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Some new C_2-symmetric bicyclo[2.2.1]heptadiene ligands: synthesis and catalytic activity in rhodium(I)-catalyzed asymmetric 1,4- and 1,2-additions

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Abstract—C_2-Symmetric bicyclo[2.2.1]hepta-2,5-dienes with various substituents (R=Bn, *i*-Bu, *c*-Hex, allyl) are prepared starting from the corresponding enantiomerically pure bis-triflate (R=OTf). These chiral ligands are tested and compared in rhodium(I)-catalyzed 1,4- and 1,2-addition of phenylboronic acid to cyclic enones and aryl aldehydes, respectively. Some interesting reactivity and selectivity effects due to the introduction of sterically demanding or olefinic substituents are reported. Moreover, remarkably high catalytic activity is observed for the rhodium(I)-catalyzed 1,2-addition.

1. Introduction

The use of chiral dienes as spectator ligands in asymmetric catalysis has been recently explored by various groups.[1–3] Some of these chiral dienes show very high reactivity and selectivity in several rhodium- and iridium-catalyzed asymmetric reactions.[2] From the various backbones reported,[2,4,5] chiral 2,5-disubstituted bicyclo[2.2.1]heptadienes (nbd*) and bicyclo[2.2.2]octadienes appeared to be privileged structures, showing high reactivity and selectivity in several asymmetric reactions.[2,3] Recently a new C_2-symmetric diene ligand based on a bicyclo[3.3.0]octadiene framework was synthesized and showed high reactivity and selectivity in the rhodium(I)-catalyzed asymmetric arylation of *N*-tosylarylimines.[6] A major drawback of these bicyclo[2.2.1]heptadienes is their elaborate synthesis.[2a] Our group has been able to synthesize for the first time the intermediate bis-triflate **3** as a racemic and stable compound in good yield.[7] We used the chiral bis-triflate (1*S*,4*S*)-**3** as a key intermediate in a concise synthesis of highly selective chiral diene ligands **4a–d** possessing the bicyclo[2.2.1]hepta-2,5-diene backbone. Very recently, the same approach towards **4a**, based on our own method for obtaining previously inaccessible bis-triflate **3**,[7] has also been reported by Hayashi et al.,[2q] prompting us to disclose our results on sterically demanding ligands **4b** and **4c** and diallyl ligand **4d**, which have, however, not been reported before. The catalytic activity and selectivity of the corresponding rhodium(I)-complexes of these new ligands were subsequently tested in the 1,4-addition of phenylboronic acid to unsaturated cyclic ketones, and in the 1,2-addition to aryl aldehydes.

2. Results and discussion

The synthetic route towards enantiomerically pure 2,5-disubstituted bicyclo[2.2.1]heptadiene ligands **4a–d** started with the Pd(0)-catalyzed asymmetric hydrosilylation of norbornadiene, resulting in the formation of the (1*S*,2*R*,4*S*,5*R*)-diol **1** (>99% ee).[8,9] Swern oxidation, followed by enolization with KHMDS and trapping with triflating agent $PhNTf_2$ afforded bis-triflate **3** as a stable compound[10] in good yield (Scheme 1).

Bis-triflate **3** was subjected to a Pd(0)-catalyzed Grignard cross-coupling reaction resulting in Hayashi's (*S*,*S*)-Bn-nbd* (**4a**) and a set of new ligands with more sterically demanding substituents (**4b**: R=*i*-Bu, **4c**: R=*c*-Hex; Table 1, entries 2 and 3) or containing exocyclic double bonds (**4d**: R=allyl; Table 1, entry 4). Carreira et al. reported the effects of an extra exocyclic double bond.[3b] In the latter case, ^{1}H NMR indicated coordination of the metal with all three double bonds, leading to an enhanced enantioselectivity in certain cases. Therefore, the two exocyclic olefinic double bonds in the C_2-symmetrical ligand **4d** could potentially influence the reactivity and selectivity.

Keywords: Asymmetric 1,4-addition; Asymmetric 1,2-addition; Chiral norbornadienes; Transition metal catalysis.
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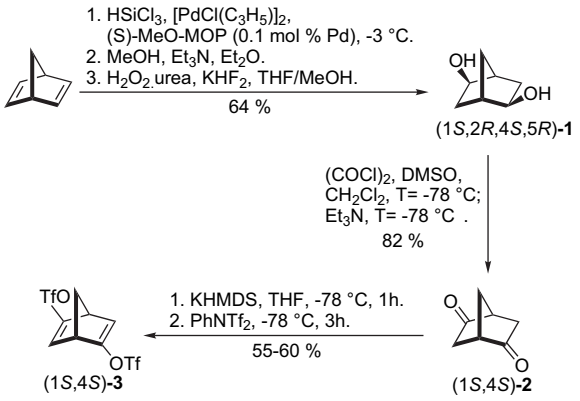
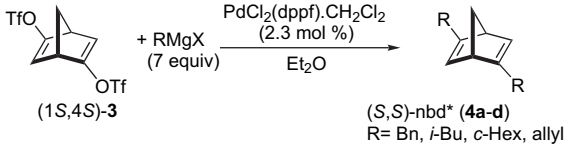


Scheme 1. Synthesis of bis-triflate **3**.

