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Aqueous Asymmetric 1,4-Addition of Arylboronic Acids to Enones Catalyzed by an Amphiphilic Resin-Supported Chiral Diene Rhodium Complex Under Batch and Continuous-Flow Conditions

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KEYWORDS: rhodium catalysis, asymmetric catalysis, heterogeneous catalysis, amphiphilic polymer support, asymmetric 1,4-addition, aqueous condition, continuous-flow reaction

ABSTRACT: A rhodium–chiral diene complex immobilized on amphiphilic polystyrene–poly(ethylene glycol) (PS–PEG) resin (PS–PEG–diene*–Rh) has been developed. The immobilized rhodium–chiral diene complex (PS–PEG–diene*–Rh) efficiently catalyzed the asymmetric 1,4-addition of various arylboronic acids to cyclic or linear enones in water under batch conditions to give the corresponding β-arylated carbonyl compounds in excellent yields and with excellent enantioselectivity. The catalyst was readily recovered by simple filtration and reused 10 times without loss of its catalytic activity and enantioselectivity. Moreover, a continuous-flow asymmetric 1,4-addition in a flow reactor containing PS–PEG–diene*–Rh proceeded efficiently at 50 °C with retention of high enantioselectivity. Long-term continuous-flow asymmetric 1,4-addition during 12 hours readily gave the desired product on a ten-gram scale with high enantioselectivity.

INTRODUCTION

The development of green sustainable catalytic organic transformations is an important challenge in recent organic chemistry.[1] A key strategy for achieving green sustainable organic transformations is to reduce use of hazardous and nonsustainable organic solvents produced from petroleum feedstocks. Water is an ideal solvent because it is ecofriendly, cheap, nontoxic, and abundant.[1,2] Moreover, enzymatic reactions in nature occur efficiently in aqueous media. Despite the great benefits of water as a solvent, organic transformations in water tend to suffer from low reactivity as a result of the low solubility of the organic substrates and catalysts. To overcome this difficulty, various methods have been developed for conducting catalytic organic reactions in water. As part of our continuing efforts in this field of research, we have previously developed various transition-metal catalysts immobilized on amphiphilic polystyrene–poly(ethylene glycol) (PS–PEG) resin and we have applied them in a wide variety of organic transformations in water under heterogeneous conditions.[3] In addition to the high recyclability of the immobilized catalysts, the amphiphilic part of PS–PEG provides a reaction environment for the organic substrates in water to that realizes the efficient green, and sustainable organic transformations.

The asymmetric rhodium-catalyzed 1,4-addition of organometallic reagents to enones is widely used as an efficient and important C–C bond-forming process, providing chiral β-substituted carbonyl compounds, which are useful as chiral building blocks in organic synthesis.[4] After the first report of an asymmetric 1,4-addition of arylboronic acids to enones catalyzed by rhodium(I)/BINAP,[5] various excellent asymmetric transition-metal catalysts with chiral ligands have been developed to achieve highly enantioselective 1,4-addition. In particular, chiral diene ligands have recently attracted much attention and they have been recognized as novel chiral ligands especially in rhodium- and iridium-catalyzed asymmetric reactions, providing a catalytic activity and selectivity[6,7] that are superior to those of common chiral phosphine ligands. [8,9] However the asymmetric transi-

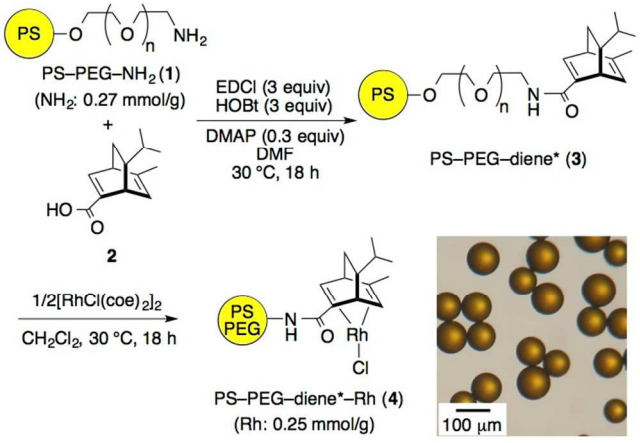
tion-metal-catalyzed transformations using chiral dienes are generally performed in organic solvents under homogeneous conditions. The conversion of the asymmetric reactions involving chiral diene catalysts into green sustainable processes in water remains an immature technique.[10,11]

Herein, we report the development of a rhodium–chiral diene complex immobilized on amphiphilic polystyrene–poly(ethylene glycol) (PS–PEG) resin and its use in the 1,4-addition of arylboronic acids to enones in water under heterogeneous conditions. The immobilized rhodium–chiral diene complex efficiently promoted the asymmetric 1,4-addition of arylboronic acids to enones in water at 50 °C to give the corresponding β-substituted carbonyl compounds in good-to-excellent yields with excellent enantioselectivity as well as with high recyclability of the catalyst. Moreover, the immobilized rhodium–chiral diene complex was successfully applied to a continuous-flow asymmetric 1,4-addition reaction, showing a high productivity (11.7 g) of the desired β-substituted carbonyl compound with a high turnover number (TON = 1073) and excellent enantioselectivity (93% ee) over 12 hours.

RESULTS AND DISCUSSION

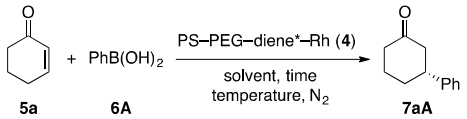
The rhodium–chiral diene complex immobilized on amphiphilic PS–PEG resin **4** was prepared according to Scheme 1. Treatment of amino-functionalized PS–PEG **1** with (1*R*,4*R*,7*R*)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (**2**)[7e] in the presence of 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI·HCl; 3.0 equiv), 1-hydroxybenzotriazole (HOBt; 3.0 equiv), and *N*,*N*-dimethyl-4-aminopyridine (DMAP; 0.3 equiv) in DMF at 30 °C for 18 hours gave PS–PEG-supported chiral diene (PS–PEG–diene*, **3**). Complexation of **3** with chlorobis(1,5-cyclooctadiene)rhodium(I) dimer ([RhCl(coe)$_2$]$_2$) in CH_2Cl_2 at 30 °C for 18 hours afforded brown polymer beads of PS–PEG-supported rhodium–chiral diene complex (PS–PEG–diene*–Rh, **4**). ICP analysis revealed that this had a rhodium content of 0.25 mmol/gr.

Scheme 1. Preparation of PS–PEG–diene*–Rh (4)



Initially, we screened the reaction conditions for the asymmetric 1,4-addition of phenylboronic acid (**6A**) to cyclohex-2-en-1-one (**5a**) in the presence of PS–PEG-diene*–Rh (**4**) (Table 1). The reaction of **5a** with **6A** (1.5 equiv) in the presence of **4** (2.5 mol % Rh) in H_2O at 50 °C was completed in 5 hours, giving (*R*)-3-phenylcyclohexanone (**7aA**) in 94% isolated yield and 95% ee (Table 1, entry 1). Notably, no additives such as bases were necessary for our standard conditions, whereas conventional Rh-catalyzed 1,4-addition reactions in organic solvents require the presence of a base. Decreasing the reaction temperature resulted in an incomplete reaction (entries 2–4), although the enantioselectivity was retained. When the reaction was performed at 40 °C under air, the isolated yield of **7aA** dropped to 34% suggesting that the catalytic activity decreases under air (entry 5). Reducing the catalyst loading affected the yield of **7aA** (entries 6 and 7). Interestingly, PS–PEG-diene*–Rh (**4**) showed poor activity in organic solvents (toluene, MeOH, dioxane, THF, or DMF; entries 8–12).[12] These results clearly suggest that water is the best solvent for catalysis by the amphiphilic PS–PEG-supported rhodium–chiral diene catalysis. It is also noteworthy that the enantioselectivity for the 1,4-addition in water using PS–PEG-diene*–Rh (**4**) was higher than its homogeneous counterpart reported so far which was performed in dioxane–water (10:1) (**7aA**, 86% ee; using a combination of [RhCl(C_2H_4)$_2$]$_2$ (3 mol% Rh) and the methyl ester of **2** (3.3 mol%) at 20 °C),[7e] presumably because of the steric effect of the C2-carboxamide group and water-based improvement of the reactivity. To optimize the reaction time, the completion of the 1,4-addition at 50 °C was investigated at 1, 2, 3, and 4 hours (entries 13–16). The reaction was completed in 3 hours, giving **7aA** in 91% isolated yield with 95% ee (entry 15).

