Fine-Tuning the Bicyclo[3.3.1]nona-2,6-diene Ligands: Second Generation 4,8-Substituted Dienes for Rh-Catalyzed Asymmetric 1,4-Addition Reactions

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Design and synthesis of the second generation C_2-symmetric 4,8-*endo,endo*-bis(alkoxy) bicyclo[3.3.1]nona-2,6-diene ligands possessing additional 4,8-*exo,exo* substituents is reported. The 4,8-*exo,exo* groups provide a further element for fine-tuning of the ligand structure by enforcing conformational rigidity of the 4,8-*endo,endo* side chains. Such tetrasubstituted bicyclo[3.3.1]nona-2,6-dienes were employed as steering ligands in the rhodium-catalyzed arylation of cyclic enones with arylboronic acids, providing the corresponding 1,4-addition products in good to excellent yields (69–99%) and enantioselectivities up to 99% ee.

Introduction

Over the past two decades chiral dienes have emerged as a new type of bidentate steering ligands for transition metal-catalyzed asymmetric transformations.[1] The pioneering reports on the application of bicyclic dienes in the asymmetric rhodium and iridium-catalyzed reactions by Hayashi[2] and Carreira[3] spurred intense research effort directed towards the synthesis and study of novel steering ligands. A variety of structurally diverse dienes based on bicyclo[2.2.1]heptadiene,[2,4] bicyclo[2.2.2]octadiene,[3,4c,5] bicyclo[3.3.0]octadiene[6] and propelladiene,[7] bicyclo[3.3.1]nonadiene,[8,9] dicyclopentadiene,[10] cyclooctadiene,[11] as well as acyclic[12] frameworks have been developed. Ligands of this type have been found to be particularly effective in the asymmetric rhodium-catalyzed conjugate addition of boronic acids to α,β-unsaturated carbonyl compounds and arylation of imines. Due to exceptional levels of stereoselectivity, functional group tolerance, and ready availability and stability of many organoboron reagents this methodology became a practical tool for the assembly of complex chiral molecules, intermediates and building blocks in drug discovery.[13]

Chiral dienes often surpass conventional phosphine ligands in terms of both catalytic activity and enantioselectivity, therefore it is not surprising that their synthesis, structural studies and application in the Rh-catalyzed asymmetric transformations remains active research endeavor. Plentiful examples include 1,2-,[14] 1,4-[15] and 1,6-additions[16] to a wide variety of substrates, intramolecular [4 + 2] cycloadditions[17] and arylative (carbo)cyclizations,[18] benzannulations,[19] cyclopropanations,[20] dynamic kinetic asymmetric transformations of allylic trichloroacetimidates,[21] carbene insertions into B–H[22] and Si–H[23] bonds and other synthetically useful procedures.[24] While the utility of privileged bicyclo[2.2.1]heptadiene, bicyclo[2.2.2]octadiene and bicyclo[3.3.0]octadiene skeletons is particularly amply demonstrated, the potential of the bicyclo[3.3.1]nonadiene framework for construction of steering ligands remains underexplored. To this end, we have reported synthesis of C_2-symmetric 4,8-*endo,endo*-disubstituted bicyclo[3.3.1]nona-2,6-diene chelating ligands and demonstrated their utility in the asymmetric rhodium-catalyzed 1,4-addition of boronic acids to cyclic enones.[9] In contrast to the common tactics, which involves manipulation of steering substituents at the vinylic positions, our approach to tuning the chiral environment around the diene-coordinated Rh atom relied on the functionalization of the ligand skeleton at the allylic positions. In comparison with the parent bicyclo[3.3.1]nona-2,6-diene,[25] the 4,8-bis(alkoxy) congeners displayed enhanced levels of enantioselectivity, thus demonstrating the beneficial effect of 4,8-*endo,endo*-substitution on asymmetric induction. Herein, we report the design and synthesis of the second generation C_2-symmetric 4,8-*endo,endo*-bis(alkoxy) bicyclo[3.3.1]nona-2,6-dienes, decorated with additional bulky 4,8-*exo,exo* substituents for fine-tuning of the ligand structure. The scope of benchmark Rh-catalyzed arylation of cyclic enones using the novel bicyclo[3.3.1]nona-2,6-diene steering ligands is also presented.

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Results and Discussion

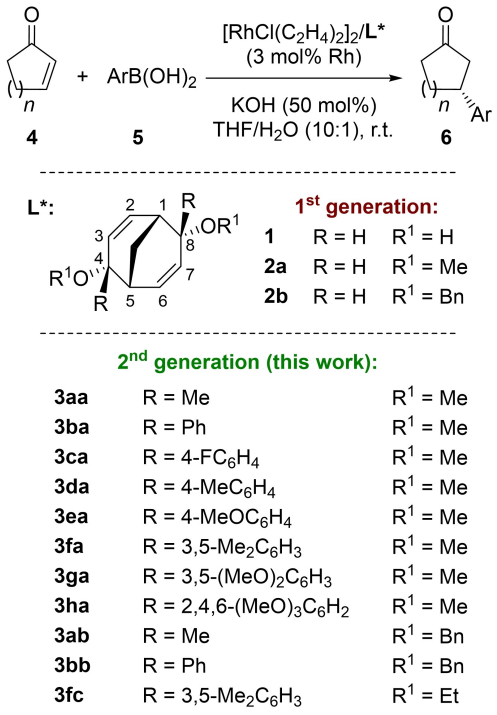
The design of the first generation diene ligands **2** (Scheme 1) derived from *endo,endo*-diol **1** was based on the assumption that the chiral environment around the diene-coordinated rhodium atom could be tuned in a straightforward manner by changing the steric bulk of the 4,8-*endo,endo* substituents. Indeed, rhodium complex with 4,8-bis(benzyloxy) diene **2b**, which emerged as a champion ligand, exhibited excellent catalytic activity and high enantioselectivity (up to 96% *ee*) in the asymmetric arylation of cyclic enones **4** with arylboronic acids **5**.[9] Nevertheless, conformational analysis of **2b** (*vide infra*) and inspection of the X-ray structure of $[RhCl(\mathbf{2b})]_2$ revealed that 4,8-benzyloxy side chains are rather conformationally flexible and distant from the catalytically active center (for details, see Supporting Information, Figure S1).

We reasoned that introduction of 4,8-*exo,exo* substituents could enforce conformational rigidity of the 4,8-*endo,endo* side chains and provide another element for fine-tuning of the ligand structure. To test this hypothesis, conformational analysis of the selected ligands **2a**–**b**, **3aa**–**ba**, **3fa** and **3ha** was performed using MMFF94 force field, followed by further geometry optimization at the B3LYP/6-31G(d) level.[26] Analysis of **2a**–**b** revealed that (*ap, ap*)-, (*-sc, ap*)- and (*-sc, -sc*)-conformers with alkoxy groups synclinal (*sc*) and antiperiplanar (*ap*) to $C_{4(8)}$–$C_{3(7)}$ bonds are close in energy and thus comparably populated (Figures S2–S3). Steric hindrance imposed even by the smallest *exo*-substituents, such as methyl groups in **3aa**, is sufficient to significantly affect conformational mobility of the 4,8-*endo,endo* side chains. Moreover, in the most stable conformer of **3aa**, the 4,8-*exo,exo* substitution enforces a spatial arrangement of methyl groups proximal to double bonds, *i.e.*, synclinal and antiperiplanar conformation of the methoxy groups with respect to $C_{4(8)}$–$C_{3(7)}$ and $C_{4(8)}$–$C_{5(1)}$ bonds, respectively (Figure S4). This effect is even more pronounced in the case of **3ba**, **3fa** and **3ha** with bulky *exo*-aryl substituents – virtually single stable C_2-symmetric (*-sc, -sc*)-conformation with two methoxy groups synclinal to $C_{4(8)}$–$C_{3(7)}$ bonds was found (Figures S5–S6), whereas other conformers were found to be insignificantly populated. Coordination of the chiral dienes with Rh(I) obviously induces conformational changes of both bicyclic framework and side chains. Nevertheless, calculations suggest that the second generation ligands **3** should provide a more effective chiral environment in their transition metal complexes due to the steric restrictions imposed by the 4,8-*exo,exo* substituents.