Table 1. Palladium(0)-catalyzed Grignard cross-coupling



Entry	RMgX	Product	Yield (%)
1	BnMgCl[a]	(*S*,*S*)-Bn-nbd* (**4a**)	72
2	*i*-BuMgBr[b]	(*S*,*S*)-*i*-Bu-nbd* (**4b**)	33
3	*c*-HexMgCl[b]	(*S*,*S*)-*c*-Hex-nbd*(**4c**)	77
4	AllylMgBr[c]	(*S*,*S*)-Allyl-nbd* (**4d**)	41

[a] 20 w/w % in THF.
[b] Two molar in Et_2O.
[c] One molar in Et_2O.

The cross-coupling reaction with BnMgCl (Table 1, entry 1) produced a significant amount of 1,2-diphenylethane via homocoupling. The latter readily sublimed from ligand **4a** under reduced pressure at room temperature. The ligands with *i*-Bu- (**4b**) and allyl-substituents (**4d**) appeared to be volatile because of their low molar mass, their branched structure and the absence of any functionality.

Interestingly, a study of the rhodium(I) complex of (*S*,*S*)-allyl-nbd* by ^1H NMR and APT indicated no coordination of rhodium with the exocyclic double bonds: large high field shifts are only observed for the ^1H and ^{13}C nuclei of the norbornadiene double bonds. The Rh–^{13}C coupling constants are shown in Figure 1. The largest coupling constants are observed for the ^{13}C nuclei of the norbornadiene double bonds, which are involved in the complexation. No coupling between rhodium and the carbon atoms of the exocyclic double bonds is observed, indicating that the latter are not involved in the bonding with rhodium.

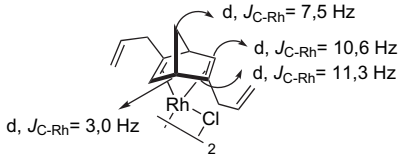


Figure 1. Coupling constants observed in APT spectra of [RhCl(*S*,*S*)-allyl-nbd*]$_2$.

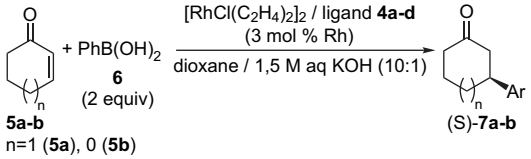
The catalytic activity of the ligands **4a–d** was subsequently evaluated in the rhodium(I)-catalyzed 1,4-addition of phenylboronic acid to some cyclic enones (Table 2).

In the addition of $PhB(OH)_2$ to 2-cyclohexenone, all of the newly synthesized ligands **4b–d** show high selectivities comparable with (*S*,*S*)-Bn-nbd* (**4a**). Remarkably, increasing sterical demand of the ligand substituents did not lead to a difference in selectivity, whereas the reaction rate is greatly influenced (entries 2 and 3). We were very pleased to see that the enantioselectivity did not drop with (*S*,*S*)-allyl-nbd* (**4d**) (entry 4). The addition to 2-cyclopentenone, a more difficult substrate, led to some surprising results. The highest selectivity was obtained with (*S*,*S*)-allyl-nbd* (**4d**) (90% ee) (entry 7), which is slightly better than the selectivity reported for (*R*,*R*)-Bn-nbd* (**4a**) (88% ee).[2a] The presence of two exocyclic double bonds seems to enhance the selectivity slightly, although the reaction rate is suppressed. The more sterically demanding (*S*,*S*)-*c*-Hex-nbd* (**4c**) showed a considerably lower reactivity than (*S*,*S*)-*i*-Bu-nbd* (**4b**), but, surprisingly, also a somewhat lower selectivity (Table 2, entries 5 and 6).

Next, our ligands were tested in the rhodium(I)-catalyzed 1,2-addition to aryl aldehydes, which is considered as a more challenging reaction.[11,12] The examples of successful asymmetric additions of arylboronic acids to aldehydes are quite scarce.[11] In general, selectivities up to 41% ee have been reported.[11a] Only very few papers recently appeared reporting higher enantioselectivities. Zhou et al. have reported the enantioselective Rh(I)-catalyzed addition of arylboronic acids to aldehydes by using a chiral spiro-monophosphite ligand, affording diarylmethanols in high yields and selectivities up to 87% ee.[13] Also phosphoramidites have been proven recently by Feringa et al. to be effective chiral ligands with selectivities of up to 75% ee.[14] Initially we tried to find optimal reaction conditions using commercially available achiral $[Rh(nbd)Cl]_2$ because of the similarity of this catalyst with our own asymmetric catalysts (Table 3).

In the absence of KOH, no conversion was observed (Table 3, entry 1)[15] whereas in dioxane/1.5 M aq KOH (10/1) **9** was

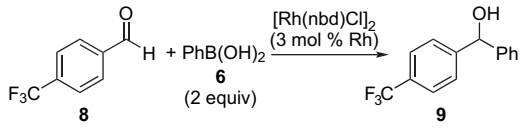
Table 2. Rhodium(I)-catalyzed asymmetric 1,4-addition of $PhB(OH)_2$ to cyclic enones



Entry	**5**	Ligand	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**5a**	**4a**	30	1.5	95	96
2	**5a**	**4b**	30	5	80	95
3	**5a**	**4c**	30	16	94	95
4	**5a**	**4d**	30	4.5	72	95
5	**5b**	**4b**	25	16[c]	73	85
6	**5b**	**4c**	25	16[c]	54	82
7	**5b**	**4d**	25	16[c]	44	90

[a] Isolated yield.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralpak AS-H).
[c] The reaction was not complete after the indicated time.

