Rhodium-Catalyzed Asymmetric 1,4-Addition of Organoboron Reagents to 5,6-Dihydro-2(1*H*)-pyridinones. Asymmetric Synthesis of 4-Aryl-2-piperidinones

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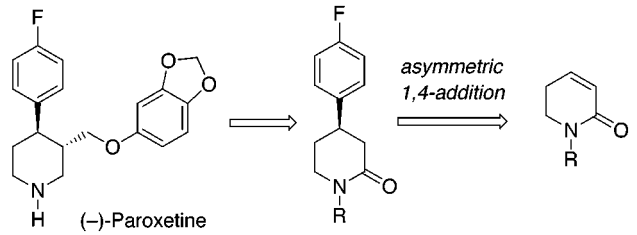
Catalytic asymmetric synthesis of 4-aryl-2-piperidinones was realized for the first time by asymmetric 1,4-addition of arylboron reagents to 5,6-dihydro-2(1*H*)-pyridinones in the presence of a chiral bisphosphine−rhodium catalyst. In the reaction introducing 4-fluorophenyl group, the use of 4-fluorophenylboroxine and 1 equiv (to boron) of water at 40 °C gave the highest yield of the arylation product with high enantioselectivity (98% ee). The (*R*)-4-(4-fluorophenyl)-2-piperidinone obtained here is a key intermediate for the synthesis of (−)-Paroxetine.

Introduction

Enantiomerically pure 4-aryl-2-piperidinones are key intermediates for the synthesis of biologically active compounds. They are readily converted into pharmacologically important molecules such as Baclofen homologues[1] and 3,4-disubstituted piperidines represented by (−)-Paroxetine.[2,3] Although considerable efforts have been made for their synthesis, to our best knowledge, asymmetric catalysis has not been applied to the synthesis of 4-aryl-2-piperidinones. We have previously reported that a rhodium complex coordinated with binap ligand catalyzes the asymmetric 1,4-addition of organoboron reagents to electron-deficient olefins including α,*β*-unsaturated ketones,[4] esters,[5] 1-alkenylphosphonates,[6] and 1-nitroalkenes[7] to give the corresponding arylation or alkenylation products with high enantioselectivity, usually over 95% ee.[8] Here we wish to report the use of α,*β*-unsaturated lactams[9] as substrates for the rhodium-catalyzed asymmetric arylation, which provides a new efficient and general route to optically active 4-aryl-2-piperidinones (Scheme 1).

Scheme 1



Results and Discussion

As the first target compound to be synthesized by the rhodium-catalyzed asymmetric addition, 4-(4-fluorophenyl)-2-piperidinone was chosen because it is known to be readily converted into (−)-Paroxetine by reported procedures.[2] Under our standard conditions used for the reaction of α,*β*-unsaturated ketones,[4] that is, 3 mol % of the rhodium catalyst coordinated with (*R*)-binap[10] in dioxane/H_2O (10/1) at 100 °C for 3 h, the reaction of *N*-benzyl-5,6-dihydro-2(1*H*)-pyridinone (**1**) with 4-fluorophenylboronic acid (**2a**) (5 equiv to **1**) gave only a poor yield (17%) of the arylation product, *N*-benzyl-4-(4-fluorophenyl)-2-piperidinone (**3a**) whose enantiomeric purity is 92%. Considering that the reaction of **1** with phenylboronic acid (**2b**) gave a good yield (70%) of the phenylation product **3b** under the same reaction conditions, the low yield is ascribed mainly to the use of 4-fluorophenylboronic acid (**2a**). It turned out that the hydrolysis of **2a** giving fluorobenzene is very fast under the reaction conditions and the boronic acid **2a** is consumed before the 1,4-addition is completed. We tried