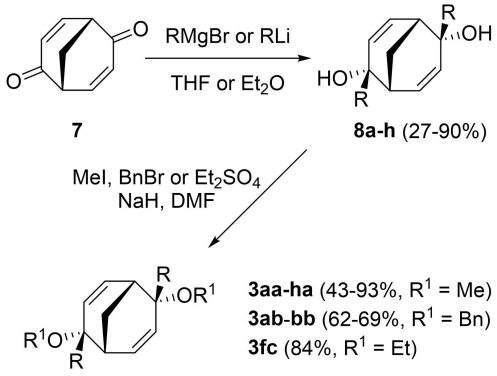
It was envisioned that a library of bicyclo[3.3.1]nonadiene ligands **3** could be prepared from a single starting compound (+)-(1*R*,5*R*)-bicyclo[3.3.1]nona-3,7-diene-2,6-dione (**7**, Scheme 2)[9,27] *via* reaction with corresponding organometallic reagents, followed by *O*-alkylation. The 1,2-addition of methylmagnesium bromide and phenyllithium to dienone **7** in THF proceeded uneventfully to give the respective diols **8a**–**b** in 72–77% yields (Scheme 2). Subsequent alkylation of **8a**–**b** in DMF using methyl iodide and benzyl bromide as alkylating agents and NaH as a base afforded the corresponding C_2-symmetric second generation ligands **3aa**–**ab** and **3ba**–**bb** in moderate to good yields (43–84%).

With new dienes **8a**–**b**, **3aa**–**ab** and **3ba**–**bb** in hand, we tested their performance as chiral ligands in the rhodium-catalyzed asymmetric 1,4-addition reaction (Table 1). In order to obtain an early insight about the properties of second generation ligands, arylation of 2-cyclohexenone (**4a**) with phenylboronic acid (**5a**) and 2-cyclopentenone (**4b**) with 4-bromophenylboronic acid (**5b**)[28] were tested with *in situ* formed diene-Rh catalysts (3 mol% Rh) under optimal conditions, previously established for ligand **2b**.[9]

In the arylation of 2-cyclohexenone (**4a**) with **5a**, rhodium complexes of diols **8a**–**b** (entries 2 and 3) and corresponding *O*-methyl derivatives **3aa**–**ba** (entries 6 and 7) exhibited catalytic activity similar to that observed with the first generation

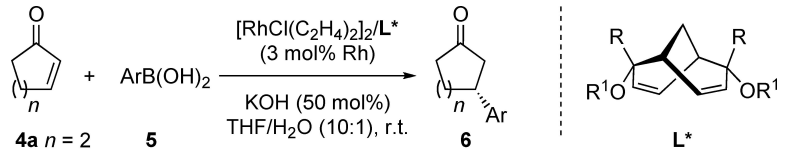


Scheme 1. Asymmetric Rh-catalyzed 1,4-addition of arylboronic acids to cyclic enones and 4,8-substituted bicyclo[3.3.1]nona-2,6-diene ligands.



Scheme 2. Synthesis of 2nd generation 4,8-substituted bicyclo[3.3.1]nona-2,6-diene ligands. For R and R^1, see Scheme 1.

Table 1. Rhodium-catalyzed asymmetric arylation of cyclic enones with arylboronic acids: ligand screening.



4a n = 2, **4b** n = 1 — **5** — **6** — **L***

Entry[a]	Ligand	R	R^1	**4**	Ar (**5**)	t [h]	Product	Yield [%][b]	ee [%][c]
1[d]	**1**	H	H	**4a**	Ph (**5a**)	0.5	**6aa**	92	92
2	**8a**	Me	H	**4a**	Ph (**5a**)	0.75	**6aa**	90	92
3	**8b**	Ph	H	**4a**	Ph (**5a**)	0.5	**6aa**	92	94
4[d,e]	**2a**	H	Me	**4a**	Ph (**5a**)	0.5	**6aa**	91	92
5[d]	**2b**	H	Bn	**4a**	Ph (**5a**)	0.5	**6aa**	98	95
6	**3aa**	Me	Me	**4a**	Ph (**5a**)	0.5	**6aa**	88	96
7	**3ba**	Ph	Me	**4a**	Ph (**5a**)	1	**6aa**	90	96
8	**3ab**	Me	Bn	**4a**	Ph (**5a**)	0.5	**6aa**	86	89
9	**3bb**	Ph	Bn	**4a**	Ph (**5a**)	1.25	**6aa**	85	94
10	**3ca**	4-FC_6H_4	Me	**4a**	Ph (**5a**)	1	**6aa**	86	97
11	**3da**	4-MeC_6H_4	Me	**4a**	Ph (**5a**)	1	**6aa**	94	96
12	**3ea**	4-$MeOC_6H_4$	Me	**4a**	Ph (**5a**)	1	**6aa**	90	97
13	**3fa**	3,5-$Me_2C_6H_3$	Me	**4a**	Ph (**5a**)	1	**6aa**	88	98
14	**3ga**	3,5-$(MeO)_2C_6H_3$	Me	**4a**	Ph (**5a**)	1	**6aa**	57	97
15	**3ha**	2,4,6-$(MeO)_3C_6H_2$	Me	**4a**	Ph (**5a**)	3	**6aa**	59	85
16	**3fc**	3,5-$Me_2C_6H_3$	Et	**4a**	Ph (**5a**)	1	**6aa**	57	96
17[d]	**2b**	H	Bn	**4b**	4-BrC_6H_4 (**5b**)	0.5	**6bb**	98	79
18	**3aa**	Me	Me	**4b**	4-BrC_6H_4 (**5b**)	1.5	**6bb**	63	87
19	**3ba**	Ph	Me	**4b**	4-BrC_6H_4 (**5b**)	1	**6bb**	70	87
20	**3ab**	Me	Bn	**4b**	4-BrC_6H_4 (**5b**)	2	**6bb**	28	54
21	**3bb**	Ph	Bn	**4b**	4-BrC_6H_4 (**5b**)	2	**6bb**	14	63
22	**3fa**	3,5-$Me_2C_6H_3$	Me	**4b**	4-BrC_6H_4 (**5b**)	1	**6bb**	47	88
23	**3fc**	3,5-$Me_2C_6H_3$	Et	**4b**	4-BrC_6H_4 (**5b**)	1	**6bb**	39	84

[a] The reactions were carried out with enone **4** (0.3 mmol), **5** (0.36 mmol, 1.2 equiv.), $[RhCl(C_2H_4)_2]_2$ (3 mol% Rh), ligand (3.3 mol%) and 1.5 M aq. KOH (100 μL, 50 mol%) in THF (1 mL) at room temperature. [b] Isolated yield. [c] *ee* values determined by chiral HPLC; products **6aa** and **6bb** were of (*R*)-configuration, as revealed by the comparison of their HPLC behavior with the data reported earlier.[9] [d] Ref. [9]. [e] The reaction was carried out in 1,4-dioxane.

congeners **1** (entry 1) and **2a**–**b** (entries 4 and 5), respectively. In terms of enantioselectivity, marginally improved asymmetric induction was attained with both **3aa** and **3ba** (entries 6 and 7 *vs* entry 5), whereas 1,4-addition of **5b** to 2-cyclopentenone (**4b**) revealed clear superiority of second generation ligands **3aa**–**ba** (entries 18 and 19 *vs* entry 17). 4,8-Bis(benzyloxy) dienes **3ab** (entries 8 and 20) and **3bb** (entries 9 and 21), on the other hand, displayed notably lower activity and selectivity than their *O*-methyl counterparts **3aa**–**ba** and parent diols **8a**–**b**. This stands in stark contrast to the behavior of the first generation ligands, where *O*-benzyl derivative **2b** offered the best performance. An overall decrease of reaction rate with the second generation ligands, especially in the case of cyclopentenone **4b**, resulting from increased steric crowding at the catalytic site is also noteworthy.