Table 3. [Rh(nbd)Cl]$_2$-catalyzed 1,2-addition of PhB(OH)$_2$ to *p*-trifluoromethylbenzaldehyde

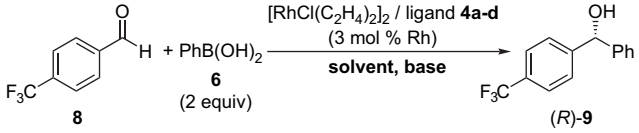


Entry	Solvent	Temp (°C)	Time (h)	Yield[a] (%)
1	Dioxane/H_2O (10:1)	60	48	0
2	Dioxane/1.5 M aq KOH (10:1)	60	48	32
3[b]	Dioxane/1.5 M aq KOH (10:3)	50	6	78
4[c]	Dioxane/1.5 M aq KOH (10:3)	50	16	50

[a] Isolated yield.
[b] PhB(OH)$_2$ of 6 equiv were added in portions to obtain complete conversion.
[c] Compound **8** (0.5 mmol), **6** (1 mmol), [Rh(C_2H_4)$_2$Cl]$_2$ (3 mol % Rh) and norbornadiene (norbornadiene/Rh, 1.1/1.0) were used.

obtained in low yield (Table 3, entry 2): up to 6 equiv of PhB(OH)$_2$ were needed to obtain full conversion in dioxane/1.5 M aq KOH (10/3) (Table 3, entry 3). In addition, when the catalyst was formed in situ, no significant improvement of the catalytic activity was noticed (Table 3, entry 4). Quite remarkably, with (*S*,*S*)-Bn-nbd* (**4a**) as a chiral ligand (Table 4), the reaction was finished within 1 h, using only 2 equiv of PhB(OH)$_2$ (Table 4, entry 1). The reaction was highly accelerated by this catalyst, although the selectivity was only 25% ee. Changing the solvent did not improve the ee (Table 4, entries 2 and 3). Adding 2 equiv of KF instead of KOH, which was reported to boost the yield and the enantioselectivity in the chiral spiro-monophosphite catalyzed reaction,[13] did not lead to any improvement (Table 4, entry 4). Lowering the reaction temperature resulted in higher selectivity up to 33% ee, while—remarkably—no loss of catalytic activity was observed (Table 4, entries 5 and 6). Changing the ligand showed higher selectivity and equal reactivity for (*S*,*S*)-*i*-Bu-nbd* (**4b**) (37% ee) (Table 4, entry 7), while the selectivity and reactivity were considerably lower for the more bulky (*S*,*S*)-*c*-Hex-nbd* (**4c**) (12% ee) (Table 4, entry 8). The selectivity of (*S*,*S*)-allyl-nbd* (**4d**) was slightly lower than for (*S*,*S*)-Bn-nbd* (**4a**) (Table 4, entries 9 and 6). Changing the rhodium source appeared to have a pronounced influence on the reactivity. Use of [Rh(acac)(C_2H_4)$_2$]$_2$ as a catalyst precursor led to a comparable enantioselectivity but a much slower reaction at room temperature in combination with **4d** (Table 4, entry 10). Using [Rh(COD)$_2$]$BF_4\cdot xH_2O$ as a catalyst precursor in combination with **4d** resulted in a high yield, albeit after a considerably longer reaction time, but poor enantioselectivity (Table 3, entry 11).

Table 4. Rhodium-catalyzed asymmetric 1,2-addition of PhB(OH)$_2$ to *p*-trifluoromethylbenzaldehyde



Entry	Ligand	Solvent/base	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**4a**	Dioxane/1.5 M aq KOH (10:3)	50	1	96	25
2	**4a**	DME/1.5 M aq KOH (10:3)	50	1	95	21
3	**4a**	Toluene/1.5 M aq KOH (10:3)	50	6	72	22
4	**4a**	Dioxane/H_2O (10:3)/KF (2 equiv)	50	3	96	25
5	**4a**	Dioxane/1.5 M aq KOH (10:3)	25	1	97	28
6	**4a**	Dioxane/1.5 M aq KOH (10:3)	0	1	95	33
7	**4b**	Dioxane/1.5 M aq KOH (10:3)	0	1	99	37
8	**4c**	Dioxane/1.5 M aq KOH (10:3)	0	16	89	12
9	**4d**	Dioxane/1.5 M aq KOH (10:3)	0	1	81	31
10[c]	**4d**	Dioxane/1.5 M aq KOH (10:3)	25	16	60	28
11[d]	**4d**	Dioxane/1.5 M aq KOH (10:3)	25	16	91	11
12	**4b**	Dioxane/EtOH/1.5 M aq KOH (5:5:3)	−25	72	23	44
13	**4b**	MeOH/1.5 M aq KOH (10:3)	25	16	93	40
14	**4b**	EtOH/1.5 M aq KOH (10:3)	0	3	98	41
15	**4b**	*i*-PrOH/1.5 M aq KOH (10:3)	0	5	92	42
16	**4b**	EtOH/1.5 M aq KOH (10:3)	−25	72	26	48

[a] Isolated yield.
[b] Determined by HPLC analysis with a chiral stationary phase column (Chiralcel OJ-H).
[c] [Rh(acac)(C_2H_4)$_2$] as a rhodium source.
[d] [Rh(COD)$_2$]$BF_4\cdot xH_2O$ as a rhodium source.

