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Preparation of C_2-Symmetric Bicyclo[2.2.2]octa-2,5-diene Ligands and Their Use for Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids

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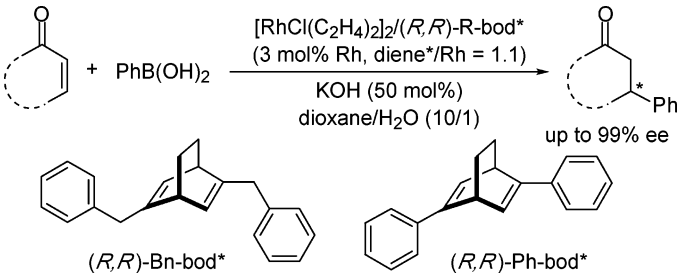

C_2-Symmetric bicyclo[2.2.2]octa-2,5-dienes containing benzyl, phenyl, and substituted phenyl groups at 2 and 5 positions were prepared enantiomerically pure by way of bicyclo[2.2.2]octane-2,5-dione as a key intermediate. These chiral diene ligands were successfully applied to rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones. High enantioselectivity (up to 99% ee) as well as high catalytic activity was observed in the addition to both cyclic and linear substrates.

Introduction

Successful use of chiral dienes as a new type of chiral ligand is one of the most significant developments in the research field of asymmetric catalysis. They have been demonstrated to be highly effective for some of the asymmetric reactions catalyzed by late transition metal complexes.[1] In 2003, we prepared, as a first example of the chiral diene ligand, (1*R*,4*R*)-2,5-dibenzylbicyclo[2.2.1]-hepta-2,5-diene (Bn-nbd*)[2] using palladium-catalyzed asymmetric hydrosilylation of norbornadiene as a key step. This C_2-symmetric diene ligand showed high enantioselectivity in rhodium-catalyzed asymmetric addition of organoboronic acids to α,β-unsaturated ketones[2] and fumaric and maleic compounds.[3] Next year Carreira reported C_1-symmetric bicyclo[2.2.2]octadienes and their successful use for iridium-catalyzed kinetic resolution of allyl carbonates[4] and the rhodium-catalyzed asymmetric 1,4-addition.[5] The bicyclo[2.2.1]heptadiene skeleton, on which our chiral diene Bn-nbd* is based, was found to have a drawback in that the dienes substituted with aryl groups at 2 and 5 positions are not stable enough to be handled in the air under light. Very recently, we reported[6] (1*R*,4*R*)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (Ph-bod*) and its dibenzyl-substituted analogue (Bn-bod*) as a new family of C_2-symmetric chiral diene ligands and their application to two types of rhodium-catalyzed asymmetric addition of arylboron reagents: one is asymmetric arylation of *N*-tosylarylimines giving diarylmethylamines[6] and the other is asymmetric arylative cyclization of alkynals.[7] Here we wish to report a full description of the preparation of enantiomerically pure 2,5-disubstituted bicyclo[2.2.2]octa-2,5-dienes (R-bod*) and their use for the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones.[8]

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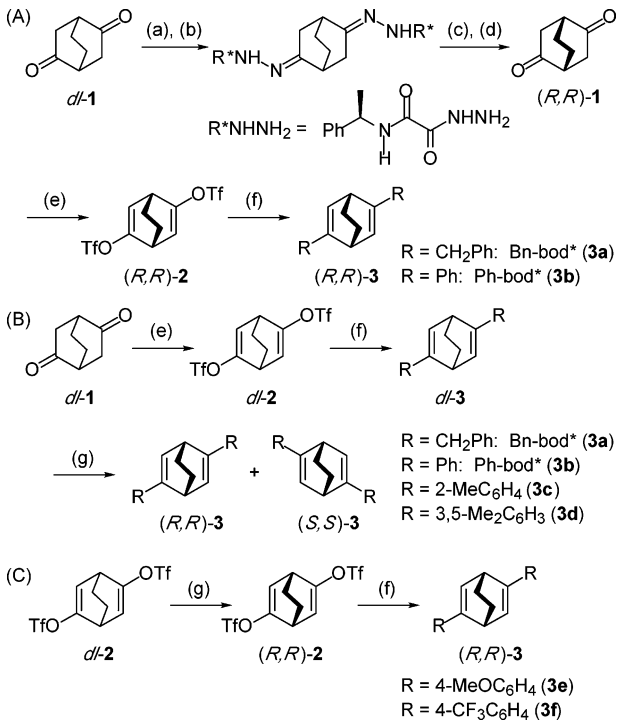
SCHEME 1[a]



[a] Reagents and conditions: (a) R*NHNH$_2$, cat. NaOAc, cat. AcOH, EtOH, reflux. (b) resolution by recrystallization from MeOH. (c) 20% H_2SO_4, reflux. (d) Recrystallization from EtOH; (e) (i) LDA, THF; (ii) Tf_2NPy-2. (f) RMgBr, $PdCl_2$(dppf) (1 mol %), Et_2O, reflux. (g) Resolution by HPLC with Chiralcel OJ (hexane/2-propanol).