Table 1. Optimization of Conditions for the Asymmetric 1,4-Addition[a]



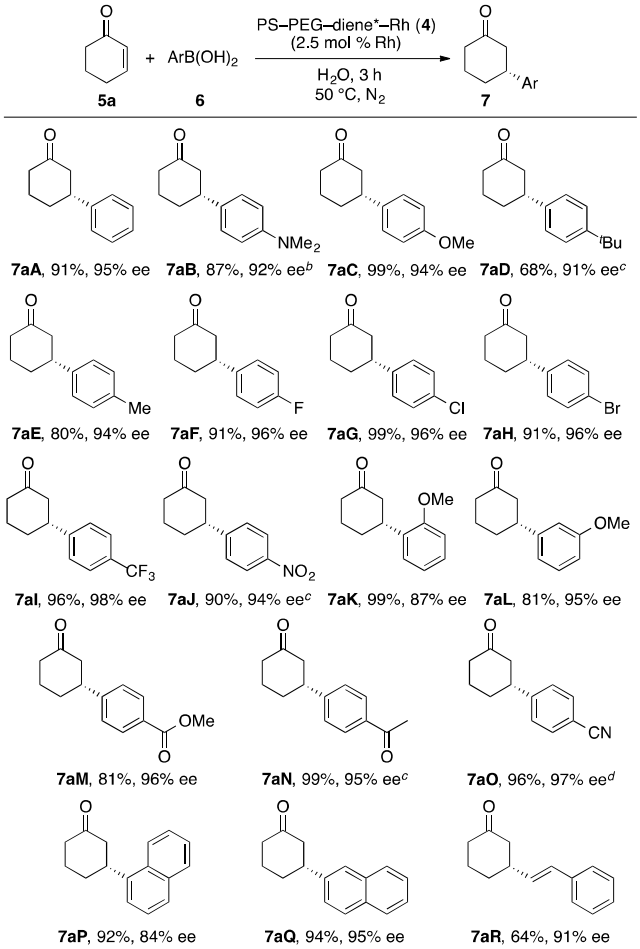
Entry	Cat. Loading (mol %)	Solvent	Temp (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	2.5	H_2O	50	5	>99 (94)	95
2	2.5	H_2O	40	5	86 (61)	95
3	2.5	H_2O	30	5	40 (30)	94
4	2.5	H_2O	25	5	25 (13)	94
5[d]	2.5	H_2O	40	5	40 (34)	95
6	1.3	H_2O	50	5	87 (68)	95
7	0.65	H_2O	50	5	73 (55)	94
8	2.5	toluene–H_2O (9:1)	50	5	57 (48)	95
9	2.5	MeOH–H_2O (9:1)	50	5	17 (15)	96
10	2.5	1,4-dioxane–H_2O (9:1)	50	5	0	–
11	2.5	THF–	50	5	0	–

12	2.5	H_2O (9:1) DMF–H_2O (9:1)	50	5	0	–
13	2.5	H_2O	50	1	(47)	95
14	2.5	H_2O	50	2	(77)	95
15	2.5	H_2O	50	3	(91)	95
16	2.5	H_2O	50	4	(91)	95

[a] Reaction conditions: enone **5a** (0.3 mmol), $PhB(OH)_2$ (**6A**; 0.45 mmol), PS–PEG–diene*–Rh (**4**; 0.65–2.5 mol%), solvent (1 mL), 25–50 °C, 1–5 h. [b] Determined by ^1H NMR with an internal standard (CH_3NO_2). The isolated yields were shown in parenthesis. [c] Determined by HPLC on a chiral stationary column (DAICEL CHIRALCEL AD-H). The absolute configuration of **7aA** was determined to be *R* on the basis of its optical rotation. [d] The reaction was performed under air.

With the optimized conditions in hand, we investigated the substrate scope of arylboronic acids **6** in the asymmetric 1,4-addition to cyclohex-2-en-1-one (**5a**) in water (Scheme 2). Phenylboronic acids **6B**–**E** bearing electron-donating groups at the *para* position underwent the asymmetric 1,4-addition to **5a** in water at 50 °C under N_2 to give the corresponding β-substituted cyclohexanones **7aB**–**aE** in 68–99% yield and 91–95% ee, although the reactions of **6B** and **6D** required longer reaction times (5 and 6 h, respectively). Various (*p*-halophenyl)boronic acids also reacted to afford the products **7aF**–**aH** in excellent yields and with excellent enantioselectivity. The reaction of phenylboronic acids bearing the electron-withdrawing substituents CF_3 and NO_2 proceeded smoothly to afford the corresponding cyclohexanones **7aI** and **7aJ** in 96% and 90% yield and with 98% ee and 94% ee, respectively. The presence of *ortho* or *meta*-methoxy groups on the phenylboronic acids (**6K** and **6H**) did not affect the asymmetric reaction. Other functionalities, such as ester and ketone groups, were also tolerated and the products **7aM** and **7aN** were obtained in excellent yields and with excellent enantioselectivity. The reaction of (4-cyanophenyl)boronic acid (**6O**) proceeded slowly under the optimized conditions, but the addition of 50 mol% of KOH promoted the reaction to give **7aO** in 96% yield with 97% ee.[13] The 1,4-addition of 1- and 2-naphthylboronic acids (**6P** and **6Q**, respectively) or [(*E*)-2-phenylvinyl]boronic acid (**6R**) also proceeded to afford the corresponding adducts **7aP**–**aR** in 64–94% yield and 84–95% ee.

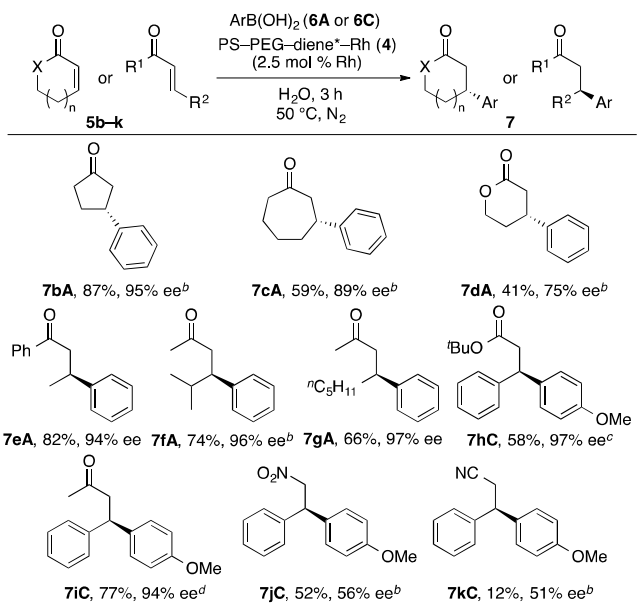
Scheme 2. Scope of the Arylboronic Acids[a]



[a] Reaction Conditions: enone **5a** (0.3 mmol), arylboronic acid **6** (0.45 mmol), PS–PEG–diene*–Rh (**4**; 2.5 mol% Rh), H_2O (1 mL), 50 °C, 3 h. Isolated yields were shown. The ee values were determined by HPLC on a chiral stationary column. The absolute configuration of products **7** were assigned based on their optical rotation. [b] The reaction was performed for 5 h. [c] The reaction was performed for 6 h. [d] The reaction was performed in the presence of KOH (50 mol%) for 4 h.