In an attempt to further improve enantioselectivity by lowering reaction temperature to −25 °C, a combination of dioxane and ethanol (1/1) was used (Table 4, entry 12), resulting in a significantly higher enantioselectivity but a slow and incomplete reaction. Because of the apparent beneficial influence of a protic solvent on the ee, dioxane was omitted and replaced by methanol, ethanol or isopropanol at 0–25 °C (Table 4, entries 13–15). In all cases, high yields and an improved selectivity were obtained as compared to dioxane (Table 4, entry 7). In methanol, the reaction rate at room temperature had decreased as compared to dioxane at 0 °C (Table 4, entries 13 and 7), while for ethanol and isopropanol at 0 °C it was comparable (Table 4, entries 14 and 15). Performing the reaction in ethanol at −25 °C (Table 4, entry 16) led to the highest selectivity observed (48% ee), but a slow and incomplete reaction resulting in low yields.

3. Conclusion

In summary, (*S*,*S*)-Bn-nbd* (**4a**) and a set of three new ligands with different substituents (*S*,*S*)-*i*-Bu-nbd* (**4b**), (*S*,*S*)-*c*-Hex-nbd* (**4c**) and (*S*,*S*)-allyl-nbd* (**4d**) were concisely synthesized starting from chiral bis-triflate (*S*,*S*)-**3**[7,2q] using a Pd(0)-catalyzed Grignard cross-coupling reaction. All ligands showed high enantioselectivities in the Rh(I)-catalyzed asymmetric 1,4-addition of phenylboronic acid to cyclic enones. A slightly enhanced selectivity was noticed in the [RhCl(*S*,*S*)-allyl-nbd*]$_2$-catalyzed 1,4-addition to cyclopentenone. This is remarkable, since NMR experiments indicate that complexation of (*S*,*S*)-allyl-nbd* with rhodium occurs exclusively via the norbornadiene endocyclic double bonds, in contrast with earlier reported comparable ligands.[3b]

Furthermore, we reported the first [RhCl(nbd*)]$_2$-catalyzed 1,2-addition of phenylboronic acids to aryl aldehydes. The presence of the alkyl side chains on the ligand appeared to be crucial for the catalytic effect, resulting in a dramatically higher reactivity as compared to unsubstituted norbornadiene as a ligand. On the other hand, enantioselectivities could be improved from poor to fair. Best conditions are ethanol or isopropanol as the solvent at 0 °C, leading to a fast reaction, high yields and 41–42% ee. Further lowering the reaction temperature to −25 °C in ethanol or a mixture of

dioxane and ethanol (1/1) resulted in higher selectivities (up to 48% ee), but a low reactivity. Nevertheless, these results are quite promising and further research is in progress.

4. Experimental

4.1. General

All reactions were carried out under argon atmosphere in dry solvents under anhydrous conditions, unless otherwise stated. $HSiCl_3$ was distilled from quinoline. Norbornadiene was passed through neutral alumina and subsequently distilled. Cyclohexenone was distilled prior to use. All other reagents were purchased and used without purification. Flash chromatography was carried out with Merck Kieselgel 60, 30–75 μm. ^1H NMR and ^{13}C NMR were recorded on a Bruker Avance 300 or a Bruker AM 500 spectrometer as indicated, with chemical shifts reported in parts per million relative to TMS, using the residual solvent signal as a standard. IR spectra were recorded on a Perkin–Elmer 160 FT-IR spectrometer. EI Mass spectra were recorded with a Hewlett–Packard 5988A mass spectrometer. APCI Mass spectra and ES Mass spectra were recorded with an Agilent 1100 series single quadrupole MS detector type VL with an APCI source and an API-ES source. Exact molecular masses were measured on a Kratos MS50TC mass spectrometer. Analytical chiral HPLC separations were performed on an Agilent 1100 series system with DAD detection and ES-MS detection.