Results and Discussion

The synthetic routes to the C_2-symmetric chiral dienes, 2,5-disubstituted bicyclo[2.2.2]octa-2,5-dienes, are shown in Scheme 1. The key compound in this reaction scheme is racemic bicyclo[2.2.2]octane-2,5-dione (*dl*-**1**), which was readily obtained by Diels–Alder cycloaddition of 2-acetoxypropenenitrile with a trimethylsilyl enol ether derived from 2-cyclohexenone according to the reported procedures.[9] The diketone **1** was treated with excess lithium diisopropylamide (LDA) and *N*-(2-pyridyl)-triflimide to give 70% yield of di(alkenyl triflate) **2**, which was subjected to the cross-coupling with the Grignard reagents (RMgBr) catalyzed by $PdCl_2$(dppf)[10] leading to the corresponding 2,5-disubstituted bicyclo[2.2.2]octa-2,5-dienes **3** in high yields.

The enantiomerically pure dienes **3** were obtained through optical resolution of either diketone **1** (route A), dienes **3** themselves (route B), or ditriflate **2** (route C). In route A, racemic diketone *dl*-**1** was converted into a diastereomeric mixture of dihydrazones by condensation with (*R*)-5-(1-phenylethyl)semioxamazide[11] and fractional recrystallization of the dihydrazone from methanol gave one of the diastereomeric isomers with high selectivity. Acidic hydrolysis of this dihydrazone gave diketone (*R*,*R*)-(−)-**1**, whose enantiomeric purity was determined to be 97.5% ee by an HPLC analysis with a chiral stationary phase column. Its recrystallization from ethanol provided the enantiomerically pure (>99% ee) diketone (*R*,*R*)-**1**. The absolute configuration (*R*,*R*) was assigned by comparison of its optical rotation with the literature value.[12] Ditriflate formation followed by palladium-catalyzed cross-coupling of (*R*,*R*)-ditriflate **2** with $PhCH_2MgBr$ and PhMgBr gave (1*R*,4*R*)-(+)-2,5-dibenzylbicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-Bn-bod* (**3a**)) and (1*R*,4*R*)-(−)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-Ph-bod* (**3b**)), respectively. It is remarkable that bicyclo[2.2.2]octadiene ditriflate **2** can be isolated as a stable compound and can be used for the subsequent cross-coupling reaction while its norbornadiene analogue, bicyclo[2.2.2]heptadiene ditriflate, readily undergoes decomposition during the workup.[2]

Some of the chiral dienes **3** were found to be optically resolved by use of a chiral stationary phase column (Chiralcel OJ) of a preparative size (route B). Both enantiomers of **3a** and **3b** were obtained in an enantiomerically pure form. The enantiomers of C_2-symmetric chiral dienes substituted with 2-methylphenyl (**3c**) and 3,5-dimethylphenyl (**3d**) groups were also separated efficiently by the chiral HPLC technique. Route C shows the preparation route by way of optical resolution of ditriflate **2**. This route is particularly useful for the diaryl-substituted dienes whose enantiomers are not separable using the chiral HPLC columns. Enantiomerically pure (*R*,*R*)-dienes containing 4-methoxyphenyl (**3e**) and 4-trifluoromethylphenyl (**3f**) were obtained through this route. Considering that the optical resolution of diketone **1** by recrystallization of the diastereomeric dihydrazone shown in route A is not very efficient, route B or C is more practically useful than route A.

Treatment of (*S*,*S*)-Ph-bod* (**3b**) with $[RhCl(C_2H_4)_2]_2$ in CH_2Cl_2 at room temperature for 30 min gave diene–rhodium complex [RhCl((*S*,*S*)-Ph-bod* (**3b**))]$_2$, whose X-ray crystal structure is shown in Figure 1. The steric difference between a bulky phenyl group and a small hydrogen on the ligand is effectively dissecting the space in a C_2-fashion, thereby creating a very good chiral environment around the rhodium.

The C_2-symmetric bicyclo[2.2.2]octa-2,5-dienes **3** containing substituents at 2 and 5 positions were examined as chiral ligands for the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids **5** to α,β-unsaturated ketones **4** (Scheme 2).[8,13–15] As a general procedure, to a solution containing an arylboronic acid **5** (0.60 mmol) and

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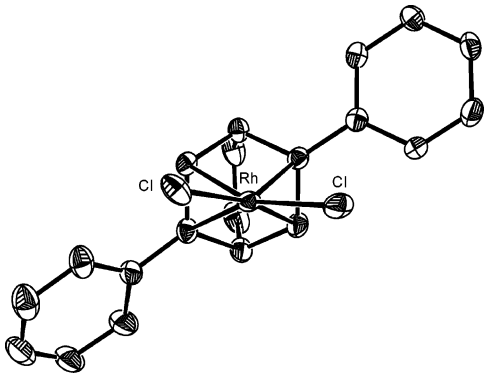
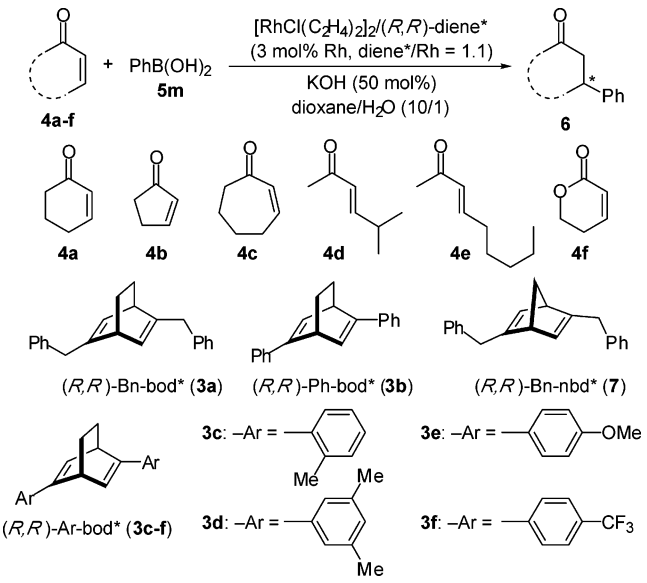


FIGURE 1. ORTEP illustration of [RhCl((*S*,*S*)-Ph-bod* (**3b**))]$_2$ with thermal ellipsoids drawn at the 50% probability level (shown as a monomer for clarity). The ORTEP for the whole dimeric molecule is shown in the Supporting Information.