Numerous attempts to introduce bulkier *exo*-isopropyl substituents by a reaction of dienone **7** (Scheme 2) with isopropyl magnesium bromide or the corresponding organocerium reagent (anh. $CeCl_3$, *i*-PrMgBr, THF, −78 °C to r.t.)[29] produced only traces of the desired diol. Thus, despite the good performance of ligand **3aa**, 4,8-*exo,exo*-dialkyl substituted series offered little room for further modifications. Properties of ligand **3ba**, however, could be further fine-tuned by changing the substitution pattern of the 4,8-*exo,exo*-aryl substituents. Therefore, a small library of diols **8c**–**h** was prepared in 27–90% yields by 1,2-addition of corresponding aryllithium reagents to dienone **7** (Scheme 2). Aryllithium reagents were freshly prepared from the appropriate aryl bromides or iodides and *n*-butyllithium by lithium-halogen exchange in diethyl ether at 0 °C. Exceptions include 2,4,6-trimethoxyphenyllithium, which was prepared from 1,3,5-trimethoxybenzene by direct *ortho*-lithiation with *n*-butyllithium,[30] and 2,4,6-trimethylphenyllithium, which had to be prepared by lithiation of 1-bromo-2,4,6-trimethylbenzene with metallic lithium.[31] The latter, however, failed to produce corresponding diol from dienone **7** (Scheme 2) under a number of different conditions tested. Alkylation of the diols **8c**–**h** with methyl iodide and diethyl sulphate under standard conditions (NaH, DMF) proceeded uneventfully to yield corresponding *O*-alkyl derivatives **3ca**–**ha** and **3fc** in moderate to excellent yields (51–93%, Scheme 2).

Efficiency of the obtained diene ligands **3ca**–**ha** and **3fc** in the Rh-catalyzed asymmetric 1,4-addition reaction was then examined (Table 1), terminating the reactions after 60 minutes to get better insight into the catalytic activity. Apart from **3ha** (entry 15), dienes **3ca**–**ga** provided similar levels of enantioselectivity (entries 10–14) in the 1,4-addition of phenylboronic acid (**5a**) to 2-cyclohexenone (**4a**). The 4,8-*exo,exo*-bis(3,5-dimethylphenyl) congener **3fa** exhibited marginally enhanced levels of asymmetric induction in arylation of both 2-cyclo-

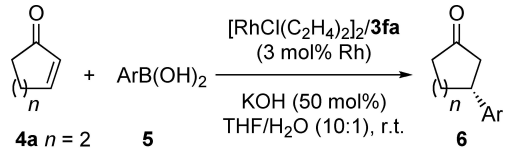
hexenone (**4a**) (entry 13 *vs* entries 7, 10–12 and 14) and 2-cyclopentenone (**4b**) (entry 22 *vs* entry 19), and was selected as a ligand of choice for further studies. A ligand exchange reaction of $[RhCl(C_2H_4)_2]_2$ with dienes **3ba** and **3fa** cleanly produced corresponding $[RhCl(\mathbf{3ba})]_2$ and $[RhCl(\mathbf{3fa})]_2$ complexes, which were characterized by NMR spectroscopy; nevertheless, numerous attempts to obtain single crystals suitable for X-ray analysis were unsuccessful.

Homologation of the *O*-alkyl chains, as exemplified by **3fc**, proved to be detrimental to both catalytic activity and selectivity (entries 16 and 23), likely due to increased steric congestion at the catalytic site. This assumption is further supported by the inferior performance of extremely sterically hindered 4,8-*exo,exo*-bis(2,4,6-trimethoxyphenyl) congener **3ha** (entry 15), which, in sharp contrast to every other member of the series, exhibited virtually the same selectivity as the parent diol **8h** (86% ee) and the lowest selectivity out of the investigated dienes overall. In addition, Rh/**3ha** complex was much less catalytically active and required 3 hours to achieve appreciable level of conversion. In comparison with **3ba**, **3fa** and the first generation ligands **2a**–**b**, DFT calculations suggest different geometry of the cyclooctadiene core in **3ha** and the parent diol **8h** (for details, see Supporting Information). The difference in "crossed diene coordination",[32] expressed by a notably smaller dihedral angle between the two double bonds, likely accounts for the moderate enantioselectivity attained with both **8h**[33] and **3ha**. As evidenced by the ^1H and ^{13}C NMR data, rotation about $C_{4(8)}$-aryl bonds in **3ha** is also severely restricted. Thus, poor catalytic activity of Rh/**3ha** complex probably is a result of both the unfavorable geometry of cyclooctadiene core and difficulty to undergo conformational changes needed to accommodate two substrate-derived actor ligands around the Rh atom.

Finally, with the diene **3fa** as the ligand of choice, the scope of asymmetric 1,4-addition of different arylboronic acids **5** to 5-, 6- and 7-membered cyclic enones was investigated (Table 2). To ensure full conversion, loading of **5** was increased to 1.4–1.8 equivalents and reaction time was increased to 3 h for 2-cyclohexenone (**4a**), and to 5 h for both 2-cyclopentenone (**4b**) and 2-cycloheptenone (**4c**). Arylation of 2-cyclohexenone (**4a**) afforded the desired products **6aa**–**al** in good to excellent yields (entries 1–12, Table 2). Excellent enantioselectivities were maintained with a number of *p*- and *m*-substituted boronic acids **5a**–**c** (entries 1–3) and **5e**–**h** (entries 5–8), with the exception of electron-rich 4-methoxyphenylboronic acid (**5d**), which led to product **6ad** in a slightly lower selectivity (94% ee, entry 4). *Ortho*-substituents on the boronic acids were also well tolerated and the adducts were isolated in high enantioselectivities (94–99% ee, entries 9–12). The superiority of ligand **3fa** in arylation of enone **4a** with sterically encumbered boronic acids is particularly noteworthy, as the first generation diene **2b** exhibited notably decreased levels of enantioselection with **5i**–**k** (83, 76 and 72% ee, respectively).[9]

Similar trends were also observed with 5- and 7-membered enones **4b** and **4c**. 1,4-adition reactions to 2-cyclopentenone (**4b**) proceeded in high yields, but with a generally lower enantioselectivity (Table 2, entries 13–22). In particular, the sterically hindered *o*-substituted donors **5j**–**l** provided notably decreased stereoselectivities (55–72% ee, entries 20–22). Such erosion of asymmetric induction with smaller ring enone **4b** is in accord with the behavior of ligand **2b**,[9] as well as unsubstituted bicyclo[3.3.0]octadiene and propelladiene steering ligands reported by Lin[6d] and Christmann.[7] 2-cycloheptenone (**4c**) exhibited lowest reactivity under standard conditions and 1.8 equivalents of the arylboronic acids **5** were required to achieve full conversions. Surprisingly, reaction of **4c** with some boronic acids, such as **5e** and **5h** (entries 27 and 29), was extremely sluggish in tetrahydrofuran and produced only traces of the desired addition products. Poor reactivity could be remedied by performing the reaction in 1,4-dioxane, in which

Table 2. Rhodium/**3fa**-catalyzed asymmetric arylation of cyclic enones with arylboronic acids: substrate scope.