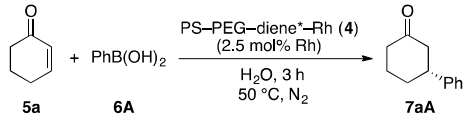
Next, we investigated the scope of the enones in the asymmetric 1,4-addition in water catalyzed by PS–PEG–diene*–Rh (**4**) (Scheme 3). Cyclopent-2-en-1-one (**5b**) on reaction for 6 hours gave **7bA** in 87% yield with 95% ee. In the reaction of the 7-membered cyclic enone **5c**, the yield of the product **7cA** decreased to 59% yield, but a high enantioselectivity was retained. The reaction of 5,6-dihydro-2*H*-pyran-2-one (**5d**) fairly proceeded for 6 hours to afford the adduct **7dA** in moderate yield (41%) and moderate enantioselectivity (75% ee). Linear *E*-enones **5e**–**i** also underwent asymmetric 1,4-addition in water catalyzed by PS–PEG–diene*–Rh **4** to give the corresponding products **7eA**–**7iC** in 58–82% yield and excellent enantioselectivity (94–97% ee), whereas addition of 50 mol% of KOH was required to promote formation of **7hC**.[13] β-Nitrostyrene **5j** was also tolerated in the reaction giving adduct **7jC** in moderate yield (52%) and moderate enantioselectivty (56% ee).[14] The reactivity of cinnamonitrile was poor; only a 12% of the adduct **7kC** was obtained, with moderate enantioselectivity.[15] The moderate enantioselectivity in the 1,4-addition of nitro- and cyanoolefins is probably due to coordination of the corresponding functional groups to the chiral rhodium center.

Scheme 3. Scope of Enones[a]



[a] Reaction conditions: enone **5** (0.3 mmol), arylboronic acid **6** (0.45 mmol), PS–PEG–diene*–Rh (**4**; 2.5 mol% Rh), H_2O (1 mL), 50 °C, 3 h. Isolated yields are shown. The ee values were determined by HPLC on a chiral stationary column. The absolute configuration of products **7** were assigned based on the basis of their optical rotations. [b] The reaction was performed for 6 h. [c] The reaction was performed in the presence of KOH (50 mol%) for 12 h. [d] The reaction was performed for 7 h.

Table 2. Recycling Experiment of PS–PEG–diene*–Rh (4) in the Asymmetric 1,4-Addition of 6A to 5a[a]



Run	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th	11th
Yield[b] (%)	91	92	92	89	92	94	92	93	90	91	91
Ee[c] (%)	95	95	94	94	94	94	94	93	93	92	92

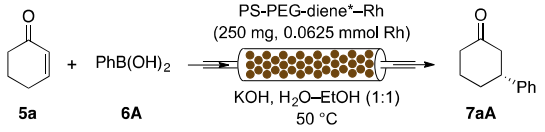
[a] Reaction conditions: enone **5a** (0.3 mmol), $PhB(OH)_2$ (**6A**; 0.45 mmol), PS–PEG–diene* (**4**; 2.5 mol% Rh), H_2O (1 mL), 50 °C, 3 h. [b] Isolated yields. [c] Determined by HPLC on a chiral stationary column (Daicel CHIRALCEL AD-H).

The PS–PEG–diene*–Rh **4** displayed good recyclability (Table 2). After completion of the asymmetric 1,4-addition of phenylboronic acid (**6A**) to cyclohex-2-en-1-one (**5a**) under the optimized conditions, ethyl acetate was added. Under an inert atmosphere, the catalyst was then separated from the reaction mixture by simple filtration, washed with ethyl acetate, and dried in vacuo before being reused in subsequent runs. The catalyst was successfully reused 10 times without loss of its catalytic activity or enantioselectivty. The eleventh reaction run still gave (*R*)-3-phenylcyclohexanone **7aA** in 91% yield and 92% ee. ICP analysis of the recovered catalyst after the eleventh run showed a 29.2% of rhodium content was leached from the initial catalyst. In fact, after the eleventh reaction run, the activity of the catalyst gradually decreased.

The success of the asymmetric 1,4-addition reaction under batch conditions prompted us to apply the PS–PEG–diene*–Rh **4** in a continuous-flow reaction. Continuous-flow organic reactions provide remarkable advantages in terms of improved safety, high efficiency, precise control of reaction conditions, and simple scale-up.[16] Consequently, switching to the continuous-flow reactions to realize further efficient, practical, and green sustainable transformations has become an important recent challenge in organic chemistry.

The continuous-flow asymmetric 1,4-addition of phenylboronic acid (**6A**) to cyclohex-2-en-1-one (**5a**) catalyzed by PS–PEG–diene*–Rh (**4**) was carried out in a flow reactor (Table 3). A solution of **5a** (25 mM) and **6A** (37.5 mM, 1.5 equiv) in a 1:1 mixture of H_2O and EtOH[17] was introduced into the reactor at a flow rate of 1.0 mL/min and passed through a catalyst cartridge (internal diameter: 4 mm; length: 70 mm), charged with PS–PEG–diene*–Rh (**4**; 250 mg, 0.0625 mmol Rh) at 50 °C. The contact time of the solution with the catalyst was 29 seconds. However, no reaction occurred in this case (entry 1). The addition of 1 equivalent of KOH (25 mM) significantly promoted the reaction, which was complete within 29 seconds (entry 2).[13] When the flow rate was increased to 2.0 mL/min (contact time: 15 seconds), full conversion of the substrates was observed (entry 3). Increasing the concentration of the substrate solution to 50 mM did not affect the conversion (entry 4). Further increasing the flow rate to 3 mL/min (contact time: 10 seconds) in the flow reaction using 50 mM solution still maintained a high activity (97% conversion).[18] The desired (*R*)-3-phenylcyclohexan-1-one (**7aA**) was obtained in 79% isolated yield with 96% ee (entry 5).

Table 3. Optimization for the Continuous-Flow Asymmetric 1,4-Addition[a]



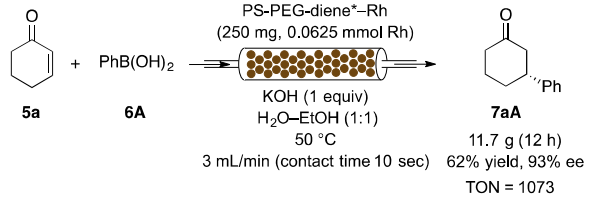
Entry	**5a** (mM)	KOH (mM)	Flow Rate (mL/min)	Contact Time (sec)	Conv. (%)[b]
1	25	–	1.0	29	0
2	25	25	1.0	29	>99
3	25	25	2.0	15	>99
4	50	50	2.0	15	>99
5	50	50	3.0	10	97 (79,[c] 96[d])

[a] Reaction conditions: A 1:1 (v/v) H_2O–EtOH solution containing cyclohex-2-en-1-one (**5a**; 25 or 50 mM), $PhB(OH)_2$ (**6A**; 1.5 equiv), and KOH (0 or 1 equiv) was introduced into a flow reactor equipped with a cartridge of PS–PEG–diene*–Rh **4** (250 mg, 0.0625 mmol Rh) at 50 °C at a flow rate of 1.0–3.0 mL/min. [b] Determined by GC-MS. were shown. [c] Isolated yield. [d] Enantiomeric excess as determined

by HPLC on a chiral stationary column (DAICEL CHIRALCEL AD-H).