SCHEME 2



a chiral diene−rhodium catalyst[16] (3 mol %) generated from [RhCl(C_2H_4)$_2$]$_2$ and a chiral diene ligand (*R*,*R*)-**3** in dioxane (1.0 mL) was added enone **4** (0.30 mmol) and 1.5 M aqueous KOH (0.1 mL), and the mixture was stirred at 30 °C for 1 h. The 1,4-addition product **6** was isolated by silica gel chromatography after the filtration through a pad of silica gel. Table 1 summarizes the results obtained for the addition of phenylboronic acid (**5m**) to 2-cyclohexenone (**4a**) and 5-methyl-3-hexene-2-one (**4d**),

TABLE 1. Asymmetric 1,4-Addition of Phenylboronic Acid (5m) to Enones 4a and 4d Catalyzed by [RhCl(C_2H_4)$_2$]$_2$/Dienes (3)[a]

		[yield (%)][b] % ee[c] (config)	
entry	ligand	**6am**	**6dm**
1	**3a**	[97] 95 (*R*)	[97] 94 (*R*)
2	**3b**	[97] 96 (*R*)	[95] 85 (*R*)
3	**3c**	[97] 83 (*R*)	[89] 78 (*R*)
4	**3d**	[99] 81 (*R*)	[88] 87 (*R*)
5	**3e**	[99] 95 (*R*)	[91] 78 (*R*)
6	**3f**	[96] 94 (*R*)	[90] 92 (*R*)

[a] The reaction was carried out with enone **4a** or **4d** (0.30 mmol), phenylboronic acid (**5m**, 0.60 mmol), [RhCl(C_2H_4)$_2$]$_2$ (3 mol % Rh), diene (**3**, diene/Rh = 1.1/1.0), and 1.5 M aq KOH (0.10 mL) in dioxane (1.0 mL) at 30 °C for 1 h. [b] Isolated yield after silica gel chromatography. [c] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OD-H: hexane/2-propanol = 98/2).

which were chosen as a typical cyclic enone and a typical acyclic enone, respectively. The addition to 2-cyclohexenone (**4a**) proceeded smoothly at 30 °C with all of the diene ligands to give high yields (>96%) of 3-phenylcyclohexanone (**6am**) whose absolute configuration is *R*. Highest enantioselectivity (96% ee) was observed with Ph-bod* (**3b**). Bn-bod* (**3a**) and diaryl-dienes containing para substituents **3e** and **3f** also exhibited high enantioselectivities (94−95% ee) while diaryl-dienes substituted at ortho or meta positions **3c** and **3d** were less enantioselective ligands. For the acyclic enone **4d**, Bn-bod* (**3a**) was more enantioselective than diaryl-substituted dienes including Ph-bod* (**3b**), giving **6dm** of 94% ee. Of the diaryl-substituted dienes, that substituted with 4-trifluoromethylphenyl groups (**3f**) was better than the others. It is important that the 1,4-addition was completed at 30 °C within 1 h. It follows that the catalytic activity of the diene−rhodium complexes is higher than that of rhodium complexes coordinated with chiral phosphorus ligands, typically binap.[14]

The dienes Bn-bod* (**3a**) and Ph-bod* (**3b**), which showed the highest enantioselectivity in the asymmetric 1,4-addition to linear enone **4d** and cyclic enone **4a**, respectively, were examined for their ability in the addition to some other linear and cyclic enones and a cyclic α,β-unsaturated ester. The results are summarized in Table 2, which also contains the data reported using Bn-nbd* (**7**)[2] for comparison. In general, the results obtained with Bn-bod* (**3a**) are almost the same as those obtained with Bn-nbd* (**7**), indicating that the chiral environments constructed around the rhodium center by two benzyl groups on the diene ligands are almost the same irrespective of their diene backbone, bicyclo[2.2.2]-octadiene (bod) or bicyclo[2.2.1]heptadiene (nbd). Both of these dibenzyl-substituted dienes **3a** and **7** showed high enantioselectivity for linear enones **4d** and **4e** (entries 4 and 5), while their enantioselectivity for cyclic enones was not particularly high. The superiority of Ph-bod* (**3b**) to the dibenzyl-substituted dienes was observed for all the cyclic enones and cyclic enoate examined (entries 1−3 and 6). In particular, cyclopentenone (**4b**) gave the phenylation product **6bm** with 99% enantioselectivity.

