (m, 1H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 207.8, 141.8, 131.9, 129.6, 128.3, 47.5, 47.3, 33.2, 30.6, 20.6, 20.2. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}ClO$ ($M-H^+$) 223.0895, found 223.0890.

**(*R*)-Methyl 4-(2-methyl-5-oxohexan-3-yl)benzoate (5cq):** Pale yellow oil. 99% yield. The ee was determined on a Daicel Chiralpak IF column with hexane/2-propanol = 100/5, flow = 1.0 mL/min. Retention times: 14.4 min [major enantiomer], 16.2 min [minor enantiomer]. 92% ee, $[\alpha]^{25}_{D}$ +21 (*c* 0.94, $CHCl_3$), *R* configuration. $^1$H NMR (500 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.3 Hz, 2H), 7.22 (d, *J* = 8.3 Hz, 2H), 3.89 (s, 3H), 3.02-2.97 (m, 1H), 2.86-2.77 (m, 2H), 1.99 (s, 3H), 1.89-1.79 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.73 (d, *J* = 6.7 Hz, 3H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ 207.5, 167.0, 149.0, 129.5, 128.3, 128.3, 51.9, 47.8, 47.3, 33.1, 30.6, 20.6, 20.3. HRMS (ESI) *m/z* calcd for $C_{15}H_{20}O_3Na$ ($M+Na^+$) 271.1305, found 271.1300.

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## Notes and references

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