Long-term continuous-flow asymmetric 1,4-addition catalyzed by PS–PEG–diene*–Rh (**4**) was conducted under the optimized flow conditions [**5a** (50 mM), **6A** (75 mM), and KOH (50 mM) in H_2O–EtOH (1:1), 50 °C, flow rate = 3.0 mL/min, contact time 10 sec] (Scheme 4). The continuous-flow asymmetric 1,4-addition of phenylboronic acid (**6A**) to cyclohex-2-en-1-one (**5a**) for 12 hours produced 11.7 g of (*R*)-3-phenylcyclohexanone (**7aA**; total yield: 62%) with excellent enantioselectivity (93% ee). The total TON of the catalyst reached 1073 for 12 hours.

Scheme 4. Long-Term Continuous-Flow Asymmetric 1,4-Addition



CONCLUSION

In conclusion, we have developed a rhodium–chiral diene complex immobilized on amphiphilic polystyrene-poly(ethylene glycol) (PS–PEG) resin, that efficiently catalyzes the asymmetric 1,4-addition of various arylboronic acids to cyclic or linear enones in water under batch conditions to give the corresponding β-arylated carbonyl compounds in excellent yields and with enantioselectivity. The catalyst was readily recovered by simple filtration and reused 10 times without loss of its catalytic activity or enantioselectivity. Moreover, the immobilized rhodium–chiral diene complex was successfully applied in a continuous-flow reaction. In a flow reactor containing the immobilized rhodium–chiral diene complex, the asymmetric 1,4-addition at 50 °C was completed in 10 seconds at 50 °C with retention of high enantioselectivity. Long-term continuous-flow asymmetric 1,4-addition readily accomplished a ten-gram-scale synthesis of the desired adduct with high enantioselectivity.

EXPERIMENTAL SECTION

General. All chemicals were commercially available and were used without further purification unless otherwise mentioned. PS–PEG–amino resin (TentaGel S NH_2; average diameter 0.90 mm, 1% divinylbenzene crosslinked, loading value of amino residue 0.2–0.3 mmol/g) was purchased from Rapp Polymere. Water was deionized with a Millipore system to Milli-Q grade. NMR spectra were recorded at 25 °C on a JEOL JNM-ECS400 spectrometer (396 MHz for ^{1}H, 100 MHz for ^{13}C{^{1}H}) or a JEOL JNM–AL400 spectrometer (100 MHz for ^{13}C). Chemical shifts for ^{1}H NMR are reported in δ ppm referenced to an internal tetramethylsilane (TMS) as a standard or to the solvent peak. Chemical shifts for ^{13}C NMR are given relative to the solvent peak as an internal standard. HPLC analysis was performed on a JASCO HPLC system equipped with CD-2095plus, MD-2015plus, RI-930, UV-1570, PU-1580, and DG-2080-53. GC analysis was carried out on a Hewlett Packard 4890 system. GC-MS data were collected with an Agilent 6890 GC/5973N MS detector or a JEOL AccuTOF GC JMS-T100GC equipped with Agilent 6890N GC. Optical rotations were recorded on a JASCO P-1020 polarimeter. ICP analysis was performed on a LEEMAN LABS Profile plus plasma spectrometer. The continuous-flow reaction was carried out in an X-Cube™ reactor system (ThalesNano Nanotechnology Inc, Budapest) with no gas mode.

Preparation of PS–PEG–diene* (3). A mixture of (1*R*, 4*R*, 7*R*)-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid[7e] (0.21 g, 1.0 mmol), PS–PEG–NH_2 (**1**) (2.6 g, 0.7 mmol), EDCI·HCl (0.58 g, 3.0 mmol), HOBt·H_2O (0.46 g, 3.0 mmol), and DMAP (0.037 g, 0.3 mmol) in DMF (20 mL) was shaken at 30 °C for 18 h until the reaction was complete as demonstrated by a Kaiser test.[19] The resulting PS-PEG-diene* was collected by filtration, washed with DMF (5 x 12 mL) and EtOAc (5 x 12 mL), and dried under vacuum for 24 h to give white beads; 2.5 g (86%). ^{13}C{^{1}H} SR-MAS-NMR (100 MHz, $CDCl_3$) δ 164.3, 143.2, 142.3, 136.5, 126.4, 122.9, 111.0, 69.1, 46.3, 42.1, 38.3, 37.9, 32.4, 30.5, 20.6, 20.1, 17.6.

Preparation of PS–PEG–diene*–Rh (4). A mixture of PS–PEG–diene* (**3**; 0.78 g, 0.2 mmol) and $[RhCl(coe)_2]_2$ (0.090 g, 0.125 mmol) in CH_2Cl_2 (8 mL) was shaken at 30 °C for 18 h under N_2. The resulting PS-PEG-diene*–Rh was collected by filtration, washed with dichloromethane (5 x 8 mL), and dried under vacuum for 15 h to give brown beads; 0.79 g (97%). ^{13}C{^{1}H} SR-MAS-NMR (100 MHz, $CDCl_3$) δ 168.1, 144.0, 126.7, 105.8, 104.5, 69.1, 54.2, 50.0, 46.2, 44.5, 42.8, 38.2, 29.4, 19.5. ICP analysis; 0.25 mmol Rh/g.

Asymmetric 1,4-Addition of Arylboronic Acids 6 to Enones 5 with PS–PEG–diene*–Rh 4; General Procedure. PS–PEG–diene*–Rh (**4**) (30.0 mg, 0.0075 mmol) and arylboronic acid **6** (0.45 mmol) were charged to a vial under an inert atmosphere. After addition of degassed H_2O (1 mL) and enone **5** (0.3 mmol), the mixture was shaken at 50 °C for 3 h. After being cooled to room temperature, the resulting mixture was filtered using a Bond Elut reservoir. The polymer catalyst was washed with ethyl acetate (5 x 3 mL). The filtrates were combined and concentrated by evaporation. The resulting crude material was purified by silica gel column chromatography with *n*-hexane and ethyl acetate to afford the corresponding β-arylated carbonyl adducts **7**.

*(R)-3-Phenylcyclohexanone (**7aA**).*[5a,7a,7e] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (47.6 mg, 91% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 19.4 °C) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.26–7.22 (m, 3H), 3.01 (tt, *J* = 11.9 and 3.6 Hz, 1H), 2.63–2.34 (m, 4H), 2.18–2.08 (m, 2H), 1.91–1.76 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 211.1, 144.3, 128.7, 126.7, 126.5, 48.9, 44.7, 41.2, 32,7, 25.5; MS (GC-EI, *m/z*) 174.2 (M); 95% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 95:5, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 13.76 min for minor isomer, t_R = 15.58 min for major isomer]; $[\alpha]^{22}_D$ +20.6 (c 1.6, $CHCl_3$).