The enantioselectivity was kept high for several types of arylboronic acids in the 1,4-addition to cyclopentenone (**4b**) and 3-nonen-2-one (**4e**) catalyzed by rhodium complexes coordinated with Ph-bod* (**3b**) and Bn-bod* (**3a**),

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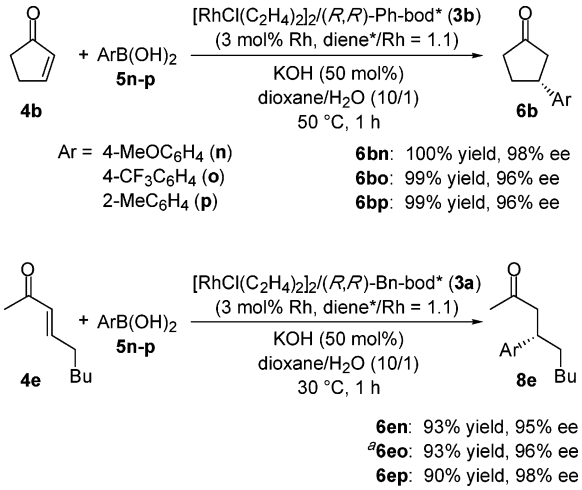
(16) We presume the formation of [Rh(OH)(**3**)]$_2$ as an active catalyst.

TABLE 2. Asymmetric 1,4-Addition of Phenylboronic Acid (5m) to Enones 4 Catalyzed by $[RhCl(C_2H_4)_2]_2$/(*R*,*R*)-dienes (3a, 3b, and 7)[a]

entry	product 6	[yield (%)][b] % ee[c] (config) Bn-bod* (3a)	Ph-bod* (3b)	Bn-nbd* (7)
1	**6am**	[97] 95 (*R*)	[97] 96 (*R*)	[94] 96 (*R*)[d]
2[e]	**6bm**	[94] 86 (*R*)	[97] 99 (*R*)	[88] 88 (*R*)[d]
3[e]	**6cm**	[91] 91 (*R*)	[95] 92 (*R*)	[81] 90 (*R*)[d]
4[f]	**6dm**	[97] 94 (*R*)	[95] 85 (*R*)	[81] 97 (*R*)[d]
5	**6em**	[94] 98 (*S*)	[90] 83 (*S*)	[84] 95 (*S*)
6[f]	**6fm**	[79] 65 (*R*)	[75] 95 (*R*)	[44] 89 (*R*)

[a] The reaction was carried out with enone **4a**−**f** (0.30 mmol), phenylboronic acid (**5m**, 0.60 mmol), $[RhCl(C_2H_4)_2]_2$ (3 mol % Rh), diene (**3a**, **3b**, and **7**, diene/Rh = 1.1/1.0), and 1.5 M aq KOH (0.10 mL) in dioxane (1.0 mL) at 30 °C for 1 h. [b] Isolated yield after silica gel chromatography. [c] Determined by HPLC analysis with chiral stationary phase columns: Chiralcel OD-H for **6am**, **6cm**, **6dm**, and **6em**; OB-H for **6bm**; OG for **6fm**. [d] Reported in ref 2. [e] At 50 °C. [f] For 3 h.

SCHEME 3[a]



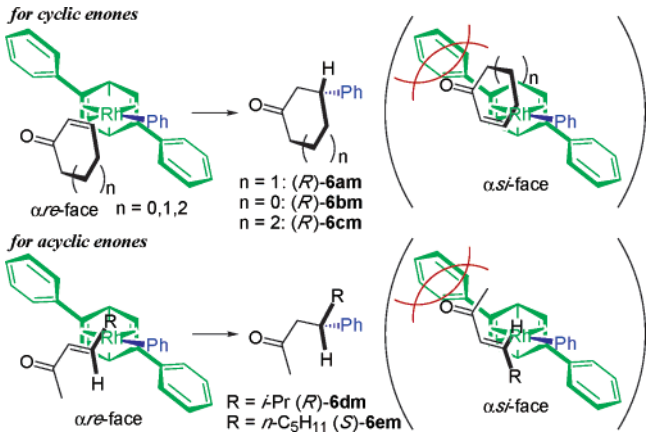
[a] The reaction was carried out for 3 h.

respectively (Scheme 3). The addition of arylboronic acids substituted with methoxy (**5n**) or trifluoromethyl group (**5o**) at the para position and methyl group at the ortho position (**5p**) all gave the corresponding 1,4-addition products with over 95% enantioselectivity for both **4b** and **4e**.

The rhodium complex coordinated with the chiral bicyclo[2.2.2]octa-2,5-dienes **3** of (*R*,*R*) absolute configuration constructs an effective C_2-symmetric environment with the benzyl or aryl substituents located at upper left and lower right positions (Scheme 4). At the addition of a phenylrhodium species to enones in the catalytic cycle,[17] the olefinic double bond of enones coordinates to the rhodium in a manner avoiding the steric repulsions between the substituent on the diene ligand and a carbonyl moiety of the enones. The alkyl substituent at the β-position is not a decisive factor on controlling the enantioface of olefin coordination. Thus, both cyclic enones and linear enones undergo the phenylrhodation from their α*re*-face giving the 1,4-arylation products of the observed absolute configuration.

(17) We have established the catalytic cycle of the rhodium-catalyzed 1,4-addition reactions: see ref 14.

SCHEME 4



Conclusions

We described the preparation of enantiomerically pure C_2-symmetric bicyclo[2.2.2]octa-2,5-dienes which bear benzyl, phenyl, and substituted phenyl groups at 2 and 5 positions. These chiral diene ligands showed high enantioselectivity (up to 99% ee) in the rhodium-catalyzed asymmetric 1,4-addition of arylboronic acids to α,β-unsaturated ketones. We are currently applying these chiral diene ligands to a variety of catalytic asymmetric reactions, especially to those where the chiral diene ligands are more suitable than other types of ligands in catalytic activity. The rhodium-catalyzed addition reactions to fumaric/maleic compounds,[3] *N*-sulfonylimines,[6] and alkynals[7] are some of the examples.