4.2. Synthesis of (1*S*,2*R*,4*S*,5*R*)-2,5-dihydroxybicyclo[2.2.1]heptane (1)

A solution of $[PdCl(\pi\text{-}C_3H_5)]_2$ (13.7 mg, 37.4 μmol) and (*S*)-MeO-MOP (70 mg, 149 μmol) in benzene (2 mL) and pyridine (0.1 mL) was placed in a double-jacketed 50 mL flask, provided with a thermometer, under argon. $HSiCl_3$ (18 mL, 179 mmol) was added and the solution was cooled to −3 °C. Norbornadiene (8.06 mL, 75 mmol) was added slowly with a syringe pump (2 mL/h). The temperature in the reaction vessel was kept constant at −3 °C. The reaction was stirred for ca. 3 days, until it turned into a pale yellowish solid. The solvent and excess $HSiCl_3$ were removed in vacuo at room temperature. The residue was dissolved in 50.0 mL of dry Et_2O under argon and cooled to 0 °C. A mixture of dry MeOH (545.0 mL, 1.34 mol), dry Et_3N (72.0 mL, 0.552 mol) and dry Et_2O (50.0 mL) was added dropwise. After the solution was stirred at room temperature overnight, the precipitated salts were filtered off and washed with Et_2O. The filtrate was concentrated in vacuo to yield a brownish oil. To this were added KHF_2 (29.17 g, 374 mmol), dry THF (80 mL), dry MeOH (80 mL) and $H_2O_2\cdot$urea (52.70 g, 560 mmol). The resulting white suspension was stirred overnight at 60 °C. The solids were filtered off and washed with MeOH. The filtrate was concentrated in vacuo to yield a white solid. This was dissolved in 150 mL satd aq NH_4Cl and extracted with 6×500 mL $CHCl_3$/EtOH (70/30). The combined organic phases were dried over Na_2SO_4 and evaporated. Diol **1** (>99% ee) was isolated as a white solid after flash chromatography over silica gel (EtOAc/pentane, 75/25), 6.08 g (64% based on norbornadiene). ^1H NMR (500 MHz, pyridine-d_5): δ 1.58–1.59 (m, 4H), 2.02 (s, 2H), 2.42 (s, 2H), 3.94 (t, *J*=4.5 Hz, 2H), 5.94 (br s, 2H) ppm. ^{13}C NMR (125.7 MHz, pyridine-d_5): δ 31.2 (CH_2), 37.7 (CH_2), 44.2 (CH), 73.5 (CH) ppm. IR (KBr, thin film): 3233, 2960, 2931, 2889, 1351, 1088, 993, 744 cm^{-1}. EIMS *m*/*z* (rel intensity %): 110 (M^+-H_2O, 17), 92 (8), 81 (21), 66 (100), 55 (38), 41 (45). $[\alpha]_D^{25}$ +8.8 (*c* 1.0, EtOH). Mp 162 °C.

4.3. Synthesis of (1*S*,4*S*)-bicyclo[2.2.1]heptane-2,5-dione (2)

Dry CH_2Cl_2 (500.0 mL) was cooled to −78 °C and oxalylchloride (18.0 mL, 189 mmol) was added under argon and magnetic stirring. DMSO (26.8 mL, 378 mmol) was added dropwise and the solution was stirred for 5 min. Diol **1** (6.10 g, 43 mmol) was dissolved in 1000 mL dry CH_2Cl_2 and canulated to the Swern reagent. The resulting solution was stirred for another 20 min. Et_3N (104.0 mL, 686 mmol) was added, and after 1 h TLC indicated complete conversion of the diol. HCl of 1 N (500 mL) was added and the mixture was extracted with CH_2Cl_2/Et_2O (1/1, 4× 500 mL). The combined organic phases were washed with satd aq $NaHCO_3$ (1000 mL) and brine (1000 mL) and dried over $MgSO_4$. The filtrate was concentrated in vacuo. The resulting yellow oil was purified by flash chromatography over silica gel (Et_2O/pentane, 2/1) resulting in a white solid, giving 4.82 g (82%) of diketone **2** (>99% ee). ^1H NMR (500 MHz, $CDCl_3$): δ 2.08–2.10 (m, 2H), 2.10–2.18 (ddd, *J*=2, 4, 18 Hz, 2H), 2.33–2.42 (ddd, *J*=2, 4, 18 Hz, 2H), 2.97–3.00 (td, *J*=1.6, 6.2 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 36.4 (CH_2), 39.0 (CH_2), 48.6 (CH), 212.3 (C). IR (KBr, thin film): 2960, 1753, 1736, 1406, 1268, 1232, 1188, 1124, 1000, 963 cm^{-1}. EIMS *m*/*z* (rel intensity %): 124 (M^+, 100), 95 (18), 82 (26), 67 (99), 55 (86), 50 (8), 41 (34). $[\alpha]_D^{25}$ −3.1 (*c* 1.0, $CHCl_3$). Mp 118–128 °C. Conditions for HPLC: Chiralcel OJ-H column, solvent: *n*-hexane/EtOH (90/10), flow rate=1 mL/min, *T*=35 °C, retention times: 14.9 min for (1*R*,4*R*)-**2**, 16.2 min for (1*S*,4*S*)-**2**.