4a n = 2 **4b** n = 1 **4c** n = 3 — **5** — **6**

Entry[a]	4	Ar (5)	Product	Yield[b] [%]	ee[c] [%]
1[d]	**4a**	C_6H_5 (**5a**)	**6aa**	99	98
2[d]	**4a**	4-BrC_6H_4 (**5b**)	**6ab**	96	99
3[d]	**4a**	4-FC_6H_4 (**5c**)	**6ac**	97	99
4[d]	**4a**	4-$MeOC_6H_4$ (**5d**)	**6ad**	97	94
5[d]	**4a**	3-BrC_6H_4 (**5e**)	**6ae**	99	99
6[d]	**4a**	3-ClC_6H_4 (**5f**)	**6af**	97	99
7[d]	**4a**	3-$MeOC_6H_4$ (**5g**)	**6ag**	98	99
8[d]	**4a**	2-naphthyl (**5h**)	**6ah**	99	98
9[d]	**4a**	2-ClC_6H_4 (**5i**)	**6ai**	97	99
10[d]	**4a**	2-$MeOC_6H_4$ (**5j**)	**6aj**	99	97
11[d]	**4a**	1-naphthyl (**5k**)	**6ak**	77	97
12[d]	**4a**	2-MeC_6H_4 (**5l**)	**6al**	96	94
13	**4b**	4-BrC_6H_4 (**5b**)	**6bb**	96	88
14	**4b**	4-FC_6H_4 (**5c**)	**6bc**	97	86
15	**4b**	4-$MeOC_6H_4$ (**5d**)	**6bd**	99	82
16	**4b**	3-BrC_6H_4 (**5e**)	**6be**	96	92
17	**4b**	3-$MeOC_6H_4$ (**5g**)	**6bg**	98	91
18	**4b**	2-naphthyl (**5h**)	**6bh**	97	80
19	**4b**	2-ClC_6H_4 (**5i**)	**6bi**	70	86
20	**4b**	2-$MeOC_6H_4$ (**5j**)	**6bj**	98	72
21	**4b**	1-naphthyl (**5k**)	**6bk**	79	68
22	**4b**	2-MeC_6H_4 (**5l**)	**6bl**	69	55
23	**4c**	C_6H_5 (**5a**)	**6ca**	94	97
24	**4c**	4-BrC_6H_4 (**5b**)	**6cb**	89	98
25	**4c**	4-FC_6H_4 (**5c**)	**6cc**	95	97
26	**4c**	4-$MeOC_6H_4$ (**5d**)	**6cd**	96	95
27[e]	**4c**	3-BrC_6H_4 (**5e**)	**6ce**	91	98
28	**4c**	3-$MeOC_6H_4$ (**5g**)	**6cg**	86	97
29[e]	**4c**	2-naphthyl (**5h**)	**6ch**	92	97
30	**4c**	2-$MeOC_6H_4$ (**5j**)	**6cj**	96	95
31	**4c**	2-MeC_6H_4 (**5l**)	**6cl**	82	99

[a] The reactions were carried out with enone **4** (0.3 mmol), **5** (1.4 equiv. for **4a**–**b**, 1.8 equiv. for **4c**), $[RhCl(C_2H_4)_2]_2$ (3 mol% Rh), **3fa** (3.3 mol%) and 1.5 M aq. KOH (100 μL, 50 mol%) in THF (1 mL) at room temperature for 5 h, unless stated otherwise. [b] Isolated yield. [c] *ee* values determined by chiral HPLC; products **6aa**–**ad**, **6af**–**ak**, **6bb**, **6bd**, **6ca**, **6cc**–**cd** and **6cg**–**ch** were of (*R*)- configuration, as revealed by the comparison of their HPLC behavior with the data reported earlier;[9] the configuration of the remaining 3-arylcycloalkanones **6** is assumed to be (*R*) in analogy with the rest of the series. [d] The reaction was carried out for 3 h. [e] The reaction was carried out in 1,4-dioxane for 2 h.

arylation occurs much faster at the expense of enantioselectivity.[34] The stereochemistry followed the scenario observed for **4a**, *i.e.*, high enantioselectivities (95–99% *ee*) were attained with a range of *p*-, *m*- and *o*-substituted boronic acids (entries 23–31). Once again, electron-rich boronic acid (**5d**) furnished addition product **6cd** in a marginally lower selectivity (95% ee, entry 26) than that attained with the other *p*- and *m*-substituted boronic acids (97–98% ee, entries 23–25, 27–29).

A plausible asymmetric induction model based on DFT calculations at the PBE0/DGDZVP level of theory (for details, see Supporting Information), which features binding of 2-cyclohexenone (**4a**) to [Rh]–Ph species coordinated to **3fa** diene ligand in (*-sc, -sc*)-conformation, is depicted in Figure 1.

According to this model, the acceptor preferentially binds into the [(diene)Rh]-aryl complex from one of the two prochiral faces of the double bond. The minimization of steric repulsion between the enone and 4,8-*endo,endo* methoxy substituents of the ligand accounts for the favorable coordination of the metal center to 2*re*,3*re* prochiral face and leads to the formation of (*R*)-configured product. DFT molecular modelling of analogous complexes of Ph–[Rh(**3fa**)] and **4a** suggests that structures involving diene ligand in (*-sc, ap*)- or (*ap, ap*)- conformations are unfavored by 2.9–6.5 kcal/mol (Figure S7) and thus are unlikely to be involved in the catalytic cycle. In comparison with the best first generation ligand **2b**, diene **3fa** exhibited enhanced enantioselectivity throughout the whole substrate range and, as far as 6- and 7-membered cyclic enones are concerned, rivals the best steering ligands reported in the literature.[35] Further application of the second generation steering ligands in other rhodium-catalyzed asymmetric transformations is currently under investigation.

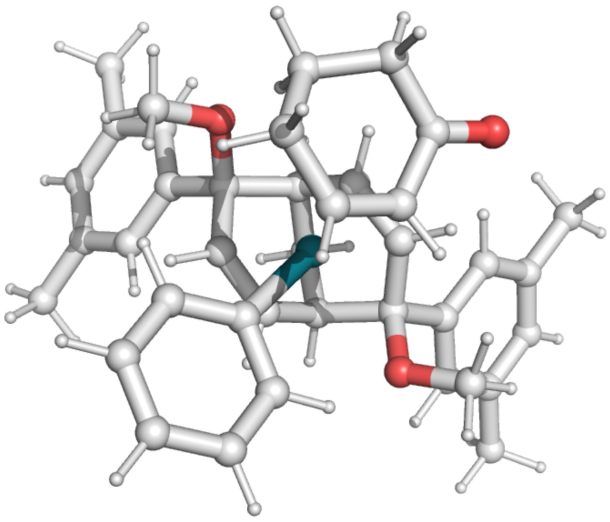


Figure 1. Plausible asymmetric induction model for the rhodium-catalyzed asymmetric 1,4-addition to 2-cyclohexenone.

Conclusion

In conclusion, synthesis of novel C_2-symmetric 4,8-*endo,endo*-substituted bicyclo[3.3.1]nona-2,6-dienes endowed with additional 4,8-*exo,exo* substituents was accomplished and their performance as steering ligands in the rhodium-catalyzed asymmetric 1,4-addition reaction was explored. Bulky 4,8-*exo,exo* substituents provide an element for fine-tuning of the chiral environment around the diene-coordinated Rh atom by enforcing conformational rigidity of the 4,8-*endo,endo* side chains. Rhodium complexes of the second generation ligands were found superior to the previously reported first generation Rh/**2b** catalyst in terms of stereoselectivity at the expense of catalytic activity as a result of increased steric hindrance at the catalytically active site. Diene **3fa** bearing *exo*-3,5-dimethylphenyl and *endo*-methoxy substituents exhibited highest stereoselectivity (up to 99% *ee*) in the asymmetric 1,4-addition of arylboronic acids to cyclic enones, whereas further increase of steric bulk of *endo*-substituents had a detrimental effect on catalytic activity and selectivity. As far as 6- and 7-membered cyclic enones are concerned, in terms of enantioselectivity diene **3fa** rivals the best steering ligands reported in the literature. The somewhat lower level of asymmetric induction in the arylation of smaller ring cyclopentenone appears to be a feature common to both first and second generation 4,8-substituted bicyclo[3.3.1]nona-2,6-diene ligands.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance™ HD III (400 MHz) spectrometer equipped with a 5 mm PABBO probe. Chemical shifts are reported in ppm relative to solvent resonance signal (^{1}H NMR $\delta = 7.26$ ppm, ^{13}C NMR $\delta =$ 77.0 ppm). FTIR spectra were recorded on a PerkinElmer Spectrum BX in KBr pellets, unless stated otherwise. Optical rotations were measured at 589 nm on a KRUSS P3001RS polarimeter; $[\alpha]_D^{20}$ values are given in 10^{-1} deg cm^2 g^{-1}, and concentrations are given in units of g/100 cm^3. Melting points were recorded in open capillaries with a Gallenkamp melting apparatus. High-resolution mass spectra (HRMS) were recorded on an Agilent 6203 LC/TOF spectrometer with electrospray ionization (ESI) in direct injection mode. The enantiomeric excess values were determined using an Agilent 1260 Infinity HPLC system, equipped with a diode array detector and CHIRALPAK IA-3, IB-3 and IC-3 analytical (250×4.6 mm) columns. The chiral HPLC methods were calibrated with the corresponding racemic mixtures.