Experimental Section

Preparation of 2,5-Disubstituted Bicyclo[2.2.2]octa-2,5-dienes 3. The enantiomerically pure dienes were obtained by optical resolution of racemic compounds, diketone **1** (route A), diene **3** (route B), or ditriflate **2** (route C).

(A) Resolution of Racemic Bicyclo[2.2.2]octane-2,5-dione (1). To a mixture of bicyclo[2.2.2]octane-2,5-dione (*dl*-**1**) (7.43 g, 53.8 mmol) and (*R*)-5-(1-phenylethyl)semioxamazide[11] (22.3 g, 107.6 mmol) in 250 mL of ethanol was added a small amount of sodium acetate and acetic acid, and the mixture was heated to reflux for 3 h. After it was cooled to room temperature, the precipitates formed were collected on a filter and washed with ethanol. The solid product was recrystallized three times from methanol to give 3.34 g (12% yield) of the dihydrazone. For hydrolysis of the hydrazone, a suspension of the dihydrazone in 100 mL of 20% sulfuric acid was heated to reflux for 4 h. The reaction mixture was extracted with CH_2Cl_2 four times. The combined organic layers were washed with 0.2 N NaOH twice and then dried over magnesium sulfate. Removal of the solvent gave the crude diketone **1**, which is 97.5% ee by HPLC analysis with chiral stationary phase column, Chiralcel OJ (hexane/2-PrOH = 1/1). The crude diketone was purified by recrystallization from ethanol to give 335 mg (4.5% yield) of (1*R*,4*R*)-bicyclo[2.2.2]-octane-2,5-dione ((*R*,*R*)-**1**) as a white solid which is >99% ee by HPLC analysis. $[\alpha]^{20}_D$ −55 (*c* 1.22, $CHCl_3$) (lit.[12d] $[\alpha]^{20}_D$ +50 (*c* 0.55, $CHCl_3$) for (*S*,*S*)-**1**).

(1*R*,4*R*)-2,5-Bis(trifluoromethanesulfonyloxy)bicyclo-[2.2.2]octa-2,5-diene ((*R*,*R*)-2). Lithium diisopropylamide (LDA) was generated by dropwise addition of a 1.59 M solution of *n*-BuLi (692 μL, 1.10 mmol) in hexane to a −78 °C solution of diisopropylamine (154 μL, 1.10 mmol) in 0.50 mL of THF. This solution was stirred for an additional 20 min before a solution of (1*R*,4*R*)-bicyclo[2.2.2]octane-2,5-dione ((*R*,*R*)-**1**) (50.0

mg, 0.362 mmol) in 1.0 mL of THF was slowly added at −78 °C. The resulting mixture was stirred at −78 °C for an additional 1 h, before a solution of *N*-(2-pyridyl)triflimide (394 mg, 1.10 mmol) in 1.0 mL of THF was slowly added at −78 °C. This mixture was warmed to room temperature while being stirred for 2 days. Ice water was added to quench the reaction and the organic solvent was removed in vacuo. The aqueous layer was extracted with Et_2O three times. The combined organic layers were washed with 10% NaOH and then dried over magnesium sulfate. Removal of the solvent gave the crude product, which was purified by chromatography on silica gel column (hexane/diethyl ether = 10/1) to give 102 mg (70% yield) of (1*R*,4*R*)-2,5-bis(trifluoromethanesulfonyloxy)bicyclo-[2.2.2]octa-2,5-diene ((*R*,*R*)-**2**) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 1.56−1.64 (m, 2H), 1.82−1.90 (m, 2H), 3.69−3.73 (m, 2H), 6.16 (dd, J = 7.2 and 2.9 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 24.7, 40.2, 118.6 (q, J_{C-F} = 320 Hz), 119.4, 155.1. Anal. Calcd for $C_{10}H_8F_6O_6S_2$: C, 29.86; H, 2.00. Found: C, 29.99; H, 2.13.

(1*R*,4*R*)-2,5-Dibenzylbicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-Bn-bod* (3a)). To a mixture of (1*R*,4*R*)-2,5-bis(trifluoromethanesulfonyloxy)bicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-**2**) (78.9 mg, 0.20 mmol) and $PdCl_2$(dppf) (1.4 mg, 2.0 μmol) in 1.5 mL of Et_2O was added benzylmagnesium bromide (3.33 mL, 0.36 M, 1.2 mmol) in Et_2O at room temperature, and the reaction mixture was heated to reflux for 24 h. After being cooled to room temperature, the reaction mixture was quenched with water and extracted with Et_2O. The combined organic layers were dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by preparative TLC (silica gel, hexane/ethyl acetate = 10/1) and GPC to give 33.8 mg (59% yield) of (1*R*,4*R*)-2,5-dibenzylbicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-**3a**) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.07−1.15 (m, 2H), 1.18−1.26 (m, 2H), 3.22−3.28 (m, 2H), 3.43 (s, 4H), 5.82 (dd, J = 6.1 and 1.2 Hz, 2H), 7.12 (d, J = 7.6 Hz, 4H), 7.17 (t, J = 7.6 Hz, 2H), 7.26 (t, J = 7.6 Hz, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 26.1, 40.1, 41.1, 125.9, 128.15, 128.24, 129.0, 139.7, 147.2. Anal. Calcd for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 92.17; H, 7.85. $[\alpha]^{20}_D$ +86 (*c* 0.71, $CHCl_3$).