*(R)-3-[4-(Dimethylamino)phenyl]cyclohexanone (**7aB**).*[20] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (56.7 mg, 87% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.6 °C) δ 7.10 (dt, *J* = 8.7 and 3.2 Hz, 2H), 6.71 (dt, *J* = 9.1 and 3.2 Hz, 2H), 2.96–2.89 (m and s, 7H), 2.59–2.35 (m, 4H), 2.15–2.03 (m, 2H), 1.82–1.72 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.0 °C) δ 211.6, 149.4, 132.4, 127.1, 112.8, 49.3, 43.9, 41.2, 40.7, 33.0, 25.5; HRMS (GC-TOF-EI, *m/z*) calcd for $C_{14}H_{19}NO$ (M) 217.1467, found 217.1455; 92% ee [HPLC conditions: two Chiralcel OD-H columns, hexane: *i*PrOH = 100:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 49.43 min for major isomer, t_R = 68.67 min for minor isomer]; $[\alpha]^{23}_D$ +19.9 (c 2.7, $CHCl_3$).

*(R)-3-(4-Methoxyphenyl)cyclohexanone (**7aC**).*[5c,7a,7e] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.33) as a colorless oil (60.7 mg, 99% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.3 °C) δ 7.14 (dt, *J* = 8.7 and 3.2 Hz, 2H), 6.87 (dt, *J* = 8.7 and 3.2 Hz, 2H), 3.79 (s, 3H), 2.96 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.59–2.36 (m, 4H), 2.16–2.04 (m, 2H), 1.83–1.74 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.3 °C) δ 211.2, 158.2, 136.5, 127.4, 113.9, 55.2, 49.2, 43.9, 41.1, 32.9, 25.4; MS (GC-EI, *m*/*z*) 204.2 (M); 94% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 100:1, flow rate 0.6 mL/min, wavelength = 249 nm, t_R = 18.56 min for minor isomer, t_R = 19.35 min for major isomer]; $[\alpha]^{24}_D$ + 17.7 (c 1.8, $CHCl_3$).

*(R)-3-[4-(tert-Butyl)phenyl]cyclohexanone (**7aD**).*[8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.58) as a white solid (47.0 mg, 68% yield): mp 39–40 °C; ^{1}H NMR (396 MHz, $CDCl_3$, 20.0 °C) δ 7.35 (dt, *J* = 8.3 and 2.0 Hz, 2H), 7.16 (dt, *J* = 7.9 and 1.6 Hz, 2H), 2.98 (tt, *J* = 11.5 and 3.9 Hz, 1H), 2.61–2.37 (m, 4H), 2.17–2.06 (m, 2H), 1.86–1.75 (m, 2H), 1.31 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.3 °C) δ 211.3, 149.5, 141.3, 126.2, 125.5, 49.0, 44.2, 41.2, 34.4, 32,8, 31.3, 25.6; MS (GC-EI, *m*/*z*) 230.2 (M); 91% ee [HPLC conditions: Chiralcel OJ-H column, hexane: *i*PrOH = 97:3, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 16.65 min for minor isomer, t_R = 18.55 min for major isomer]; $[\alpha]^{24}_D$ +13.6 (c 0.6, $CHCl_3$).

*(R)-3-(4-Methylphenyl)cyclohexanone (**7aE**).*[7a,8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (45.2 mg, 80% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.15–7.10 (m, 4H), 2.96 (tt, *J* = 11.9 and 4.3 Hz, 1H), 2.59–2.34 (m, 4H), 2.33 (s, 3H), 2.16–2.04 (m, 2H), 1.85–1.74 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 211.2, 141.4, 136.2, 129.3, 126.4, 49.0, 44.3, 41.1, 32.8, 25.5, 21.0; MS (GC-EI, *m*/*z*) 188.2 (M); 94% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 97:3, flow rate 0.6 mL/min, wavelength = 249 nm, t_R = 11.46 min for minor isomer, t_R = 12.49 min for major isomer]; $[\alpha]^{24}_D$ +10.1 (c 2.05, $CHCl_3$).

*(R)-3-(4-Fluorophenyl)cyclohexanone (**7aF**).*[7a,8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (52.5 mg, 91% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C): δ 7.21–7.16 (m, 2H), 7.05–6.99 (m, 2H), 3.00 (tt, *J* = 11.9 and 3.6 Hz, 1H), 2.60–2.37 (m, 4H), 2.17–2.06 (m, 2H), 1.88–1.75 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.1 °C): δ 210.7, 161.5 (d, *J* = 245 Hz), 140.0 (d, *J* = 2.9 Hz), 127.9 (d, *J* = 7.7 Hz), 115.4 (d, *J* = 21 Hz), 49.0, 43.9, 41.1, 32,8, 25.3; MS (GC-EI, *m*/*z*) 192.2 (M); 96% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 9:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 12.61 min for minor isomer, t_R = 14.68 min for major isomer]; $[\alpha]^{23}_D$ +11.3 (c 1.7, $CHCl_3$).

*(R)-3-(4-Chlorophenyl)cyclohexanone (**7aG**).*[8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (62.0 mg, 99% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 19.8 °C) δ 7.29 (dt, *J* = 8.7 and 1.9 Hz, 2H), 7.15 (d, *J* = 8.7 Hz, 2H), 2.99 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.59–2.33 (m, 4H), 2.18–2.05 (m, 2H), 1.87–1.74 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 21.5 °C) δ 210.5, 142.7, 132.3, 128.7, 127.9, 48.7, 44.0, 41.1, 32.6, 25.3; MS (GC-EI, *m*/*z*) 208.2 (M); 96% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 98:2, flow rate 0.8 mL/min, wavelength = 249 nm, t_R = 12.98 min for minor isomer, t_R = 13.84 min for major isomer]; $[\alpha]^{23}_D$ +7.3 (c 1.2, $CHCl_3$).

*(R)-3-(4-Bromophenyl)cyclohexanone (**7aH**).*[8b] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (69.1 mg, 91% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.1 °C) δ 7.45 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 2.98 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.59–2.33 (m, 4H), 2.17–2.05 (m, 2H), 1.87–1.71 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 19.8 °C) δ 210.5, 143.2, 131.7, 128.3, 120.3, 48.7, 44.1, 41.1, 32, 6, 25.3; MS (GC-EI, *m*/*z*) 252.1 (M); 96% ee [HPLC conditions: Chiralcel OJ-H column, hexane: *i*PrOH = 95:5, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 33.88 min for minor isomer, t_R = 37.04 min for major isomer]; $[\alpha]^{23}_D$ +6.8 (c 1.2, $CHCl_3$).

*(R)-3-[4-(Trifluoromethyl)phenyl]cyclohexanone (**7aI**).*[7a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (69.8 mg, 96% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 21.1 °C) δ 7.59 (d, *J* = 7.9 Hz, 2H), 7.34 (d, *J* = 7.9 Hz, 2H), 3.09 (tt, *J* = 11.5 and 4.0 Hz, 1H), 2.63–2.36 (m, 4H), 2.21–2.08 (m, 2H), 1.93–1.75 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.8 °C): δ 210.2, 148.2, 129.0 (q, *J* = 32.4 Hz), 127.0, 125.7 (q, *J* = 3.8 Hz), 124.1 (d, *J* = 271.8 Hz), 48.5, 44.5, 41.1, 32,5, 25.4; MS (GC-EI, *m*/*z*) 242.2 (M); 98% ee [HPLC conditions: two Chiralcel OD-H columns, hexane: *i*PrOH = 97:3, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 20.19 min for major isomer, t_R = 21.68 min for minor isomer]; $[\alpha]^{22}_D$ +11.4 (c 3.4, $CHCl_3$).