All reactions involving air and/or moisture sensitive materials were conducted under an argon atmosphere. All reagents for the reactions were of reagent grade and were used as received. Solvents were dried and distilled under argon before use as follows: diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone and kept over 4 Å molecular sieves before use. Thin-layer chromatography was carried out on Kieselgel 60 F_{254} (Merck) silica gel coated aluminum sheets and Kieselgel 60 silica gel (0.040–0.063 mm, Merck) was used for column chromatography. Petroleum ether refers to the fraction boiling in the range 40–60 °C. (+)-(*1R,5R*)-bicyclo[3.3.1]nona-3,7-diene-2,6-dione (**7**) was prepared following the procedure reported earlier.[9]

(+)-(1*R*,2*R*,5*R*,6*R*)-2,6-dimethylbicyclo[3.3.1]nona-3,7-diene-2,6-diol (8a). Methylmagnesium bromide (270 μL, 0.8 mmol, 3.0 M

solution in diethyl ether) was added dropwise to a vigorously stirred solution of dienone **7** (29.6 mg, 0.2 mmol) in THF (1 mL) at 0 °C. The reaction mixture was stirred for 5 min., quenched with aqueous 2 M NH_4Cl (8 mL) and extracted with MTBE (3×10 mL). Pooled organic extracts were washed with brine (2×5 mL), dried with Na_2SO_4 and evaporated under reduced pressure. Residue was purified by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (6:4) to afford diol **8a** (26 mg, 72%; dr (*diendo:endo,exo*) 95:5) as a colorless crystalline mass, mp 183–184 °C (EtOAc:Hexane). $[\alpha]_D^{20} = +245$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.84 (ddt, $J = 10.1$, 5.8, 0.7 Hz, 2H), 5.61 (dq, $J = 10.1$, 0.8 Hz, 2H), 2.36–2.29 (m, 2H), 1.93 (tt, $J = 3.2$, 0.7 Hz, 2H), 1.64 (s, 2H), 1.38 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7 (CH), 128.2 (CH), 74.2 (C), 40.3 (CH), 29.4 (CH_2), 27.6 (CH_3) ppm; IR: $\tilde{\nu}$ = 3357, 3318, 1365, 1137, 1115, 1099 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{11}H_{16}O_2Na$ $[M+Na]^+$: 203.1043; found 203.1036.

(+)-(1*R*,2*R*,5*R*,6*R*)-2,6-diphenylbicyclo[3.3.1]nona-3,7-diene-2,6-diol (8b). Phenyllithium solution (1.5 mL, 3.0 mmol, 2.0 M in dibutyl ether) in THF (5 mL) was added dropwise to a vigorously stirred solution of dienone **7** (148.2 mg, 1.0 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred for 5 min., quenched with aqueous 2 M NH_4Cl (10 mL) and extracted with MTBE (3×10 mL). Pooled organic extracts were washed with brine (2×5 mL), dried with Na_2SO_4 and evaporated under reduced pressure. Residue was purified by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (7:3) and subsequently recrystallized from cyclohexane to afford diol **8b** (234 mg, 77%) as fine colorless needles, mp 141–143 °C. $[\alpha]_D^{20} = +200$ ($c = 2.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62–7.51 (m, 4H), 7.39–7.30 (m, 4H), 7.30–7.22 (m, 2H), 6.38 (dd, $J = 10.1$, 5.4 Hz, 2H), 5.83 (dq, $J = 10.0$, 0.9 Hz, 2H), 2.66–2.60 (m, 2H), 2.05 (s, 2H), 1.54 (t, $J = 3.1$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.5 (C), 132.9 (CH), 130.7 (CH), 128.0 (CH), 127.5 (CH), 126.5 (CH), 78.2 (C), 41.2 (CH), 25.4 (CH_2) ppm; IR: $\tilde{\nu}$ = 3461, 3421, 1489, 1446, 759, 702 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{19}O$ $[M–OH]^+$: 287.1430; found 287.1425.

General procedure for the synthesis of 2,6-*exo,exo*-diaryl diols 8c-g. *n*-butyllithium (625 μL, 1.5 mmol, 2.4 M solution in hexanes) was added dropwise to a vigorously stirred solution of a corresponding haloarene (2.00 mmol) in Et_2O (1 mL) at 0 °C, and the reaction mixture was stirred for 15 min. The formed organolithium reagent was then added dropwise to a stirred solution of dienone **7** (74.1 mg, 0.50 mmol) in Et_2O (5 mL) at 0 °C. The resulting mixture was stirred for 15 min., quenched with aqueous 2 M NH_4Cl (5 mL) and extracted with MTBE (3×10 mL). Pooled organic extracts were washed with brine (2×5 mL), dried with Na_2SO_4 and evaporated under reduced pressure. Residue was purified by flash chromatography on silica gel to afford the corresponding diols.

(+)-(1*R*,2*R*,5*R*,6*R*)-2,6-bis(4-fluorophenyl)bicyclo[3.3.1]nona-3,7-diene-2,6-diol (8c). Organolithium reagent was prepared from 1-fluoro-4-iodobenzene. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (6:4) afforded diol **8c** (153 mg, 90%) as colorless oil that solidified on standing, mp 68–71 °C. $[\alpha]_D^{20} = +146$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59–7.51 (m, 4H), 7.06–6.99 (m, 4H), 6.39 (dd, $J = 10.1$, 5.4 Hz, 2H), 5.85 (d, $J = 10.0$ Hz, 2H), 2.62–2.57 (m, 2H), 1.97 (s, 2H), 1.53 (t, $J = 3.1$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2 (d, $J = 246.3$ Hz, C), 141.2 (d, $J = 3.2$ Hz, C), 132.9 (CH), 130.8 (CH), 128.4 (d, $J = 8.1$ Hz, CH), 114.8 (d, $J = 21.3$ Hz, CH), 77.9 (C), 41.3 (CH), 25.3 (CH_2) ppm; IR: $\tilde{\nu}$ = 3031, 1507, 1199, 1064, 820 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{21}H_{17}OF_2$ $[M–OH]^+$: 323.1242; found 323.1235.

(+)-(1*R*,2*R*,5*R*,6*R*)-2,6-di-*p*-tolylbicyclo[3.3.1]nona-3,7-diene-2,6-diol (8d). Organolithium reagent was prepared from 4-iodotoluene. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (7:3) and subsequent recrystallization from ethyl acetate – hexane mixture afforded diol **8d** (100 mg, 60%) as colorless needles, mp 182–183 °C. $[\alpha]_D^{20} = +212$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46 (d, $J = 8.1$ Hz, 4H), 7.16 (d, $J = 8.0$ Hz, 4H), 6.37 (dd, $J = 10.0$, 5.4 Hz, 2H), 5.83 (d, $J = 10.0$ Hz, 2H), 2.66–2.59 (m, 2H), 2.34 (s, 6H), 1.97 (s, 2H), 1.56 (t, $J = 2.8$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7 (C), 137.2 (C), 133.0 (CH), 130.6 (CH), 128.8 (CH), 126.5 (CH), 78.1 (C), 41.2 (CH), 25.6 (CH_2), 21.0 (CH_3) ppm; IR: $\tilde{\nu}$ = 3456, 3427, 1601, 1449, 1156, 1064 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{23}O$ $[M–OH]^+$: 315.1743; found 315.1743.