(1*R*,4*R*)-2,5-Diphenylbicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-Ph-bod* (3b)). Grignard cross-coupling of (*R*,*R*)-**2** (78.9 mg, 0.20 mmol) with phenylmagnesium bromide (1.0 mL, 1.2 M, 1.2 mmol) and $PdCl_2$(dppf) (1.4 mg, 2.0 μmol) in Et_2O was carried out at reflux for 8 h in a manner similar to the preparation of (*R*,*R*)-**3a**. The crude product was purified by preparative TLC (silica gel, hexane/benzene = 10/1) to give 39.5 mg (78% yield) of (1*R*,4*R*)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-**3b**) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 4H), 4.23 (d, J = 6.3 Hz, 2H), 6.63 (dd, J = 6.3 and 2.0 Hz, 2H), 7.22 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 4H), 7.44 (d, J = 7.5 Hz, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 25.8, 40.0, 124.7, 126.8, 128.5, 129.1, 138.2, 146.8. Anal. Calcd for $C_{20}H_{18}$: C, 92.98; H, 7.02. Found: C, 93.03; H, 7.14. $[\alpha]^{20}_D$ −30 (*c* 0.72, $CHCl_3$).

(B) Resolution of Racemic 2,5-Disubstituted Bicyclo-[2.2.2]octa-2,5-dienes. Racemic 2,5-bis(trifluoromethanesulfonyloxy)bicyclo[2.2.2]octa-2,5-diene (*dl*-**2**) and dienes *dl*-**3a** and *dl*-**3b** were prepared in a same manner as described above. Enantiomerically pure samples of dienes **3a** and **3b** were obtained by separation of the racemic dienes on Chiralcel OJ column with hexane/2-propanol = 200/1, flow = 5 mL/min, wavelength = 254 nm, and hexane/2-propanol = 98/2, flow = 8 mL/min, wavelength = 254 nm, respectively.

(1*R*,4*R*)-2,5-Di(2-methylphenyl)bicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-2-MeC_6H_4-bod* (3c)). In a manner similar to the preparation of (*R*,*R*)-**3a**, cross-coupling of *dl*-**2** (402 mg, 1.0 mmol) with 2-methylphenylmagnesium bromide (6.5 mL, 0.93 M, 6.0 mmol) and $PdCl_2$(dppf) (7.3 mg, 10 μmol) in Et_2O for 24 h gave 207 mg (72% yield) of racemic 2,5-di(2-methylphenyl)bicyclo[2.2.2]octa-2,5-diene (*dl*-**3c**) as a colorless oil. Enantiomerically pure diene (*R*,*R*)-**3c** was obtained by separation of the racemic diene on Chiralcel OJ column with hexane/2-propanol = 90/10, flow = 10 mL/min, wavelength = 254 nm. ^{1}H NMR ($CDCl_3$) δ 1.52−1.64 (m, 4H), 2.30 (s, 6H), 3.83 (dd, J = 6.2 and 1.9 Hz, 2H), 6.34 (dd, J = 6.2 and 1.9 Hz, 2H), 7.11−7.20 (m, 8H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 20.7, 25.5, 43.0, 125.6, 126.7, 128.1, 130.2, 131.1, 135.6, 140.3, 148.4. Anal. Calcd for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 92.40; H, 7.81. $[\alpha]^{20}_D$ +178 (*c* 0.65, $CHCl_3$).

(1*R*,4*R*)-2,5-Bis(3,5-dimethylphenyl)bicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-3,5-Me$_2$C$_6$H$_3$-bod* (3d)). Similarly, the reaction of *dl*-**2** (402 mg, 1.0 mmol) with 3,5-dimethylphenylmagnesium bromide (5.31 mL, 1.13 M, 6.0 mmol) and $PdCl_2$(dppf) (7.3 mg, 10 μmol) in Et_2O gave 257 mg (82% yield) of racemic 2,5-bis(3,5-dimethylphenyl)bicyclo[2.2.2]octa-2,5-diene (*dl*-**3d**) as a white solid. Enantiomerically pure diene (*R*,*R*)-**3d** was obtained by separation of the racemic diene on Chiralcel OJ column with hexane/2-propanol = 90/10, flow = 10 mL/min, wavelength = 254 nm. ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 4H), 2.31 (s, 12H), 4.18 (d, J = 6.3 Hz, 2H), 6.58 (dd, J = 6.3 and 1.7 Hz, 2H), 6.86 (s, 2H), 7.05 (s, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 21.4, 25.8, 40.2, 122.7, 128.4, 128.9, 137.9, 138.3, 146.9. Anal. Calcd for $C_{24}H_{26}$: C, 91.67; H, 8.33. Found: C, 91.39; H, 8.42. $[\alpha]^{20}_D$ −13 (*c* 0.66, $CHCl_3$).

(C) Resolution of Racemic 2,5-Bis(trifluoromethanesulfonyloxy)bicyclo[2.2.2]octa-2,5-diene (2). Racemic 2,5-bis(trifluoromethanesulfonyloxy)bicyclo[2.2.2]octa-2,5-diene (*dl*-**2**) was prepared in the same manner as described above. Enantiomerically pure ditriflate (*R*,*R*)-**2** was obtained by separation of the racemic ditriflate on Chiralcel OJ column with hexane/2-propanol = 98/2, flow = 5 mL/min, wavelength = 210 nm.