*(R)-3-(4-Nitrophenyl)cyclohexanone (**7aJ**).*[21] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (59.2 mg, 90% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.9 °C) δ 8.20 (d, *J* = 7.9 Hz, 2H), 7.40 (d, *J* = 8.7 Hz, 2H), 3.15 (tt, *J* = 11.5 and 4.0 Hz, 1H), 2.64–2.37 (m, 4H), 2.22–2.11 (m, 2H), 1.95–1.77 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 21.1 °C) δ 209.6, 151.5, 146.8, 127.5, 124.0, 48.2, 44.4, 41.0, 32.3, 25.3; HRMS (GC-TOF-EI, *m*/*z*) calcd for $C_{12}H_{13}NO_3$ (M) 219.0895, found 219.0900; 94% ee [HPLC conditions: Chiralcel AS-H column, hexane: *i*PrOH = 9:1, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 38.07 min for minor isomer, t_R = 43.19 min for major isomer]; $[\alpha]^{23}_D$ +7.3 (c 0.7, $CHCl_3$).

*(R)-3-(2-Methoxyphenyl)cyclohexanone (**7aK**).*[8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.41) as a colorless oil (60.7 mg, 99% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.6 °C) δ 7.22 (dd, *J* = 7.5 and 2.0 Hz, 1H), 7.19 (td, *J* = 7.9 and 1.6 Hz, 1H), 6.94 (td, *J* = 7.5 and 1.6 Hz, 1H), 6.87 (dd, *J* = 8.3 and 0.8 Hz, 1H), 3.81 (s, 3H), 3.41 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.60–2.36 (m, 4H), 2.14–2.00 (m, 2H), 1.92–1.71 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.6 °C) δ 211.7, 156.6, 132.4, 127.5, 126.5, 120.6, 110.5, 55.2, 47.5, 41.3, 37.9, 30.9, 25.5; MS (GC-EI, *m*/*z*) 204.1 (M); 87% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 97:3, flow rate 0.7 mL/min, wavelength = 249 nm, t_R = 12.68 min for minor isomer, t_R = 13.81 min for major isomer]; $[\alpha]^{24}_D$ +36.4 (c 0.97, $CHCl_3$).

*(R)-3-(3-Methoxyphenyl)cyclohexanone (**7aL**).*[5a,7a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.33) as a colorless oil (49.6 mg, 81% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.1 °C) δ 7.25 (td, *J* = 7.5 and 0.8 Hz, 1H), 6.83–6.76 (m, 3H), 3.81 (s, 3H), 2.97 (tt, *J* = 11.9 and 4.4 Hz, 1H), 2.62–2.37 (m, 4H), 2.18–2.07 (m, 2H), 1.87–1.75 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.6 °C): δ 211.0, 159.8, 146.0, 129.7, 118.9, 112.7, 111.6, 55.2, 48.9, 44.7, 41.2, 32.6, 25.5; MS (GC-EI, *m*/*z*) 204.2 (M); 95% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 90:10, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 14.92 min for major isomer, t_R = 15.74 min for minior isomer]; $[\alpha]^{25}_D$ +15.1 (c 1.1, $CHCl_3$).

*(R)-Methyl-4-(3-oxocyclohexyl)benzoate (**7aM**).*[11] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (56.4 mg, 81% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.0 °C) δ 8.00 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 3.91 (s, 3H), 3.08 (tt, *J* = 11.9 and 3.9 Hz, 1H), 2.63–2.35 (m, 4H), 2.20–2.05 (m, 2H), 1.93–1.70 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.4 °C) δ 210.4, 166.8, 149.4, 130.0, 128.6, 126.6, 52.1, 48.4, 44.6,

41.1, 32,4, 25.4; MS (GC-EI, *m*/*z*) 232.1 (M); 96% ee [HPLC conditions: Chiralcel OJ-H column, hexane: *i*PrOH = 97:3, flow rate 0.8 mL/min, wavelength = 249 nm, t_R = 90.63 min for minor isomer, t_R = 96.09 min for major isomer]; $[\alpha]^{23}_D$ +7.3 (c 0.9, $CHCl_3$).

*(R)-3-(4-Acetylphenyl)cyclohexanone (**7aN**).*[8c] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.16) as a colorless oil (64.2 mg, 99% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.3 °C) δ 7.94 (dt, *J* = 8.7 and 2.0 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 3.09 (tt, *J* = 11.5 and 3.6 Hz, 1H), 2.63–2.40 (m, 7H), 2.21–2.08 (m, 2H), 1.91–1.77 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 210.3, 197.6, 149.6, 135.7, 128.8, 126.8, 48.4, 44.6, 41.1, 32.4, 26.6, 25.4; MS (GC-EI, *m*/*z*) 216.1 (M); 95% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 9:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 34.32 min for major isomer, t_R = 40.32 min for minor isomer]; $[\alpha]^{23}_D$ +14.7 (c 2.1, $CHCl_3$).

*(R)-3-(4-Cyanophenyl)cyclohexanone (**7aO**).*[22] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.19) as a colorless oil (57.4 mg, 96% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.4 °C) δ 7.65 (dt, *J* = 8.7 and 2.0 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 3.10 (tt, *J* = 11.9 and 4.0 Hz, 1H), 2.63–2.39 (m, 4H), 2.21–2.09 (m, 2H), 1.90–1.78 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.3 °C) δ 209.8, 149.5, 132.5, 127.4, 118.7, 110.6, 48.1, 44.5, 40.9, 32.2, 25.2; HRMS (GC-TOF-EI, *m*/*z*) calcd for $C_{13}H_{13}NO$ (M) 199.0997, found 199.0982; 97% ee [HPLC conditions: Chiralcel OJ-H column, hexane: *i*PrOH = 97:3, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 66.62 min for minor isomer, t_R = 70.05 min for major isomer]; $[\alpha]^{23}_D$ +1.8 (c 0.9, $CHCl_3$).

*(R)-3-(1-Naphthyl)cyclohexanone (**7aP**).*[8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.45) as a white solid (82.9 mg, 92% yield): mp 69–71°C; ^{1}H NMR (396 MHz, $CDCl_3$, 20.3 °C) δ 8.02 (d, *J* = 8.3 Hz, 1 H), 7.86 (d, *J* = 7.5 Hz, 1 H), 7.74 (d, *J* = 7.5 Hz, 1 H), 7.54–7.37 (m, 4H), 3.84 (tt, *J* = 11.5 and 4.0 Hz, 1H), 2.78–2.40 (m, 4H), 2.24–2.15 (m, 2H), 2.04–1.87 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 19.9 °C) δ 211.3, 140.0, 133.9, 130.8, 129.0, 127.2, 126.2, 125.6, 125.5, 122.6, 122.4, 48.5, 41.4, 39.3, 32.2, 25.5; MS (GC-EI, *m*/*z*) 224.2 (M); 84% ee [HPLC conditions: Chiralcel AS-H column, hexane: *i*PrOH = 98:2, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 12.62 min for major isomer, t_R = 21.23 min for minor isomer]; $[\alpha]^{24}_D$ +53.2 (c 1.4, $CHCl_3$).

*(R)-3-(2-Naphthyl)cyclohexanone (**7aQ**).*[7a,8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.43) as a white solid (84.7 mg, 94% yield): mp 69–71 °C; ^{1}H NMR (396 MHz, $CDCl_3$, 19.9 °C) δ 7.82–7.79 (m, 3H), 7.64 (s, 1H), 7.50–7.46 (m, 2H), 7.36 (dd, *J* = 7.9 and 1.6 Hz, 1H), 3.17 (tt, *J* = 11.1 and 7.5 Hz, 1H), 2.69–2.60 (m, 2H), 2.51–2.37 (m, 2H), 2.21–2.14 (m, 2H), 2.00–1.78 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.6 °C) δ 211.0, 141.7, 133.5, 132.3, 128.3, 127.6, 127.6, 126.2, 125.6, 125.3, 124.7, 48.8, 44.8, 41.2, 32.7, 25.5; MS (GC-EI, *m*/*z*) 224.1 (M); 95% ee [HPLC conditions: Chiralcel AS-H column, hexane: *i*PrOH = 98:2, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 22.49 min for major isomer, t_R = 31.89 min for minor isomer]; $[\alpha]^{23}_D$ +47.3 (c 1.4, $CHCl_3$).