(+)-(1*R*,2*R*,5*R*,6*R*)-2,6-bis(4-methoxyphenyl)bicyclo[3.3.1]nona-3,7-diene-2,6-diol (8e). Organolithium reagent was prepared from 1-iodo-4-methoxybenzene. Filtration through a short pad of silica gel with ethyl acetate and subsequent recrystallization from ethyl acetate – hexane mixture afforded diol **8e** (49 mg, 27%) as colorless needles, mp 192–193 °C. $[\alpha]_D^{20} = +225$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3 + CD_3OD$): δ = 7.47 (d, $J = 8.6$ Hz, 4H), 6.84 (d, $J = 8.5$ Hz, 4H), 6.32 (dd, $J = 10.0$, 5.4 Hz, 2H), 5.79 (d, $J = 10.1$ Hz, 2H), 3.77 (s, 6H), 2.60–2.53 (m, 2H), 1.85 (s, 2H), 1.51 (t, $J = 2.7$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3 + CD_3OD$): δ = 158.8 (C), 137.9 (C), 132.8 (CH), 130.5 (CH), 127.7 (CH), 113.3 (CH), 77.7 (C), 55.2 (CH_3), 41.3 (CH), 25.5 (CH_2) ppm; IR: $\tilde{\nu}$ = 3034, 1602, 1501, 1174, 1060, 1025 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{23}H_{23}O_3$ $[M–OH]^+$ 347.1642; found 347.1640.

(+)-(1*R*,2*R*,5*R*,6*R*)-2,6-bis(3,5-dimethylphenyl)bicyclo[3.3.1]nona-3,7-diene-2,6-diol (8f). Organolithium reagent was prepared from 1-bromo-3,5-dimethylbenzene. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (7:3) and subsequent recrystallization from ethyl acetate – hexane mixture afforded diol **8f** (121 mg, 67%) as colorless needles, mp 212–214 °C. $[\alpha]_D^{20} = +200$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (s, 4H), 6.92 (s, 2H), 6.38 (dd, $J = 10.0$, 5.4 Hz, 2H), 5.84 (d, $J = 10.0$ Hz, 2H), 2.70–2.65 (m, 2H), 2.32 (s, 12H), 1.98 (s, 2H), 1.58 (t, $J = 3.1$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 145.6 (C), 137.6 (C), 133.1 (CH), 130.6 (CH), 129.2 (CH), 124.3 (CH), 78.2 (C), 41.1 (CH), 25.6 (CH_2), 21.4 (CH_3) ppm; IR: $\tilde{\nu}$ = 3456, 3427, 1601, 1449, 1156, 1064 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{28}O_2Na$ $[M+Na]^+$: 383.1984; found 383.1981.

(+)-(1*R*,2*R*,5*R*,6*R*)-2,6-bis(3,5-dimethoxyphenyl)bicyclo[3.3.1]nona-3,7-diene-2,6-diol (8g). Organolithium reagent was prepared from 1-iodo-3,5-dimethoxybenzene. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (7:3) afforded diol **8g** (83 mg, 39%) as colorless foam, mp 56–59 °C. $[\alpha]_D^{20} = +112$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.73 (d, $J = 2.3$ Hz, 4H), 6.38 (t, $J = 2.3$ Hz, 2H), 6.35 (dd, $J = 10.0$, 5.4 Hz, 2H), 5.81 (d, $J = 10.0$ Hz, 2H), 3.79 (s, 12H), 2.66–2.60 (m, 2H), 2.04 (br. s, 2H), 1.62 (t, $J = 3.2$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5 (C), 148.1 (C), 132.8 (CH), 130.8 (CH), 105.0 (CH), 99.4 (CH), 78.3 (C), 55.4 (CH_3), 40.9 (CH), 25.6 (CH_2) ppm; IR: $\tilde{\nu}$ = 3424, 1596, 1458, 1426, 1205, 1155 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{27}O_5$ $[M–OH]^+$: 407.1853; found 407.1860.

(+)-(1*R*,2*R*,5*R*,6*R*)-2,6-bis(2,4,6-trimethoxyphenyl)bicyclo[3.3.1]nona-3,7-diene-2,6-diol (8h). *n*-butyllithium (0.83 mL, 2.0 mmol, 2.4 M solution in hexanes) was added dropwise to a vigorously stirred solution of 1,3,5-trimethoxybenzene (505 mg, 3 mmol) in THF (2 mL) at 0 °C and the reaction mixture was stirred for 1 h. The resulting suspension was added dropwise to a stirred solution of dienone **7** (74.1 mg, 0.50 mmol) in Et_2O (5 mL) at 0 °C. The resulting mixture was stirred for 3 h, quenched with aqueous 2 M NH_4Cl (5 mL) and extracted with MTBE (3×10 mL). Pooled organic extracts were washed with brine (2×5 mL), dried with Na_2SO_4 and evaporated under reduced pressure. Residue was purified by flash chromatography on silica gel with petroleum ether – ethyl acetate

mixture (1:1) and subsequent recrystallization from ethyl acetate – hexane mixture to afford diol **8h** (120 mg, 49%) as a colorless crystalline solid, mp 168–170 °C. $[\alpha]_D^{20} = +200$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.14$ (s, 4H), 5.97–5.88 (m, 4H), 4.64 (s, 2H), 3.79 (s, 12H), 3.78 (s, 6H), 2.90 (s, 2H), 1.56 (t, $J = 2.9$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.8$ (C), 159.2 (C), 133.1 (CH), 124.6 (CH), 116.1 (C), 92.7 (CH), 77.1 (C), 56.1 (CH_3), 55.2 (CH_3), 39.5 (CH), 26.3 (CH_2) ppm; IR: $\tilde{\nu} = 1607$, 1583, 1147, 1122, 1109, 814 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{31}O_7$ $[M–OH]^+$: 467.2064; found 467.2064.