(1*R*,4*R*)-2,5-Di(4-methoxyphenyl)bicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-4-MeOC_6H_4-bod* (3e)). Grignard cross-coupling of (*R*,*R*)-**2** (121 mg, 0.30 mmol) with 4-methoxyphenylmagnesium bromide (2.0 mL, 1.2 mmol) and $PdCl_2$(dppf) (2.2 mg, 3.0 μmol) in Et_2O for 6 h, followed by aqueous workup and GPC purification, gave 60.9 mg (64% yield) of (1*R*,4*R*)-2,5-di(4-methoxyphenyl)bicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-**3e**) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 4H), 3.80 (s, 6H), 4.15 (d, J = 6.4 Hz, 2H), 6.51 (dd, J = 6.4 and 2.1 Hz, 2H), 6.87 (d, J = 8.9 Hz, 4H), 7.37 (d, J = 8.9 Hz, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 25.9, 40.0, 55.4, 113.9, 125.9, 127.1, 131.0, 146.5, 158.7. Anal. Calcd for $C_{22}H_{22}O_2$: C, 82.99; H, 6.96. Found: C, 82.73; H, 7.08. $[\alpha]^{20}_D$ −5.0 (*c* 0.55, $CHCl_3$).

(1*R*,4*R*)-2,5-Bis(4-trifluoromethylphenyl)bicyclo[2.2.2]-octa-2,5-diene ((*R*,*R*)-4-CF_3C$_6$H$_4$-bod* (3f)). Grignard cross-coupling of (*R*,*R*)-**2** (121 mg, 0.30 mmol) with 4-trifluoromethylphenylmagnesium bromide (2.0 mL, 1.2 mmol) and $PdCl_2$(dppf) (2.2 mg, 3.0 μmol) in Et_2O for 6 h, followed by aqueous workup and purification by preparative TLC (silica gel, hexane/benzene = 20/1), gave 82.9 mg (70% yield) of (1*R*,4*R*)-2,5-bis(4-trifluoromethylphenyl)bicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-**3f**) as a white solid. ^{1}H NMR ($CDCl_3$) δ 1.58, (s, 4H), 4.26 (d, J = 6.4 Hz, 2H), 6.75 (dd, J = 6.4 and 2.0 Hz, 2H), 7.52 (d, J = 8.3 Hz, 4H), 7.58 (d, J = 8.3 Hz, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$) δ 25.5, 40.1, 124.3 (q, J = 271 Hz), 125.0, 125.5 (q, J = 3.8 Hz), 129.0 (q, J = 32 Hz), 131.4, 141.4, 145.8. Anal. Calcd for $C_{22}H_{16}F_6$: C, 67.01; H, 4.09. Found: C, 67.08; H, 4.18. $[\alpha]^{20}_D$ −12 (*c* 0.84, $CHCl_3$).

Rhodium-Catalyzed Asymmetric 1,4-Addition of Arylboronic Acids to Enones. The reaction conditions and results are summarized in Tables 1 and 2, and Scheme 3. A typical experimental procedure (entry 2 in Table 1) is shown below: A solution of $[RhCl(C_2H_4)_2]_2$ (1.8 mg, 9.0 μmol Rh), (1*R*,4*R*)-2,5-diphenylbicyclo[2.2.2]octa-2,5-diene ((*R*,*R*)-**3b**) (2.6 mg, 9.9 μmol), and phenylboronic acid (**5m**) (73.2 mg, 0.60 mmol) in 1 mL of dioxane was stirred at room temperature for 5 min. To this mixture was added 2-cyclohexenone (**4a**) (28.8 mg, 0.30 mmol) and aqueous KOH (0.1 mL, 1.5 M, 0.15 mmol). After being stirred at 30 °C for 1 h, the mixture was passed through a short silica gel column (eluent: diethyl ether). Evaporation of the solvent followed by preparative TLC (silica gel, hexane/ethyl acetate = 3/1) gave 50.8 mg (97% yield)

of (*R*)-**6am**, which is 96% ee. The products **6** obtained by the rhodium-catalyzed asymmetric 1,4-addition were fully characterized by comparison of their spectral and analytical data with those reported in the literature: ref 13a for **6am**, **6bm**, **6cm**, **6dm**, and **6em**. ref 13c for **6fm**, and ref 13d for **6bn** and **6bo**.

3-(2-Methylphenyl)cyclopentanone (6bp): The ee was determined on a Chiralcel OD-H column with hexane/2-propanol = 98/2, flow = 0.3 mL/min. ^{1}H NMR ($CDCl_3$) δ 1.97−2.06 (m, 1H), 2.25−2.42 (m, 3H), 2.38 (s, 3H), 2.44−2.51 (m, 1H), 2.63 (dd, J = 18.3 and 7.5 Hz, 1H), 3.57−3.65 (m, 1H), 7.13−7.23 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 19.6, 30.0, 38.3, 38.5, 45.3, 124.7, 126.4, 126.5, 130.6, 135.9, 141.0, 218.6. Anal. Calcd for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.43; H, 8.29. $[\alpha]^{20}_D$ +59 (*c* 1.00, $CHCl_3$) for the *R* isomer of 96% ee.