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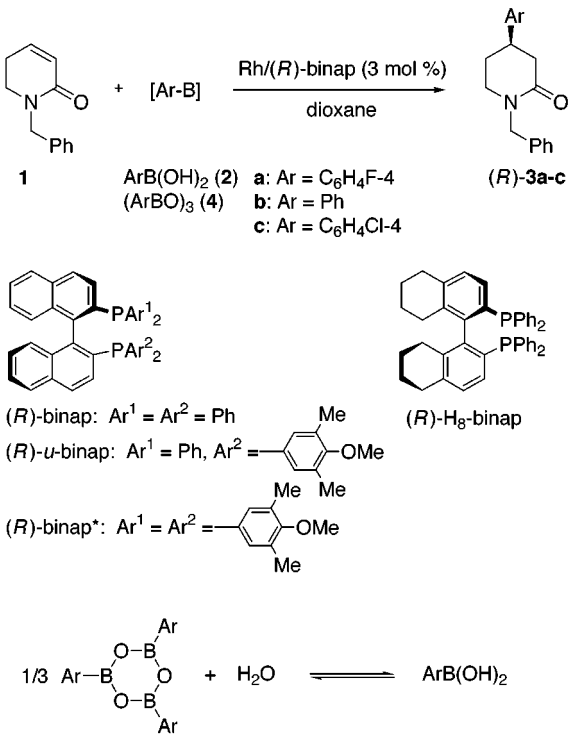
Table 1. Asymmetric 1,4-Addition of Arylboronic Acid 2 or Arylboroxine 4 to *N*-Benzyl-5,6-dihydro-2(1*H*)-pyridinone (1) Catalyzed by (*R*)-binap-Rhodium(I) Complexes[a]

entry	$ArB(OH)_2$ **2** or $(ArBO)_3$ **4**	solvent	ligand	temp (°C)	time (h)	yield[b] (%) of **3**	% ee[c]
1	4-$FC_6H_5B(OH)_2$ (**2a**)	dioxane/H_2O (10/1)	(*R*)-binap	100	3	17 (**3a**)	92
2	4-$FC_6H_5B(OH)_2$ (**2a**)	dioxane	(*R*)-binap	100	3	33 (**3a**)	89
3	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-binap	100	3	36 (**3a**)	93
4	(4-$FC_6H_5BO)_3$ (**4a**)	dioxane	(*R*)-binap	100	3	<5 (**3a**)	–
5	$PhB(OH)_2$ (**2b**)	dioxane/H_2O (10/1)	(*R*)-binap	100	3	70 (**3b**)	93[e]
6	$(PhBO)_3$ (**4b**)/H_2O[d]	dioxane	(*R*)-binap	100	3	75 (**3b**)	94
7	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-binap	40	12	63 (**3a**)	97
8	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-binap*	40	12	74 (**3a**)	96[f]
9	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-*u*-binap	40	12	54 (**3a**)	96
10	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-H_8-binap	40	12	53 (**3a**)	96
11	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-binap*	100	12	40 (**3a**)	94
12	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-binap*	80	12	49 (**3a**)	94
13	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-binap*	60	12	55 (**3a**)	95
14	(4-$FC_6H_5BO)_3$ (**4a**)/H_2O[d]	dioxane	(*R*)-binap*	20	12	54 (**3a**)	97
15	$(PhBO)_3$ (**4b**)/H_2O[d]	dioxane	(*R*)-binap	40	12	43 (**3b**)	97
16	(4-$ClC_6H_5BO)_3$ (**4c**)/H_2O[d]	dioxane	(*R*)-binap	60	6	68 (**3c**)	95[g]

[a] The reaction was carried out with **1** (0.20 mmol) and boronic acid **2** (1.0 mmol) or arylboroxine **4** (0.33 mmol) in 1.0 mL of solvent in the presence of 3 mol % of the catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*R*)-binap or its analogue (1/1.1). [b] Isolated yield by silica gel chromatography. [c] Determined by HPLC analysis with chiral stationary phase columns (Daicel Chiralpak AD, hexane/2-propanol = 9/1). [d] One equivalent (to boron) of water was added. [e] $[\alpha]^{20}_D$ +35 (*c* 1.10, $CHCl_3$). [f] $[\alpha]^{20}_D$ +33 (*c* 1.07, $CHCl_3$). [g] $[\alpha]^{20}_D$ +41 (*c* 1.28, $CHCl_3$).

Scheme 2



to improve the yield in the reaction of **2a** by modification of three factors of the reaction conditions, that is, (1) the amount of water, (2) the reaction temperature, and (3) a chiral phosphine ligand (Scheme 2). The results are summarized in Table 1, which also includes the data obtained for the reaction with phenyl and 4-chlorophenylboron reagents.