General procedure for the synthesis of *O*-alkylated derivatives 3. Alkylating agent (0.8 mmol) and sodium hydride (32 mg, 0.8 mmol, 60% suspension in mineral oil) were sequentially added to a stirred solution of a corresponding diol **8** (0.2 mmol) in DMF (0.8 mL) at 0 °C. The resulting mixture was allowed to warm up to room temperature and stirred overnight, then poured into aqueous 0.1 M HCl solution (20 mL) and extracted with MTBE (3×10 mL). Pooled organic extracts were washed with brine (2×5 mL), dried with Na_2SO_4 and evaporated under reduced pressure. The obtained residue was purified by flash chromatography on silica gel to afford the corresponding *O*-alkyl derivatives.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-dimethoxy-4,8-dimethylbicyclo[3.3.1]nona-2,6-diene (3aa). Prepared from **8a** and methyl iodide. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (9:1) afforded diene **3aa** (18 mg, 43%) as a colorless oil. $[\alpha]_D^{20} = +237$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.81$ (ddt, $J = 10.4$, 5.6, 0.7 Hz, 2H), 5.65 (dq, $J = 10.3$, 0.8 Hz, 2H), 3.28 (s, 6H), 2.49–2.30 (m, 2H), 1.90 (t, $J = 3.2$ Hz, 2H), 1.36 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 130.9$ (CH), 129.1 (CH), 78.1 (C), 49.7 (CH_3), 38.5 (CH), 28.4 (CH_2), 23.6 (CH_3) ppm; IR (neat): $\tilde{\nu} = 2943$, 1119, 1096, 1074, 759 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{13}H_{20}O_2Na$ $[M+Na]^+$: 231.1356; found 231.1353.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-bis(benzyloxy)-4,8-dimethylbicyclo[3.3.1]nona-2,6-diene (3ab). Prepared from **8a** and benzyl bromide. Purification by flash chromatography on silica gel with toluene afforded diene **3ab** (50 mg, 69%) as a colorless oil. $[\alpha]_D^{20} = +158$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.37–7.28$ (m, 8H), 7.27–7.20 (m, 2H), 5.93 (dd, $J = 10.3$, 5.6 Hz, 2H), 5.74 (ddd, $J = 10.2$, 1.4, 0.7 Hz, 2H), 4.60 (ABq, $J_{AB} = 12.4$ Hz, $\Delta\delta_{AB} = 3.3$ Hz, 4H), 2.55–2.49 (m, 2H), 1.98 (t, $J = 3.2$ Hz, 2H), 1.49 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 139.9$ (C), 131.1 (CH), 129.7 (CH), 128.2 (CH), 127.00 (CH), 126.98 (CH), 79.0 (C), 64.4 (CH_2), 39.3 (CH), 28.9 (CH_2), 25.1 (CH_3) ppm; IR (neat): $\tilde{\nu} = 3029$, 1453, 1118, 1101, 696 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{25}H_{28}O_2K$ $[M+K]^+$: 399.1721; found 399.1728.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-dimethoxy-4,8-diphenylbicyclo[3.3.1]nona-2,6-diene (3ba). Prepared from **8b** and methyl iodide. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (95:5) afforded diene **3ba** (56 mg, 84%) as an amorphous colorless solid, mp 118–119 °C (Hexane). $[\alpha]_D^{20} = +228$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.52–7.45$ (m, 4H), 7.38–7.30 (m, 4H), 7.29–7.23 (m, 2H), 6.43 (dd, $J = 10.4$, 5.3 Hz, 2H), 6.10 (ddd, $J = 10.4$, 1.6, 0.9 Hz, 2H), 3.05 (s, 6H), 2.64–2.58 (m, 2H), 1.38 (br. t, $J = 3.2$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.2$ (C), 132.8 (CH), 127.93 (CH), 127.88 (CH), 127.4 (CH), 125.4 (CH), 83.4 (C), 50.6 (CH_3), 41.6 (CH), 25.1 (CH_2) ppm; IR: $\tilde{\nu} = 2897$, 1445, 1086, 1069, 753, 701 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{21}O$ $[M–CH_3O]^+$: 301.1587; found 301.1581.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-bis(benzyloxy)-4,8-diphenylbicyclo[3.3.1]nona-2,6-diene (3bb). Prepared from **8b** and benzyl bromide. Purification by flash chromatography on silica gel with hexane – toluene mixture (7:3) and subsequent recrystallization from hexane afforded diene **3bb** (60 mg, 62%) as fine colorless needles, mp 142–143 °C. $[\alpha]_D^{20} = +145$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.62–7.55$ (m, 4H), 7.40–7.21 (m, 16H), 6.54 (dd, $J = 10.4$, 5.3 Hz, 2H), 6.13 (dq, $J = 10.4$, 0.9 Hz, 2H), 4.45 (d, $J = 12.0$ Hz, 2H), 4.20 (d, $J = 12.0$ Hz, 2H), 2.71 (dt, $J = 4.0$, 3.3 Hz, 2H), 1.45 (br. t, $J = 3.1$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.8$ (C), 139.8 (C), 133.2 (CH), 128.1 (CH), 128.0 (CH), 127.9 (CH), 127.5 (CH), 126.93 (CH), 126.91 (CH), 125.8 (CH), 83.7 (C), 64.7 (CH_2), 41.9 (CH), 25.0 (CH_2) ppm; IR: $\tilde{\nu} = 3031$, 2911, 1191, 1084, 1055, 702 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{35}H_{32}O_2K$ $[M+K]^+$: 523.2034; found 523.2032.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-bis(4-fluorophenyl)-4,8-dimethoxybicyclo[3.3.1]nona-2,6-diene (3ca). Prepared from **8c** and methyl iodide. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (95:5) afforded diene **3ca** (50 mg, 68%) as a colorless foam, mp 49–51 °C. $[\alpha]_D^{20} = +183$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.49–7.40$ (m, 4H), 7.08–6.95 (m, 4H), 6.40 (dd, $J = 10.4$, 5.3 Hz, 2H), 6.06 (ddd, $J = 10.4$, 1.7, 0.9 Hz, 2H), 3.03 (s, 6H), 2.59–2.50 (m, 2H), 1.33 (br. t, $J = 3.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.1$ (d, $J = 246.1$ Hz, C), 138.9 (d, $J = 3.1$ Hz, C), 132.9 (CH), 129.5 (d, $J = 8.0$ Hz, CH), 125.2 (CH), 114.8 (d, $J = 21.2$ Hz, CH), 82.9 (C), 50.5 (CH_3), 41.8 (CH), 24.9 (CH_2) ppm; IR: $\tilde{\nu} = 2938$, 1600, 1505, 1074, 832 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{22}H_{19}OF_2$ $[M–CH_3O]^+$: 337.1398; found 337.1398.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-dimethoxy-4,8-di-*p*-tolylbicyclo[3.3.1]nona-2,6-diene (3da). Prepared from **8d** and methyl iodide. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (95:5) afforded diene **3da** (48 mg, 67%) as a colorless foam, mp 52–53 °C. $[\alpha]_D^{20} = +237$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$ (d, $J = 8.1$ Hz, 4H), 7.14 (d, $J = 8.0$ Hz, 4H), 6.39 (dd, $J = 10.3$, 5.2 Hz, 2H), 6.07 (d, $J = 10.3$ Hz, 2H), 3.04 (s, 6H), 2.72–2.50 (m, 2H), 2.34 (s, 6H), 1.38 (t, $J = 2.7$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 140.2$ (C), 137.0 (C), 132.6 (CH), 128.7 (CH), 127.8 (CH), 125.6 (CH), 83.2 (C), 50.5 (CH_3), 41.5 (CH), 25.2 (CH_2), 21.0 (CH_3) ppm; IR: $\tilde{\nu} = 2934$, 1508, 1176, 1079, 814 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{25}O$ $[M–CH_3O]^+$: 329.1900; found 329.1897.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-dimethoxy-4,8-bis(4-methoxyphenyl)bicyclo[3.3.1]nona-2,6-diene (3ea). Prepared from **8e** and methyl iodide. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (9:1) afforded diene **3ea** (73 mg, 93%) as a colorless foam, mp 121–123 °C. $[\alpha]_D^{20} = +236$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.39$ (AA′XX′, $J_{AX+AX'} = 8.8$ Hz, 4H), 6.86 (AA′XX′, $J_{AX+A'X} = 8.8$ Hz, 4H), 6.38 (dd, $J = 10.3$, 5.2 Hz, 2H), 6.07 (ddd, $J = 10.3$, 1.7, 0.9 Hz, 2H), 3.80 (s, 6H), 3.03 (s, 6H), 2.61–2.53 (m, 2H), 1.37 (t, $J = 2.9$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 158.8$ (C), 135.2 (C), 132.5 (CH), 129.0 (CH), 125.6 (CH), 113.3 (CH), 83.0 (C), 55.2 (CH_3), 50.4 (CH_3), 41.7 (CH), 25.2 (CH_2) ppm; IR: $\tilde{\nu} = 2942$, 1607, 1508, 1079, 1071, 753 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{24}H_{25}O_3$ $[M–CH_3O]^+$: 361.1798; found 361.1796.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-bis(3,5-dimethylphenyl)-4,8-dimethoxybicyclo[3.3.1]nona-2,6-diene (3fa). Prepared from **8f** and methyl iodide. Purification by flash chromatography on silica gel with toluene and subsequent recrystallization from hexane afforded diene **3fa** (63 mg, 81%) as colorless crystals, mp 180–182 °C. $[\alpha]_D^{20} = +186$ ($c = 1.00$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.08$ (s, 4H), 6.89 (s, 2H), 6.39 (dd, $J = 10.3$, 5.2 Hz, 2H), 6.07 (d, $J = 10.3$ Hz, 2H), 3.04 (s, 6H), 2.71–2.55 (m, 2H), 2.31 (s, 12H), 1.40 (br. t, $J = 3.0$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 143.1$ (C), 137.3 (C), 132.5 (CH), 129.0 (CH), 125.74 (CH), 125.71 (CH), 83.3 (C), 50.6 (CH_3), 41.4 (CH), 25.3 (CH_2), 21.4 (CH_3) ppm; IR: $\tilde{\nu} = 2935$, 1606, 1598, 1084, 854 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{26}H_{29}O$ $[M–CH_3O]^+$: 357.2213; found 357.2209.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-bis(3,5-dimethylphenyl)-4,8-diethoxybicyclo[3.3.1]nona-2,6-diene (3fc). Prepared from **8f** and diethyl sulfate. Purification by flash chromatography on silica gel with petroleum