*(R)-3-[(1E)-2-Phenylethenyl]cyclohexanone (**7aR**).*[5b,7e] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.49) as a colorless oil (53.1 mg, 64% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.36–7.20 (m, 5H), 6.39 (dd, *J* = 15.8 and 0.8 Hz, 1H), 6.16 (dd, *J* = 15.8 and 7.1, 1H), 2.69–2.66 (m, 1H), 2.56–2.50 (m, 1H), 2.44–2.37 (m, 1H), 2.36–2.28 (m, 2H), 2.11–2.07 (m, 1H), 2.05–1.99 (m, 1H), 1.78–1.68 (m 1H), 1.67–1.58 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.0 °C) δ 210.9, 137.1, 132.9, 129.1, 128.6, 127.4, 126.1, 47.4, 41.9, 41.3, 31.4, 25.0; MS (GC-EI, *m*/*z*) 200.2 (M); 91% ee [HPLC conditions: Chiralcel OD-H column, hexane: *i*PrOH = 98:2, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 17.49 min for minor isomer, t_R = 19.55 min for major isomer]; $[\alpha]^{25}_D$ –7.1 (c 1.0, $CHCl_3$).

*(R)-3-Phenylcyclopentanone (**7bA**).*[7a,8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (41.8 mg, 87% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 19.6 °C) δ 7.35 (t, *J* = 6.7 Hz, 2H), 7.27–7.26 (m, 3H), 3.43 (tt, *J* = 11.1 and 4.0 Hz, 1H), 2.67 (dd, *J* = 18.2 and 7.9 Hz, 1H), 2.51–2.26 (m, 4H), 2.05–1.94 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 19.5 °C) δ 218.5, 143.0, 128.7, 126.7, 45.8, 42.2, 38.9, 31.2; MS (GC-EI, *m*/*z*) 160.2 (M); 95% ee [HPLC conditions: two Chiralcel AS-H columns, hexane: *i*PrOH = 100:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 83.69 min for major isomer, t_R = 97.96 min for minor isomer]; $[\alpha]^{23}_D$ +47.3 (c 1.01, $CHCl_3$).

*(R)-3-Phenylcycloheptanone (**7cA**).*[7a,8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.55) as a colorless oil (33.3 mg, 59% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.8 °C) δ 7.31 (tt, *J* = 7.5 and 1.6 Hz, 2H), 7.23–7.17 (m, 3H), 2.98–2.90 (m, 2H), 2.67–2.58 (m, 3H), 2.12–1.98 (m, 3H), 1.77–1.69 (m, 2H), 1.52–1.48 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.7 °C) δ 213.6, 146.9, 128.6, 126.4, 126.3, 51.2, 43.9, 42.7, 39.2, 29,2, 24.2; MS (GC-EI, *m*/*z*) 188.1 (M); 89% ee [HPLC conditions: Chiralcel OD-H column, hexane: *i*PrOH = 95:5, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 16.95 min for minor isomer, t_R = 18.20 min for major isomer]; $[\alpha]^{25}_D$ +49.8 (c 0.6, $CHCl_3$).

*(R)-4-Phenyltetrahydro-2H-pyran-2-one (**7dA**).*[8a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.19) as a colorless oil (21.7 mg, 41% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 22.0 °C) δ 7.37 (tt, *J* = 7.9 and 1.6 Hz, 2H), 7.28 (tt, *J* = 7.1 and 1.6 Hz, 1H), 7.21 (dt, *J* = 7.1 and 1.6 Hz, 2H), 4.54–4.49 (m, 1H), 4.40 (td, *J* = 11.0 and 3.6 Hz, 1H), 3.25 (tt, *J* = 10.3 and 5.1 Hz, 1H), 2.93 (ddd, *J* = 17.0, 5.9, and 1.2m, 1H), 2.64 (dd, *J* = 17.8 and 10.3 Hz, 1H), 2.21–2.15 (m, 1H), 2.10–2.00 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 22.1 °C) δ 170.6, 142.7, 128.9, 127.1, 126.4, 68.6, 37.4, 37.3, 30.2; MS (GC-EI, *m*/*z*) 176.1 (M); 75% ee [HPLC conditions: Chiralcel AS-H column, hexane: *i*PrOH = 80:20, flow rate 1.0 mL/min, wavelength = 249 nm, t_R = 18.53 min for major isomer, t_R = 23.74 min for minor isomer]; $[\alpha]^{23}_D$ –0.9 (c 0.4, $CHCl_3$).

*(S)-1,3-Diphenylbutan-1-one (**7eA**).*[10a]The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (55.2 mg, 82% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 22.0 °C) δ 7.92 (dt, *J* = 6.7 and 1.2 Hz, 2H), 7.54 (tt, *J* = 7.9 and 1.6 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.32–7.28 (m, 4H), 7.22–7.17 (m, 1H), 3.50 (sext, *J* = 7.10 Hz, 1H), 3.30 (dd, *J* = 17.0 and 5.9 Hz, 1H), 3.18 (dd, *J* = 17.0 and 8.3 Hz, 1H), 1.34 (d, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 22.0 °C) δ 199.0, 146.5, 137.1, 132.9, 128.5, 128.5, 128.0, 126.8, 126.2, 47.0, 35.5, 21.8; MS (GC-EI, *m*/*z*) 224.2 (M); 94% ee [HPLC conditions: Chiralcel AD-H column, hexane: *i*PrOH = 100:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 18.49 min for major isomer, t_R = 23.53 min for minor isomer]; $[\alpha]^{23}_D$ +13.6 (c 1.1, $CHCl_3$).

*(R)-5-Methyl-4-phenylhexan-2-one (**7fA**).*[5a,7a] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.69) as a colorless oil (42.2 mg, 74% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.27 (t, *J* = 6.7 Hz, 2H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 8.3 Hz, 2H), 2.92 (q, *J* = 5.9 Hz, 1H), 2.80–2.78 (m, 2H), 1.97 (s, 3H), 1.83 (sext, *J* = 7.1 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.74 (d, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.5 °C) δ 208.4, 143.2, 128.2, 128.1, 126.2, 48.0, 47.6, 33.3, 30.6, 20.7, 20.3; MS (GC-EI, *m*/*z*) 190.2 (M); 96% ee [HPLC conditions: Chiralcel

OD-H column, hexane: *i*PrOH = 95:5, flow rate 0.7 mL/min, wavelength = 249 nm, t_R = 7.57 min for major isomer, t_R = 8.36 min for minor isomer]; $[\alpha]^{24}_D$ +27.2 (c 0.9, $CHCl_3$).

*(S)-4-Phenylnonan-2-one (**7gA**).*[5a,7e] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.69) as a colorless oil (43.2 mg, 66% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.2 °C) δ 7.28 (t, *J* = 7.1 Hz, 2H), 7.18 (t, *J* = 8.9 Hz, 1H), 7.17 (d, *J* = 8.9 Hz, 2H), 3.11 (quint, *J* = 7.5 Hz, 1H), 2.71 (dd, *J* = 7.1 and 1.6 Hz, 2H), 2.01 (s, 3H), 1.64–1.52 (m, 2H), 1.23–1.07 (m, 6H), 0.82 (t, *J* = 7.5 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.2 °C) δ 208.1, 144.6, 128.4, 127.4, 126.3, 50.9, 41.3, 36.4, 31.7, 30.7, 27.0, 22.5, 14.0; MS (GC-EI, *m/z*) 218.2 (M); 97% ee [HPLC conditions: two Chiralcel OD-H columns, hexane: *i*PrOH = 100:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 29.23 min for major isomer, t_R = 31.72 min for minor isomer]; $[\alpha]^{24}_D$ +19.8 (c 1.2, $CHCl_3$).