Higher yields were obtained by reducing the amount of water. The reaction of boronic acid **2a** in dioxane without water gave 33% of **3a** in the reaction at 100 °C for 3 h (entry 2). The combination of 4-fluorophenylboroxine ($(ArBO)_3$, Ar = 4-FC_6H_4, **4a**) and 1 equiv (to boron) of water in dioxane gave a little better result, the yield of **3a** being 36% in the reaction at 100 °C (entry 3).[11] In the absence of water, the catalytic arylation with boroxine **4a** did not take place (entry 4). Since arylboroxine and water is in an equilibrium with arylboronic acid under the reaction conditions, the reaction starting from arylboronic acid and that starting from arylboroxine and water (1 equiv to boron) should result in the same outcome. Nevertheless, the combination of the boroxine and water always gave a little better results than the boronic acid itself. Chemically pure arylboroxines can be readily obtained by dehydration of arylboronic acids by azeotropic removal of water from their benzene solution,[12] while arylboronic acids obtained by recrystallization from water are usually contaminated with arylboroxines to some extent. For these reasons, the combination of the boroxine and water was used in the experiments hereafter.

The best reaction temperature was 40 °C. Thus, the reaction of *N*-benzyl-5,6-dihydro-2(1*H*)-pyridinone (**1**) with 4-fluorophenylboroxine (**4a**) and water in the presence of Rh/(*R*)-binap catalyst in dioxane at 40 °C for 12 h gave 63% yield of (*R*)-**3a** which is 97% ee (entry 7). It is in striking contrast to the reaction of 2-cyclohexenone with phenylboronic acid which does not proceed at 40 °C.[4] Further modification by use of (*R*)-2,2′-bis[bis(3,5-dimethyl-4-methoxyphenyl)phosphino]-1,1′-binaphthyl (binap*) in place of binap improved the yield up to 74% (entry 8). Other binap analogues, *u*-binap[6] and H_8-binap,[13] were not better than the standard binap (entries 9 and 10). The enantioselectivity was essentially the same (96−97% ee) with these binap analogues. At higher temperature than 40 °C, the yield was lower, which is shown in the reaction of boroxine **4a** with binap* ligand (entries 11−13). The reaction still proceeds even at 20 °C to give arylation product **3a** with a little higher enantioselectivity (97% ee), but it is slow leaving the unreacted boroxine **4a** in a considerable amount after 12 h (entry 14).

The new chiral bisphosphine (*R*)-binap* was prepared by the reaction of ditriflate of (*R*)-1,1′-binaphthol with bis(3,5-dimethyl-4-methoxyphenyl)phosphine in the presence of $NiCl_2$(dppe) catalyst and DABCO in DMF accord-

(11) Arylboroxines have been used for the rhodium-catalyzed asymmetric 1,4-addition to alkenylphosphonates (ref 5).

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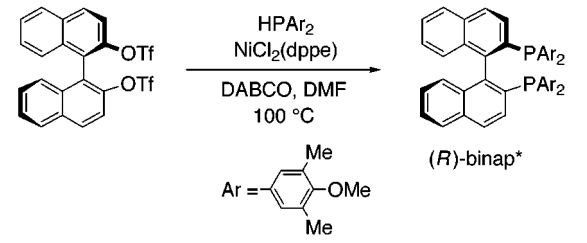
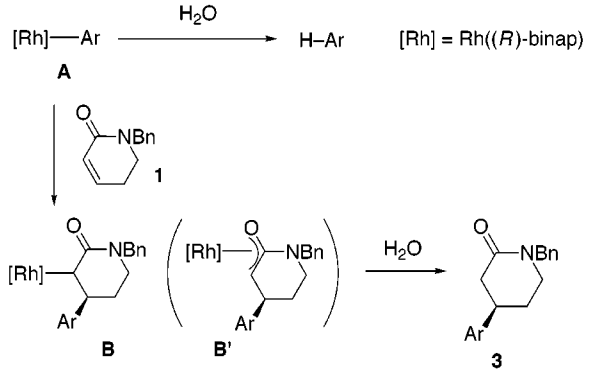
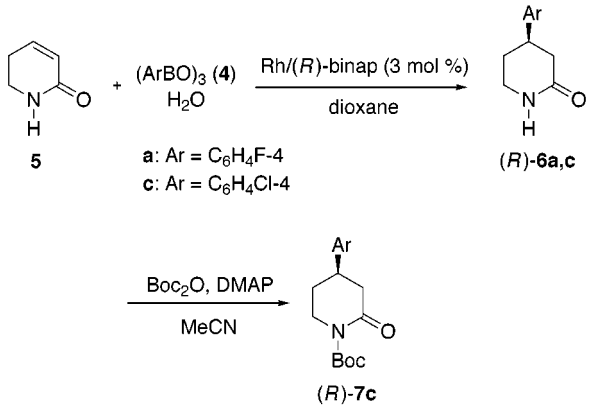
Scheme 3