4.4. Synthesis of bis-triflate (*S*,*S*)-3

Diketone (1*S*,4*S*)-**2** (4.0 g, 31.8 mmol) was dissolved in dry THF (220 mL) and cooled to −78 °C. KHMDS (166 mL, 0.5 M in toluene, 82.8 mmol) was added dropwise. After 1 h $PhNTf_2$ (29.6 mL, 82.8 mmol) dissolved in 120 mL dry THF was added. The resulting reaction mixture was stirred for another 3 h. The reaction mixture was quenched with satd aq NH_4Cl (300 mL) and extracted with pentane (2×500 mL). The combined organic phases were washed with satd aq NH_4Cl (200 mL). The organic phases were dried over $MgSO_4$ and concentrated in vacuo. The resulting brown oil was purified by flash chromatography over silica gel (gradient elution with pentane/$CHCl_3$, 96/4 to pentane/Et_2O, 95/5) resulting in a colourless oil, giving 7.08 g (55%) of bis-triflate **3**. ^1H NMR (300 MHz, $CDCl_3$): δ 2.62 (t, *J*=1.8 Hz, 2H), 3.53 (m, 2H), 6.51 (dd (app. t), *J*=2.4, 2.4 Hz, 2H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 50.3 (CH), 73.1 (CH_2), 118.4 (q, J_{C-F}=321 Hz, C), 123.7 (CH), 168.2 (C) ppm. IR (KBr, thin film): 1632, 1609, 1426, 1294, 1247, 1207, 1135, 1073, 1023, 934, 882, 84 cm^{-1}. EIMS *m*/*z* (rel intensity %): 388 (M^+, 9), 227 (4), 149 (6), 122 (9), 105 (10), 77 (41), 69 (100), 41 (26). $[\alpha]_D^{25}$ −28 (*c* 1.0, $CHCl_3$).

4.5. A typical procedure for the preparation of (*S*,*S*)-nbd*-ligands

4.5.1. Synthesis of (*S*,*S*)-Bn-nbd* (4a). A solution of bis-triflate (*S*,*S*)-**3** (104.7 mg, 269.7 μmol) and $PdCl_2$(dppf)·CH_2Cl_2 (4.7 mg, 5.79 μmol) in Et_2O (1.0 mL) was cooled in an ice bath. To the resulting red suspension was added BnMgCl (1.35 mL, 1.77 mmol, 20 w/w % in THF) under argon. The reaction mixture was stirred for 1 h at room temperature, quenched with brine (25 mL) and extracted with EtOAc (4×50 mL). The combined organic phases were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by flash chromatography over silica gel (isooctane/$CHCl_3$, 96/4) resulting in a white solid, which contained a significant amount of diphenylethane, which was removed under reduced pressure (<1 mmHg, 1 night) resulting in pure (*S*,*S*)-Bn-nbd* (**4a**) as a white solid, 53.0 mg (72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.94 (t, J=1.7 Hz, 2H), 3.14 (dt, J=3.8, 1.7 Hz, 2H), 3.49 (s, 4H), 6.02 (dt, J=3.8, 1.6 Hz, 2H), 7.09 (d, J=7.2 Hz, 4H), 7.18 (tt, J=7.2, 1.2 Hz, 2H), 7.26 (t, J=7.2 Hz, 4H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 38.0 (CH_2), 53.1 (CH), 71.4 (CH_2), 125.9 (CH), 128.1 (CH), 129.0 (CH), 134.3 (CH), 139.1 (C), 156.9 (C). IR (KBr, thin film): 2970, 2950, 2929, 2878, 1600, 1492, 1451, 1306, 1183, 1069, 1026, 948, 856, 780, 752, 737, 708 cm^{-1}. APCI-MS: 273 [M+H]$^+$. EIMS *m*/*z* (rel intensity %): 272 (M^+, 9), 181 (34), 165 (21), 156 (34), 141 (17), 128 (22), 115 (39), 103 (8), 91 (88), 84 (29), 65 (30), 49 (71), 40 (100). $[\alpha]_D^{25}$ −180 (*c* 1.07, $CHCl_3$). Mp 67 °C. HRMS (EI) calcd for $C_{21}H_{20}$ 272.1565, found 272.1569.

4.5.2. Synthesis of (*S*,*S*)-*i*-Bu-nbd* (4b). The reaction was performed on bis-triflate (*S*,*S*)-**3** (501.3 mg, 1.29 mmol) according to the typical procedure, using a *i*-BuMgCl (4.5 mL, 8.99 mmol, 2 M in Et_2O) solution. After 1 h the reaction was quenched with H_2O and extracted with pentane. The combined organic phases were dried on $MgSO_4$ and carefully concentrated in vacuo. Purification by flash chromatography over silica gel (pentane) resulted in pure (*S*,*S*)-*i*-Bu-nbd* (**4b**) as a colourless oil, 86.7 mg (33%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.81 (d, J=6.6 Hz, 6H), 0.87 (d, J=6.6 Hz, 6H), 1.71–1.80 (septet, J=6.6 Hz, 2H), 1.94 (t, J=1.6 Hz, 2H), 2.03–2.08 (dq, J=1.5, 6.8 Hz, 4H), 3.17 (dt, J=3.9, 1.6 Hz, 2H), 6.12 (td, J=1.5, 3.9 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 22.6 (CH_3), 22.8 (CH_3), 26.6 (CH), 41.0 (CH_2), 53.4 (CH), 71.9 (CH_2), 133.5 (CH), 157.9 (C). IR (KBr, thin film): 3062, 2955, 2930, 2900, 2867, 2830, 1464, 1383, 1366, 1298, 1185, 1167, 780 cm^{-1}. APCI-MS: 205 [M+H]$^+$. EIMS *m*/*z* (rel intensity %): 204 (M^+, 49), 161 (27), 147 (25), 122 (48), 117 (20), 105 (60), 91 (51), 80 (100), 66 (44), 43 (77). $[\alpha]_D^{25}$ −103 (*c* 1.14, $CHCl_3$). HRMS (EI) calcd for $C_{15}H_{24}$ 204.1878, found 204.1873.