4-(4-Methoxyphenyl)nonan-2-one (6en): The ee was determined on a Chiralcel OJ-H column with hexane/2-propanol = 100/1, flow = 0.5 mL/min. ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 7.0 Hz, 3H), 1.08−1.27 (m, 6H), 1.47−1.62 (m, 2H), 2.00 (s, 3H), 2.65 (dd, J = 15.9 and 7.1 Hz, 1H), 2.68 (dd, J = 15.9 and 7.3 Hz, 1H), 3.05 (dtd, J = 9.5, 7.3 and 5.4 Hz, 1H), 3.78 (s, 3H), 6.82 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 14.0, 22.5, 27.0, 30.6, 31.7, 36.6, 40.6, 51.2, 55.2, 113.8, 128.3, 136.6, 158.0, 208.2. Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.64; H, 9.91. $[\alpha]^{20}_D$ +18 (*c* 1.02, $CHCl_3$) for the *S* isomer of 95% ee.

4-(4-Trifluoromethylphenyl)nonan-2-one (6eo): The ee was determined on a Chiralcel AS column with hexane/2-propanol = 500/1, flow = 0.3 mL/min. ^{1}H NMR ($CDCl_3$) δ 0.83 (t, J = 6.9 Hz, 3H), 1.03−1.30 (m, 6H), 1.50−1.67 (m, 2H), 2.04 (s, 3H), 2.73 (d, J = 7.1 Hz, 2H), 3.20 (broad quint, J = 7.3 Hz, 1H), 7.29 (d, J = 8.0 Hz, 2H), 7.54 (d, J = 8.0 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 14.0, 22.4, 27.0, 30.6, 31.7, 36.2, 40.9, 50.5, 124.3 (q, J = 271 Hz), 125.4 (q, J = 3.8 Hz), 127.9, 128.6 (q, J = 32 Hz), 149.0 (q, J = 1.5 Hz), 207.1. Anal. Calcd for $C_{16}H_{21}OF_3$: C, 67.12; H, 7.39. Found: C, 67.04; H, 7.41. $[\alpha]^{20}_D$ +8.5 (*c* 0.93, $CHCl_3$) for the *S* isomer of 97% ee.

4-(2-Methylphenyl)nonan-2-one (6ep): The ee was determined on a Chiralcel OJ-H column with hexane/2-propanol = 100/1, flow = 0.3 mL/min. ^{1}H NMR ($CDCl_3$) δ 0.82 (t, J = 6.9 Hz, 3H), 1.06−1.27 (m, 6H), 1.50−1.63 (m, 2H), 2.01 (s, 3H), 2.36 (s, 3H), 2.68 (dd, J = 12.3 and 7.0 Hz, 1H), 2.72 (dd, J = 12.3 and 7.3 Hz, 1H), 3.44 (broad quint, J = 7.3 Hz, 1H), 7.05−7.18 (m, 4H). ^{13}C{^{1}H} NMR ($CDCl_3$) δ 14.0, 19.8, 22.5, 26.9, 30.6, 31.9, 35.7, 36.5, 50.6, 125.5, 125.8, 126.2, 130.4, 136.0, 143.1, 208.1. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.56; H, 10.51. $[\alpha]^{20}_D$ +17 (*c* 0.96, $CHCl_3$) for the *S* isomer of 98% ee.

X-ray Crystal Structure of [RhCl((*S*,*S*)-3b)]$_2$. A red dichloromethane solution of [RhCl((*S*,*S*)-**3b**)]$_2$ was prepared. Crystals suitable for X-ray structural analysis were obtained by layering with hexane at room temperature. A red prism of dimensions 0.50 × 0.40 × 0.30 mm^3 was mounted on a glass fiber. All measurements were made on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo Kα radiation. Indexing was performed from 3° oscillations that were exposed for 30 s. The crystal-to-detector distance was 127.40 mm.

Cell constants and an orientation matrix for data collection corresponded to a primitive monoclinic cell with dimensions a = 13.45(1) Å, b = 19.80(1) Å, c = 18.97(1) Å, α = 90°, β = 93.82(3)°, γ = 90°, V = 5039.6(6) Å^3. For Z = 6 and fw = 793.44, and the calculated density is 1.57 g/cm. Based on the systematic absences of 0k0 (k ± 2n), packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be P21 (no. 4).

The data were collected at a temperature of −150 ± 1 °C to a maximum 2θ value of 55.0°. A total of 74 oscillation images were collected. A sweep of data was done using ω scans from 130.0° to 190.0° in 3.0° steps, at χ = 45.0° and ϕ = 0.0°. The exposure rate was 90.0 s/deg. A second sweep was performed using ω scans from 0.0° to 162.0° in 3.0° steps, at χ = 45.0° and ϕ = 180.0°. The exposure rate was 90.0 s/deg. The crystal-to-detector distance was 127.40 mm. Readout was performed in the 0.100 mm pixel mode.

Of the 48 571 reflections that were collected, 11 826 were unique (R_{int} = 0.021); equivalent reflections were merged. The linear absorption coefficient, μ, for Mo Kα radiation is 11.7 cm^{-1}. The data were corrected for Lorentz and polarization effects.

The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final cycle of full-matrix least-squares refinement on F was based on 10 449 observed reflections (I > 3.00σ(I)) and 1298 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of $R = \sum||F_o| - |F_c||/\sum|F_o| = 0.029$, $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2} = 0.043$.

The standard deviation of an observation of unit weight was 2.12. Unit weights were used. Plots of $\sum w(|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 5.30 and −3.18 e$^-$/Å^3, respectively.

All calculations were performed using the CrystalStructure crystallographic software package and Tables S1−S12 in the Supporting Information provide the full crystallographic data for the X-ray structure.

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Supporting Information Available: Tables of complete X-ray crystallographic data for [RhCl((*S*,*S*)-**3b**)]$_2$ and the corresponding CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

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