Scheme 4



Scheme 5



ing to the procedures used for the preparation of binap (Scheme 3).[10d]

The catalytic cycle of the rhodium-catalyzed 1,4-addition involves an aryl−rhodium species **A** as a key intermediate, which is generated by transmetalation of the aryl group from boron to rhodium (Scheme 4). The arylation product is formed by the insertion of carbon−carbon double bond into aryl−rhodium bond followed by hydrolysis of the alkylrhodium **B** or oxo-π-allyl species **B′**. It is likely that the main side reaction giving arene is caused by hydrolysis of the arylrhodium intermediate **A**. In the reaction of 4-fluorophenylboronic acid, the hydrolysis is relatively fast compared with the insertion when the reaction is carried out in an aqueous solvent at a high temperature, and the hydrolysis was suppressed to some extent by reducing the amount of water and lowering the reaction temperature.

The reaction of 5,6-dihydro-2(1*H*)-pyridinone (**5**) with 4-fluorophenylboroxine (**4a**) and 4-chlorophenylboroxine (**4c**) was found to proceed more readily with higher enantioselectivity than that of *N*-benzyl derivative **1** (Scheme 5, Table 2). By use of the combination of the arylboroxine and 1 equiv of water under similar conditions, the reaction gave arylation products (*R*)-4-aryl-2-piperidinones (**6**) of around 98% ee in high yields. The absolute configuration of the arylation products (+)-(*R*) was unambiguously determined by correlation with known Boc-protected piperidinone (*R*)-**7b**.[1] It is consistent with the absolute configuration deduced by an empirical rule of the stereocontrol based on the face and edge orientation of the binap complex we have previously proposed.[4−6]

Table 2. Asymmetric 1,4-Addition of Arylboroxine 4 to 5,6-Dihydro-2(1*H*)-pyridinone (5) Catalyzed by (*R*)-binap-Rhodium(I) Complexes[a]

entry	$(ArBO)_3$ **4**	ligand	temp (°C)	yield[b] (%) of **6**	% ee[c]
1	$(4\text{-}FC_6H_5BO)_3$ (**4a**)	(*R*)-binap*	40	82 (**6a**)	98.3[d]
2	$(4\text{-}FC_6H_5BO)_3$ (**4a**)	(*R*)-binap	40	73 (**6a**)	97.8
3	$(4\text{-}FC_6H_5BO)_3$ (**4a**)	(*R*)-*u*-binap	40	76 (**6a**)	98.5
4	$(4\text{-}FC_6H_5BO)_3$ (**4a**)	(*R*)-H_8-binap	40	84 (**6a**)	98.4
5	$(4\text{-}ClC_6H_5BO)_3$ (**4c**)	(*R*)-binap*	60	88 (**6c**)	98.3[e]

[a] The reaction was carried out with **5** (0.20 mmol), arylboroxine **4** (0.33 mmol), and water (1.0 mmol) in 1.0 mL of dioxane in the presence of 3 mol % of the catalyst generated from $Rh(acac)(C_2H_4)_2$ and (*R*)-binap or its analogue (1/1.1) for 12 h. [b]Isolated yield by silica gel chromatography. [c]Determined by HPLC analysis with chiral stationary phase columns (Daicel Chiralpak AD, hexane/2-propanol = 9/1). [d]$[\alpha]^{20}_D$ +19 (*c* 1.02, $CHCl_3$). [e]$[\alpha]^{20}_D$ +16 (*c* 1.00, $CHCl_3$).

Conclusion

We have described the first example of catalytic asymmetric synthesis of 4-aryl-2-piperidinones (aryl = 4-FC_6H_4, 4-ClC_6H_4), which is realized by the rhodium-catalyzed asymmetric 1,4-addition of arylboron reagents to 5,6-dihydro-2(1*H*)-pyridinones. Modification of the reaction conditions by use of arylboroxine and water at a low reaction temperature brought about high enantioselectivity and high chemical yield. The optically active arylation products obtained here are synthetically very useful, being readily converted into pharmacologically important molecules such as 3,4-disubstituted piperidines.