*(R)-tert-Butyl 3-(4-methoxyphenyl)-3-phenylpropanoate (**7hC**).*[7d] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.72) as a white solid (54.4 mg, 58% yield): mp 67–68 °C; ^{1}H NMR (396 MHz, $CDCl_3$, 20.8 °C) δ 7.28–7.14 (m, 7H), 6.81 (dt, *J* = 8.3 and 2.0 Hz, 2H), 4.43 (t, *J* = 8.3 Hz, 1H), 3.76 (s, 3H), 2.92 (d, *J* = 7.9 Hz, 2H), 1.27 (s, 9H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.2 °C): δ 171.2, 158.1, 143.9, 135.7, 128.7, 128.4, 127.6, 126.3, 113.8, 80.4, 55.2, 46.6, 42.2, 27.8; MS (GC-EI, *m/z*) 312.2 (M); 97% ee [HPLC conditions: Chiralcel OJ-H column, hexane: *i*PrOH = 97:3, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 38.22 min for major isomer, t_R = 49.85 min for minor isomer]; $[\alpha]^{24}_D$ −0.9 (c 2.2, $CHCl_3$).

*(R)-4-(4-Methoxyphenyl)-4-phenylbutan-2-one (**7iC**).*[7c] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.40) as a colorless oil (58.8 mg, 77% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 19.9 °C) δ 7.28–7.12 (m, 7H), 6.80 (dt, *J* = 9.1 and 2.0 Hz, 2H), 4.53 (t, *J* = 7.1 Hz, 1H), 3.74 (s, 3H), 3.14 (d, *J* = 7.1 Hz, 2H), 2.06 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 19.9 °C) δ 207.1, 158.0, 144.1, 135.9, 128.6, 128.5, 127.5, 126.3, 113.9, 55.1, 49.8, 45.2, 30.6; MS (GC-EI, *m/z*) 254.2 (M); 94% ee [HPLC conditions: Chiralcel OJ-H column, hexane: *i*PrOH = 9:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 114.88 min for minor isomer, t_R = 120.98 min for major isomer]; $[\alpha]^{24}_D$ +0.64 (c 1.7, $CHCl_3$).

*(R)-1-Methoxy-4-(2-nitro-1-phenylethyl)benzene (**7jC**).*[7g] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.46) as a colorless oil (40.1 mg, 52% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.5 °C) δ 7.34–7.21 (m, 5H), 7.15 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.95 (d, *J* = 7.9 Hz, 2H), 4.86 (t, *J* = 7.9 Hz, 1H), 3.77 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.4 °C) δ 158.9, 139.5, 131.2, 129.0, 128.7, 127.5, 127.5, 114.4, 79.4, 55.2, 48.2; MS (GC-EI, *m/z*) 257.1 (M); 56% ee [HPLC conditions: Chiralcel OD-H column, hexane: *i*PrOH = 9:1, flow rate 0.5 mL/min, wavelength = 249 nm, t_R = 77.36 min for minor isomer, t_R = 86.66 min for major isomer]; $[\alpha]^{23}_D$ +6.4 (c 1.0, $CHCl_3$).

*(R)-3-(4-Methoxyphenyl)-3-phenylpropanenitrile (**7kC**).*[7f] The product was isolated by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1, R_f = 0.35) as a colorless oil (8.5 mg, 12% yield); ^{1}H NMR (396 MHz, $CDCl_3$, 20.1 °C) δ 7.33 (tt, *J* = 7.5 and 1.2 Hz, 2H), 7.27–7.20 (m, 3H), 7.15 (dt, *J* = 8.7 and 2.0 Hz, 2H), 6.86 (dt, *J* = 8.7 and 2.0 Hz, 2H), 4.33 (t, *J* = 7.5 Hz, 1H), 3.7 (s, 3H), 3.00 (d, *J* = 7.5 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, 20.1 °C) δ 158.7, 141.5, 133.3, 128.8, 128.6, 127.4, 127.3, 118.5, 114.2, 55.2, 46.3, 24.4; MS (GC-EI, *m/z*) 237.2 (M); 51% ee [HPLC conditions: Chiralcel OD-H column, hexane: *i*PrOH = 8:2, flow rate 0.5 mL/min, wavelength = 210 nm, t_R = 41.55 min for minor isomer, t_R = 46.68 min for major isomer]; $[\alpha]^{23}_D$ −6.4 (c 0.7, $CHCl_3$).

Recycling Experiment for Asymmetric 1,4-Addition of Phenylboronic Acid (6a) to Cyclohex-2-en-1-one (5a) with PS–PEG–diene*–Rh 4. PS–PEG–diene*–Rh (**4**) (100 mg, 0.025 mmol) and phenylboronic acid **6A** (183 mg, 1.5 mmol) were charged to a vial under inert atmosphere. After addition of degassed H_2O (3 mL) and cyclohex-2-en-1-one **5a** (96.1 mg, 1.0 mmol), the mixture was shaken at 50 °C for 3 h. After being cooled to room temperature, the resulting mixture was filtered under an inert atmosphere using a Bond Elut reservoir. The recovered catalyst was washed with ethyl acetate (5 x 3 mL), dried under vacuum, and reused in a subsequent reaction.

Continuous-Flow Reaction of Asymmetric 1,4-Addition of Phenylboronic Acid (6a) to Cyclohex-2-en-1-one (5a) with PS–PEG–diene*–Rh 4. A solution of cyclohex-2-en-1-one (**5a**; 50 mM), phenylboronic acid (**6A**; 75 mM, 1.5 equiv), and KOH (50 mM, 1 equiv) in a 1:1 (v/v) mixture of H_2O and EtOH was introduced at a flow rate of 3.0 mL/min (contact time: 10 sec) into an X-Cube reactor system fitted with a catalyst cartridge (ϕ 4.0 x 70 mm) containing PS–PEG–diene*–Rh (**4**) (250 mg, 0.0625 mmol Rh)(reaction volume in the cartridge of **4**: 0.48 mL). The flow reaction was carried out at 50 °C for 12 h. The resulting solution (2160 mL) was extracted 3 times with EtOAc, and the organic layers were combined and concentrated by evaporation. The resulting crude material was purified by silica gel column chromatography (*n*-hexane/ethyl acetate = 5:1) to afford **7aA** (11.7 g, 62%, 93% ee).

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

^{1}H and ^{13}C NMR spectra, and HPLC charts for the products (PDF)

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Notes

The authors declare no competing financial interest.

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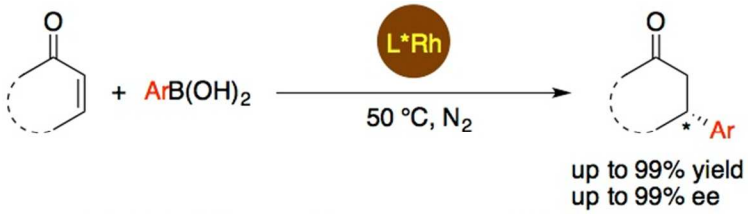
TOC Artwork



Batch & Continuous-Flow Asymmetric 1,4-Addition in Aqueous Solution