4.5.3. Synthesis of (*S*,*S*)-*c*-Hex-nbd* (4c). The reaction was performed on bis-triflate (*S*,*S*)-**3** (101.0 mg, 257.6 μmol) according to the typical procedure, using a *c*-HexMgCl (0.9 mL, 177 μmol, 2 M in Et_2O) solution. After 1 h the reaction was quenched with H_2O and extracted with pentane. The combined organic phase were dried on $MgSO_4$ and concentrated in vacuo. Purification by flash chromatography over silica gel (pentane) resulted in pure (*S*,*S*)-*c*-Hex-nbd* (**4c**) as a colourless oil, 51.0 mg (77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95–1.04 (m, 2H), 1.05–1.20 (m, 4H), 1.22–1.32 (m, 4H), 1.62–1.79 (m, 10H), 1.84 (t, J=1.6 Hz, 2H), 2.08 (m, 2H), 3.26 (dt, J=3.9, 1.6 Hz, 2H), 6.02 (td, J=1.6, 3.9 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 26.2 (CH_2), 26.5 (CH_2), 31.1 (CH_2), 31.2 (CH_2), 39.8 (CH), 51.7 (CH), 71.1 (CH_2), 130.7 (CH), 164.1 (C). IR (KBr, thin film): 3059, 2960, 2923, 2850, 1448, 1276, 1184, 890, 806, 788 cm^{-1}. APCI-MS: 257 [M+H]$^+$. EIMS *m*/*z* (rel intensity %): 256 (M^+, 43), 189 (15), 173 (33), 148 (51), 131 (21), 117 (24), 105 (34), 91 (58), 79 (38), 55 (69), 41 (100). $[\alpha]_D^{25}$ −58 (*c* 0.96, $CHCl_3$). HRMS (EI) calcd for $C_{19}H_{28}$ 256.2191, found 256.2190.

4.5.4. Synthesis of (*S*,*S*)-allyl-nbd* (4d). The reaction was performed on bis-triflate (*S*,*S*)-**3** (508.5 mg, 1.31 mmol) according to the typical procedure, using an allylMgBr solution (8.85 mL, 8.99 mmol, 1 M in Et_2O). After 30 min the reaction was quenched with H_2O and extracted with pentane. The combined organic phases were dried over $MgSO_4$ and carefully concentrated in vacuo. Purification by flash chromatography over silica gel (pentane) resulted in pure (*S*,*S*)-allyl-nbd* (**4d**) as a colourless oil, 92.5 mg (41%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.97 (t, J=1.6 Hz, 2H), 2.93 (m, 4H), 3.22 (dt, J=4.0, 1.6 Hz, 2H), 5.01 (ddt, J=10.0, 1.2, 1.2 Hz, 2H), 5.04 (ddd, J=17.0, 1.6, 3.4 Hz, 2H), 5.79 (tdd, J=3.5, 10.0, 17.0 Hz, 2H), 6.18 (td, J=1.7, 4.0 Hz, 2H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 36.0 (CH_2), 53.3 (CH), 71.8 (CH_2), 115.7 (CH_2), 133.5 (CH), 135.7 (CH), 157.0 (C). IR (KBr, thin film): 3076, 2972, 2932, 2866, 1640, 1607, 1427, 1301, 1263, 1185, 993, 912, 786 cm^{-1}. APCI-MS: 173 [M+H]$^+$. EIMS *m*/*z* (rel intensity %): 172 (M^+, 5), 131 (45), 115 (28), 106 (18), 91 (100), 78 (62), 65 (18), 51 (18), 41 (18). $[\alpha]_D^{25}$ −151.1 (*c* 1.06, $CHCl_3$). HRMS (EI) calcd for $C_{13}H_{16}$ 172.1252, found 172.1259.

4.6. Synthesis of [RhCl((*S*,*S*)-allyl-nbd*)]$_2$

(*S*,*S*)-Allyl-nbd* (**4d**) (16.9 mg, 98.1 μmol) and [RhCl(C_2H_4)$_2$]$_2$ (17.9 mg, 92.0 μmol Rh) were dissolved in $CHCl_3$ (5 mL) and stirred for 3 h under argon. Purification by flash chromatography over silica gel (hexane/CH_2Cl_2, 60/40) resulted in pure [RhCl((*S*,*S*)-allyl-nbd*)]$_2$ as a yellowish oil, 25.9 mg (78%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (s, 4H), 2.45 (dd, J=6.9, 14.6 Hz, 4H), 2.94 (dd, J=7.0, 14.6 Hz, 4H), 3.57 (m, 4H), 3.60 (m, 4H), 5.17 (dd, J=1.0, 10.0 Hz, 4H), 5.27 (dd, J=1.2, 17.0 Hz, 4H), 6.37 (tdd, J=3.2, 10.0, 17.0 Hz, 4H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 38.5 (CH_2), 47.4 (d, J_{C-Rh}=10.6 Hz, CH), 53.1 (d, J_{C-Rh}=3.0 Hz, CH), 59.5 (d, J_{C-Rh}=7.5 Hz, CH_2), 69.4 (d, J_{C-Rh}=11.3 Hz, C), 116.6 (CH_2), 135.4 (CH). IR (KBr, thin film): 3071, 2988, 2911, 1634, 1422, 1307, 1234, 1170, 991, 913 cm^{-1}. ES-MS: 584.9 ([RhOH((*S*,*S*)-allyl-nbd*)]$_2$+H$^+$), 275 (Rh$^+$((*S*,*S*)-allyl-nbd*)). EIMS *m*/*z* (rel intensity %): 620 (M^+, 44), 584 (9), 548 (26), 412 (100), 372 (41), 346 (12), 308 (9), 273 (56), 218 (41), 205 (33), 168 (15), 115 (20), 103 (24), 77 (20), 49(22). $[\alpha]_D^{25}$ +3.4 (*c* 0.90, $CHCl_3$). HRMS (EI) calcd for $C_{26}H_{32}Cl_2Rh_2$ 619.9991, found 620.0003.