Experimental Section

General. All manipulations were carried out under a nitrogen atmosphere. Nitrogen gas was dried by passage through P_2O_5. Optical rotations were measured with a JASCO DIP-370 polarimeter. NMR spectra were recorded on a JEOL JNM LA-500 spectrometer (500 MHz for ^1H, 125 MHz for ^{13}C, and 202 MHz for ^{31}P). Chemical shifts are reported in δ ppm referenced to an internal tetramethylsilane standard for ^1H NMR, residual chloroform (δ 77.0) for ^{13}C, and an external 85% H_3PO_4 for ^{31}P. HPLC analysis was performed on a JASCO PU-980 or PU-1580, with a JASCO UV-970 or UV-975 UV detector at 220 nm.

Materials. Rhodium complex $Rh(acac)(C_2H_4)_2$ was prepared by the reported method.[14] 5,6-Dihydro-2(1*H*)-pyridinone (**5**) was prepared according to the procedures reported by Hua.[15] 4-Fluorophenylboronic acid **2a** was prepared according to the reported procedures.[16] Phenylboronic acid (**2b**) was purchased from Tokyo Kasei Kogyo Co., Ltd.

***N*-(Benzyl)-5,6-dihydro-2(1*H*)-pyridinone (1)**. Prepared from *N*-benzyl-2-piperidinone according to the reported procedures:[15] ^1H NMR ($CDCl_3$) δ 2.32 (tdd, J = 7.2, 4.2, 1.8 Hz, 2H), 3.32 (t, J = 7.2 Hz, 2H), 4.63 (s, 2H), 6.00 (dt, J = 9.9,

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1.8 Hz, 1H), 6.55 (dt, J = 9.9, 4.2 Hz, 1H), 7.24−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 24.18, 44.58, 49.68, 125.41, 127.38, 128.01, 128.59, 137.46, 139.41, 164.52. Anal. Calcd for $C_{12}H_{13}NO$: C, 76.98; H, 7.00. Found: C, 77.24; H, 7.15.

Preparation of (*R*)-2,2′-Bis[bis(3,5-dimethyl-4-methoxyphenyl)phosphino]-1,1′-binaphthyl ((*R*)-binap*). Bis-(3,5-dimethyl-4-methoxyphenyl)phosphine Oxide. Finely divided sodium (18.6 g 80.8 mmol) was placed in a flask under nitrogen with dry THF (600 mL). To this was added $(EtO)_2POH$ (110 g, 80.0 mmol) by means of syringe, and then the mixture was refluxed until evolution of hydrogen gas was ceased. The solution was cooled with ice−water, and to this was added a THF solution of (3,5-Me-4-MeO−C_6H_2)MgBr (ca. 180 mmol), which was prepared from 1-Br-3,5-Me-4-MeO−C_6H_2 and Mg, at this temperature by means of cannula transfer. After refluxing the mixture for 1 h, the remaining excess Grignard reagent was quenched with dil HCl, and then most of THF was removed using a rotary evaporator. The residue was dissolved in a mixture of chloroform−H_2O and separated. The aquaous layer was extracted with chloroform twice, and the combined organic phase was dried over $MgSO_4$. Evaporation of the solvent gave the crude material. The crude material was purified by silica gel chromatography (with acetone/hexane = 1/1). The product was highly viscous colorless oil and not all the solvent could be eliminated. This material is sufficiently pure for the next step and used without further purification. Yield: 22.4 g (88%). ^{1}H NMR ($CDCl_3$) δ 2.31 (s, 12H), 3.75 (s, 6H), 7.34 (d, J_{PH} = 13.7 Hz, 4H), 7.91 (d, J_{PH} = 477 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.11, 59.62, 131.26 (d, J_{PC} = 11.9 Hz), 131.93 (d, J_{PC} = 14.5 Hz), 133.02 (d, J_{PC} = 8.8 Hz), 160.54 (d, J_{PC} = 3.6 Hz); ^{31}P NMR ($CDCl_3$) δ 22.0. **Bis(3,5-dimethyl-4-methoxyphenyl)phosphine.** To a solution of bis(3,5-dimethyl-4-methoxyphenyl)phosphine oxide (20.2 g, 63.5 mmol) in dry Et_2O (ca. 150 mL) was added $LiAlH_4$ (2.5 g, 65.9 mmol) in a small portion under nitrogen. The mixture was stirred at room temperature for 3 h and then quenched with degassed water with external cooling. The mixture was filtered, and the precipitate was washed with ether. The combined ether solution was evaporated under reduced pressure, and the residual yellow oil was purified by column chromatography over SiO_2 with Et_2O under nitrogen. The title compound was obtained as a colorless oil, and this material was sufficiently pure for the next step without further purification. Yield: 13.9 g (72%). ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 12H), 3.70 (s, 6H), 5.07 (d, J_{PH} = 19.0 Hz, 1H), 7.12 (d, J_{PH} = 7.4 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 16.07, 59.66, 129.47 (d, J_{PC} = 8.8 Hz), 131.16 (d, J_{PC} = 7.2 Hz), 134.61 (d, J_{PC} = 18.1 Hz), 157.57; ^{31}P NMR ($CDCl_3$) δ −41.6. **(*R*)-2,2′-Bis[bis(3,5-dimethyl-4-methoxyphenyl)phosphino]-1,1′-binaphthyl ((*R*)-binap*).** A DMF (20 mL) solution of $NiCl_2$(dppe) (530 mg, 1.00 mmol) and bis-(3,5-dimethyl-4-methoxyphenyl)phosphine (1.74 g, 5.75 mmol) was stirred at 100 °C for 30 min under nitrogen. To this was added a solution of (*R*)-2,2′-bis[(trifluoromethanesulfonyl)oxy]-1,1′-binaphthyl (5.50 g, 10.0 mmol) and DABCO (4.5 g, 40 mmol) in DMF (30 mL) by means of cannula transfer and the solution was stirred at 100 °C. Three additional portions of the diarylphosphine (1.74 g × 3) were added at 1, 3, and 7 h later. The solution was stirred at 100 °C for 5 days, however, complete consumption of the ditriflate could not be achieved. The solution was evaporated to dryness at 80 °C, and a dark brown residue was chromatographed over SiO_2 under nitrogen with benzene as an eluent to give the title compound as a colorless solid. An analytically pure sample was obtained by recrystallization from DMF as colorless crystals. Yield: 2.23 g (26%). ^{1}H NMR ($CDCl_3$) δ 2.06 (s, 12H), 2.07 (s, 12H), 3.63 (s, 6H), 3.65 (s, 6H), 6.68−6.70 (m, 4H), 6.80−6.81 (m, 6H), 6.95 (ddd, J = 8.4, 6.7, 1.3 Hz, 2H), 7.35 (ddd, J = 8.2, 6.7, 1.2 Hz, 2H), 7.50−7.52 (m, 2H), 7.83 (br d, J = 8.2 Hz, 2H), 7.86 (br d, J = 8.2 Hz, 2H); ^{31}P NMR ($CDCl_3$) δ −15.1. $[\alpha]^{20}_D$ +93 (*c* 1.01, $CHCl_3$). Anal. Calcd for $C_{56}H_{56}O_4P_2$: C, 78.67; H, 6.60. Found: C, 78.54; H, 6.73.

Preparation of Arylboroxines 4. They were prepared from the corresponding arylboronic acids by azeotropic removal of water from benzene solution. **4-Fluorophenylboroxine (4a)**: ^{1}H NMR ($CDCl_3$) δ 7.19 (t, J = 8.7 Hz, 6H), 8.22 (dd, J = 8.2, 6.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 115.30 (d, J_{CF} = 20.7 Hz), 138.02 (d, J_{CF} = 8.2 Hz), 166.13 (d, J_{CF} = 252.2 Hz). Anal. Calcd for $C_{18}H_{12}B_3F_3O_3$: C, 59.12; H, 3.31. Found: C, 58.83; H, 3.39. **4-Chlorophenylboroxine (4c)**: ^{1}H NMR ($CDCl_3$) δ 7.49 (d, J = 8.3 Hz, 6H), 8.14 (d, J = 8.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 128.46, 136.99, 139.40. Anal. Calcd for $C_{18}H_{12}B_3Cl_3O_3$: C, 52.08; H, 2.91. Found: C, 51.80; H, 3.12.

Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboroxines to 5,6-Dihydro-2(1*H*)-pyridinones. The results are summarized in Tables 1 and 2. A typical procedure is given for the preparation of *N*-benzyl-4-(4-fluorophenyl)-2-piperidinone (**3a**) with 4-fluorophenylboroxine (**4a**) (Table 1, entry 8): To a mixture of Rh(acac)$(C_2H_4)_2$ (1.6 mg, 6.0 μmol), (*R*)-binap* (5.6 mg, 6.6 μmol), and 4-fluorophenylboroxine (122 mg, 0.33 mmol; **4a**) was added 1,4-dioxane (1.0 mL), and the mixture was stirred at room temperature for 3 min. *N*-Benzyl-5,6-dihydro-2(1*H*)-pyridinone (37.4 mg, 0.20 mmol; **1**) and water (18 μL) were added, and the whole mixture was stirred at 40 °C for 12 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate and dried over anhydrous magnesium sulfate. Chromatography on silica gel (hexane/ethyl acetate = 1/1) gave (41.9 mg, 74% yield) of *N*-benzyl-4-(4-fluorophenyl)-2-piperidinone (**3a**). ***N*-Benzyl-4-(4-fluorophenyl)-2-piperidinone (3a)**:[2] ^{1}H NMR ($CDCl_3$) δ 1.90 (dddd, J = 13.4, 11.2, 10.5, 5.8 Hz, 1H), 2.06 (br d, J = 13.4 Hz, 1H), 2.55 (dd, J = 17.5, 11.0 Hz, 1H), 2.80 (ddd, J = 17.5, 5.3, 2.1 Hz, 1H), 3.09 (tdd, J = 11.2, 5.3, 3.1 Hz, 1H), 3.23−3.33 (m, 2H), 4.55 (d, J = 14.6 Hz, 1H), 4.74 (d, J = 14.6 Hz, 1H), 7.01 (t, J = 8.6 Hz, 2H), 7.15 (dd, J = 8.6 Hz, 2H), 7.26−7.30 (m, 3H), 7.32−7.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.31, 37.97, 39.60, 46.20, 50.00, 115.51 (d, J_{CF} = 21.8 Hz), 127.45, 127.91 (d, J_{CF} = 7.3 Hz), 128.16, 128.61, 137.02, 139.06 (d, J_{CF} = 3.1 Hz), 161.62 (d, J_{CF} = 244.9 Hz), 169.00. $[\alpha]^{20}_D$ +33 (*c* 1.07, $CHCl_3$) for **3a** of 95.9% ee. Chiral HPLC conditions: Daicel Chiralpak AD (hexane/2-propanol = 9/1). ***N*-Benzyl-4-phenyl-2-piperidinone (3b)**: ^{1}H NMR ($CDCl_3$) δ 1.93 (dddd, J = 13.2, 11.1, 10.7, 5.7 Hz, 1H), 2.04−2.11 (m, 1H), 2.60 (dd, J = 17.5, 11.1 Hz, 1H), 2.81 (ddd, J = 17.5, 5.2, 2.1 Hz, 1H), 3.10 (tdd, J = 11.1, 5.2, 3.2 Hz, 1H), 3.23−3.34 (m, 2H), 4.57 (d, J = 14.6 Hz, 1H), 4.73 (d, J = 14.6 Hz, 1H), 7.19 (d, J = 7.4 Hz, 2H), 7.24 (t, J = 7.4 Hz, 1H), 7.27−7.36 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 30.24, 38.68, 39.47, 46.34, 50.02, 126.51, 126.80, 127.42, 128.17, 128.61, 128.73, 137.13, 143.41, 169.26. Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.65; H, 7.30. $[\alpha]^{20}_D$ +35 (*c* 1.10, $CHCl_3$) for **3b** of 92.5% ee. Chiral HPLC conditions: Daicel Chiralpak AD (hexane/2-propanol = 9/1). ***N*-Benzyl-4-(4-chlorophenyl)-2-piperidinone (3c)**: ^{1}H NMR ($CDCl_3$) δ 1.90 (dtd, J = 13.4, 11.0, 5.6 Hz, 1H), 2.05 (br d, J = 13.4 Hz, 1H), 2.54 (dd, J = 17.5, 11.0 Hz, 1H), 2.79 (ddd, J = 17.5, 4.8, 1.6 Hz, 1H), 3.08 (tdd, J = 11.0, 4.8, 3.2 Hz, 1H), 3.22−3.33 (m, 2H), 4.55 (d, J = 14.6 Hz, 1H), 4.73 (d, J = 14.6 Hz, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.26−7.31 (m, 5H), 7.31−7.36 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.08, 38.09, 39.35, 46.12, 49.99, 127.45, 127.84, 128.14, 128.61, 128.83, 132.50. 136.98, 141.79, 168.84. Anal. Calcd for $C_{18}H_{18}ClNO$: C, 72.11; H, 6.05. Found: C, 72.17; H, 6.09. $[\alpha]^{20}_D$ +41 (*c* 1.28, $CHCl_3$) for **3c** of 95.2% ee. Chiral HPLC conditions: Daicel Chiralpak AD (hexane/2-propanol = 9/1). **4-(4-Fluorophenyl)-2-piperidinone (6a)**: ^{1}H NMR ($CDCl_3$) δ 1.84−1.96 (m, 1H), 2.06 (br d, J = 13.0 Hz, 1H), 2.44 (dd, J = 17.6, 11.1 Hz, 1H), 2.67 (dd, J = 17.6, 4.2 Hz, 1H), 3.09 (tdd, J = 11.1, 4.9, 3.2 Hz, 1H), 3.38−3.44 (m, 2H), 7.03 (t, J = 8.5 Hz, 2H), 7.07 (br s, 1H), 7.18 (dd, J = 8.5, 5.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.56, 37.64, 38.81, 41.16, 115.50 (d, J_{CF} = 22.0 Hz), 127.93 (d, J_{CF} = 7.3 Hz), 139.20 (d, J_{CF} = 3.1 Hz), 161.56 (d, J_{CF} = 244.9 Hz), 172.00. Anal. Calcd for $C_{11}H_{12}FNO$: C, 68.38; H, 6.26; N, 7.25. Found: C, 68.31; H, 6.29; N, 7.19. $[\alpha]^{20}_D$ +19 (*c* 1.02, $CHCl_3$) for **6a** of 98.3% ee. Chiral HPLC conditions: Daicel Chiralpak AD (hexane/2-propanol = 9/1). **4-(4-Chlorophenyl)-2-piperidinone (6c)**: ^{1}H NMR ($CDCl_3$) δ 1.86−1.97 (m, 1H), 2.04−2.11 (m, 1H), 2.45 (dd, J = 17.6, 11.0 Hz, 1H), 2.67 (ddd, J = 17.6, 5.3, 1.7 Hz, 1H), 3.09 (tdd, J = 11.0, 5.3, 3.2 Hz, 1H), 3.38−3.45 (m, 2H), 6.58