4.7. Typical procedure for the asymmetric 1,4-addition of phenylboronic acid (6) to cyclic enones 5a and 5b

Chiral ligand (*S*,*S*)-nbd* (**4**) (2.7 mg, 9.9 μmol) and [RhCl-(C_2H_4)$_2$]$_2$ (1.8 mg, 9.0 μmol) were dissolved in dioxane

(1 mL) and stirred for 15 min at room temperature under argon. To this reaction mixture was added KOH (0.1 mL, 1.5 M, 0.15 mmol) in deoxygenated H_2O and the solution was stirred for another 15 min. Subsequently, phenylboronic acid (**6**) (73.1 mg, 0.6 mmol) and 2-cyclohexenone (**5a**) (29 μL, 0.3 mmol) were added and stirred at 30 °C for 1.5 h. The reaction mixture was passed through a short pad of silica gel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/Et_2O, 85/15) resulted in (*S*)-**7a** as a colourless oil, 49.6 mg (95%, 96% ee). The adducts **7a** and **7b** obtained by the rhodium-catalyzed asymmetric 1,4-addition to **5a** and **5b**, respectively, were fully characterized by comparison of their spectral data with those reported in the literature.[16] Conditions for chiral HPLC analysis: for **7a**: Chiralpak AS-H column, solvent: *n*-hexane/*i*-PrOH (98/2), flow rate=1 mL/min, *T*=35 °C, retention times: 18.3 min for (*S*)-**7a** and 21.4 min for (*R*)-**7a**. For **7b**: Chiralpak AS-H column, solvent: *n*-hexane/*i*-PrOH (98/2), flow rate=1 mL/min, *T*=35 °C, retention times: 19.9 min for (*S*)-**7b** and 21.7 min for (*R*)-**7b**.

4.8. Typical procedure for the 1,2-addition of phenylboronic acid (6) to *p*-trifluoromethylbenzaldehyde (8) catalyzed by [Rh(norbornadiene)Cl]$_2$

[Rh(norbornadiene)Cl]$_2$ (6.9 mg, 0.015 mmol), phenylboronic acid (**6**) (121.9 mg, 1 mmol) and *p*-trifluoromethylbenzaldehyde (**8**) (68 μL, 0.5 mmol) were dissolved in dioxane (1.5 mL). Aqueous KOH (1.5 M, deoxygenated, 450 μL) was added and the resulting reaction mixture was stirred under argon at 50 °C. After 2 h, more phenylboronic acid (**6**) (121.9 mg, 1 mmol) was added, followed by another portion (121.9 mg, 1 mmol) after 4 h. After 6 h the conversion of the aldehyde was complete. The reaction mixture was passed through a short pad of silica gel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/EtOAc, 90/10) resulted in **9** as a white solid, 97 mg (78%). The adduct **9** was fully characterized by comparison of its spectral with those reported in the literature.[13]

4.9. Typical procedure for the asymmetric 1,2-addition of phenylboronic acid (6) to *p*-trifluoromethylbenzaldehyde (8)

[Rh(C_2H_4)$_2$Cl]$_2$ (1.5 mg, 7.5 μmol) and (*S*,*S*)-*i*-Bu-nbd* (**4b**) (1.6 mg, 7.8 μmol) were dissolved in dioxane (0.75 mL) and stirred for 15 min under argon. To this reaction mixture was added aq KOH (225 μL, 1.5 M, 0.34 mmol) in deoxygenated H_2O and the solution was stirred for another 15 min. The reaction mixture was cooled in an ice bath and phenylboronic acid (**6**) (61.0 mg, 0.5 mmol) and *p*-trifluoromethylbenzaldehyde (**8**) (34 μl, 0.25 mmol) were added and stirred for 1 h. The reaction mixture was passed through a short pad of silica gel and eluted with EtOAc. Evaporation in vacuo and purification by flash chromatography over silica gel (hexane/EtOAc, 90/10) resulted in (*R*)-**9** as a white solid, 62.5 mg (99%). The adduct **9** was fully characterized by comparison of its spectral with those reported in the literature.[13] For **9**: Chiralcel OJ-H column, solvent: *n*-hexane/EtOH (98/2), flow rate=1 mL/min, *T*=35 °C, retention times: 23.6 min for (*R*)-**9** and 26.5 min for (*S*)-**9**.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.10.034.

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