(br s, 1H), 7.16 (d, J = 8.4 Hz, 2H), 7.32 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 29.46, 37.87, 38.65, 41.26, 127.93, 128.92, 132.59, 141.94, 171.67. Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 62.75; H, 5.73; N, 6.63. $[\alpha]^{20}_D$ +16 (c 1.00, $CHCl_3$) for **6c** of 98.3% ee (*R*). Chiral HPLC conditions: Daicel Chiralpak AD (hexane/2-propanol = 9/1).

***N*-Boc Protection of 4-(4-Chlorophenyl)-2-piperidinone (6c).** The *N*-Boc protection was carried out according to the procedures reported by Hansen:[17] To a suspension of 4-(4-chlorophenyl)-2-piperidinone (25.4 mg, 0.12 mmol; **6c**) and Boc_2O (34.0 mg, 0.16 mmol) in CH_3CN was added DMAP (0.7 mg, 6 μmol), and the mixure was stirred at room temperature for 18 h. Chromatography on silica gel (chloroform/methanol = 40/1) gave (*R*)-1-(*tert*-butyloxycarbonyl)-4-(4-chlorophenyl)-2-piperidinone (28.8 mg, 77% yield; (*R*)-**7c**):[1] ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 1.93 (dtd, J = 13.7, 11.0, 5.0 Hz, 1H), 2.14−2.21 (m, 1H), 2.59 (dd, J = 17.1, 11.0 Hz, 1H), 2.82 (ddd, J = 17.1, 5.4, 2.1 Hz, 1H), 3.11 (tt, J = 11.0, 5.0 Hz, 1H), 3.61 (ddd, J = 13.0, 11.0, 4.5 Hz, 1H), 3.87 (dt, J = 13.0, 4.5 Hz, 1H), 7.13 (d, J = 8.5 Hz, 2H), 7.31 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 27.98, 30.23, 37.81, 41.97, 45.47, 83.18, 127.81, 128.95, 132.70, 141.48, 152.55, 170.03. $[\alpha]^{20}_D$ +16 (c 0.98, CH_2Cl_2) for (*R*)-**7c** of 98% ee. Chiral HPLC conditions: Daicel Chiralcel OD-H (hexane/2-propanol = 9/1). The specific rotation of (*R*)-**7c** has been reported[1] to be $[\alpha]^{20}_D$ +22 (c 0.98, CH_2Cl_2).

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