ether – ethyl acetate mixture (97:3) afforded diene **3fc** (70 mg, 84%) as a colorless oil that solidified on standing, mp 152–154 °C. $[\alpha]_D^{20} = +230$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.10$ (s, 4H), 6.88 (s, 2H), 6.35 (dd, $J = 10.3$, 5.2 Hz, 2H), 6.01 (br. d, $J = 10.3$ Hz, 2H), 3.36 (dq, $J = 8.7$, 6.9 Hz, 2H), 3.08 (dq, $J = 8.7$, 6.9 Hz, 2H), 2.66–2.58 (m, 2H), 2.31 (s, 12H), 1.41 (t, $J = 3.4$ Hz, 2H), 1.10 (t, $J = 6.9$ Hz, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 144.2$ (C), 137.1 (C), 132.3 (CH), 128.8 (CH), 126.7 (CH), 125.5 (CH), 82.9 (C), 57.8 (CH_2), 41.0 (CH), 25.1 (CH_2), 21.4 (CH_3), 15.8 (CH_3) ppm; IR: $\tilde{\nu} = 3034$, 1606, 1598, 1156, 1072, 703 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{27}H_{31}O$ $[M–C_2H_5O]^+$: 371.2369; found 371.2365.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-bis(3,5-dimethoxyphenyl)-4,8-dimethoxybicyclo[3.3.1]nona-2,6-diene (3ga). Prepared from **8g** and methyl iodide. Purification by flash chromatography on silica gel with petroleum ether – ethyl acetate mixture (9:1) and subsequent recrystallization from cyclohexane afforded diene **3ga** (70 mg, 77%) as colorless crystals, mp 186–187 °C. $[\alpha]_D^{20} = +112$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.64$ (d, $J = 2.1$ Hz, 4H), 6.37 (dd, $J = 10.3$, 5.6 Hz, 2H), 6.37 (t, $J = 2.1$ Hz, 2H), 6.04 (br. d, $J = 10.3$ Hz, 2H), 3.79 (s, 12H), 3.07 (s, 6H), 2.64–2.53 (m, 2H), 1.43 (br. t, $J = 3.1$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 160.5$ (C), 145.9 (C), 132.8 (CH), 125.3 (CH), 106.3 (CH), 99.2 (CH), 83.4 (C), 55.4 (CH_3), 50.7 (CH_3), 41.4 (CH), 25.2 (CH_2) ppm; IR: $\tilde{\nu} = 1598$, 1454, 1426, 1202, 1155, 738 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{26}H_{29}O_5$ $[M–CH_3O]^+$: 421.2010; found 421.2010.

(+)-(1*R*,4*R*,5*R*,8*R*)-4,8-dimethoxy-4,8-bis(2,4,6-trimethoxyphenyl)bicyclo[3.3.1]nona-2,6-diene (3ha). Prepared from **8h** and methyl iodide. Purification by flash chromatography on silica gel with methyl *tert*-butyl ether afforded diene **3ha** (52 mg, 51%) as a colorless amorphous solid, mp 70–73 °C. $[\alpha]_D^{20} = +136$ ($c = 1.00$, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.26$ (d, $J = 10.2$ Hz, 2H), 6.15 (br. s, 4H), 5.87 (dd, $J = 10.2$, 4.9 Hz, 2H), 3.80 (s, 12H), 3.68 (br. s, 6H), 3.38–3.32 (m, 2H), 3.04 (s, 6H), 1.44 (t, $J = 2.8$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 162.3$ (br. C), 160.6 (br. C), 160.2 (C), 129.6 (CH), 124.4 (CH), 112.1 (C), 93.0 (br. CH), 83.1 (C), 56.8 (br. CH_3), 55.9 (br. CH_3), 55.1 (CH_3), 50.3 (CH_3), 36.7 (CH), 27.6 (CH_2) ppm; IR: $\tilde{\nu} = 1604$, 1582, 1412, 1150, 1128, 1077 cm^{-1}; HRMS (ESI-TOF): *m/z* calcd for $C_{28}H_{33}O_7$ $[M–CH_3O]^+$: 481.2221; found 481.2215.

Preparation of [RhCl(3ba)]$_2$ and [RhCl(3fa)]$_2$. A solution of [RhCl$(C_2H_4)_2]_2$ (17.5 mg, 0.09 mmol Rh) and corresponding diene ligand (0.075 mmol) in dry benzene (1.5 mL) was stirred overnight at 50 °C under an argon atmosphere. The cooled mixture was filtered through a pad of Celite and the pad was washed with benzene. The filtrate was evaporated and passed through a pad of silica gel eluting with hexane – ethyl acetate mixture (9:1) to afford corresponding rhodium complex.

[RhCl(3ba)]$_2$. Orange glass (34 mg, 97%); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41$ (app. d, $J = 7.0$ Hz, 4H), 7.28 (app. t, $J = 7.3$ Hz, 4H), 7.22 (app. t, $J = 7.2$ Hz, 2H), 4.73 (ddd, $J = 7.4$, 5.1, 2.1 Hz, 2H), 4.66 (br. d, $J = 7.4$ Hz, 2H), 3.68 (s, 6H), 1.99–1.95 (m, 2H), 0.64 (br. t, $J = 3.6$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.3$ (C), 127.8 (CH), 127.7 (CH), 127.4 (CH), 88.6 (C), 77.6 (d, $^1J_{C\text{-}Rh} = 13.3$ Hz, CH), 71.6 (d, $^1J_{C\text{-}Rh} = 13.6$ Hz, CH), 51.2 (CH_3), 40.5 (CH), 25.2 (CH_2) ppm; IR: $\tilde{\nu} = 2919$, 1445, 1084, 1066, 756, 697 cm^{-1}.

[RhCl(3fa)]$_2$. Orange glass (38 mg, 96%); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.0$ (br. s, 4H), 6.84 (br. s, 2H), 4.71 (ddd, $J = 7.4$, 5.1, 1.9 Hz, 2H), 4.65 (br. d, $J = 7.4$ Hz, 2H), 3.67 (s, 6H), 2.27 (s, 12H), 1.98–1.95 (m, 2H), 0.66 (br. t, $J = 3.6$ Hz, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 141.4$ (C), 137.1 (C), 128.9 (CH), 125.6 (br. CH), 88.5 (C), 77.6 (d, $^1J_{C\text{-}Rh} = 13.0$ Hz, CH), 71.6 (d, $^1J_{C\text{-}Rh} = 13.6$ Hz, CH), 51.2 (CH_3), 40.5 (CH), 25.3 (CH_2), 21.4 (CH_3) ppm; IR: $\tilde{\nu} = 2920$, 1600, 1439, 1080, 1071, 848, 706 cm^{-1}.

Typical procedure for the 1,4-addition of boronic acids to cyclic enones. $[RhCl(C_2H_4)_2]_2$ (1.75 mg, 9.0 μmol Rh), ligand **3fa** (3.9 mg, 9.9 μmol) and corresponding arylboronic acid **5** (1.4–1.8 equiv.; for details, see Table 2) were combined in a flask equipped with a magnetic stir bar. The flask was flushed with argon, charged with deoxygenated THF (1 mL) and the resulting solution was stirred at 50 °C for 15 min to allow for ethylene-ligand exchange. The solution was cooled to room temperature and neat enone **4** (0.3 mmol, 1.0 equiv.) was added, followed by aqueous potassium hydroxide (100 μL, 1.5 M solution, 50 mol%). The reaction mixture was allowed to stir for 3–5 hours at room temperature, then diluted with ethyl acetate (10 mL), washed with 10% aqueous solution of NaOH (2× 5 mL) and brine (2×5 mL). The organic phase was dried (Na_2SO_4), evaporated and the obtained residue was purified by column chromatography on silica gel to afford corresponding 3-arylcycloalkanones **6**.

Conflict of Interest

The authors declare no conflict of interest.

Keywords: Asymmetric catalysis · Rhodium · Diene ligands · Michael addition · Enones

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[34] Rh/**3fa**-catalyzed arylation of **4a** with **5a** (1.4 equiv.) in 1,4-dioxane (3 mol% Rh, 50 mol% KOH, 1 h) afforded **6aa** in 96% yield and 96% ee.
[35] Rh/**3fa**-catalyzed arylation of acyclic 4-phenylbut-3-en-2-one and unsaturated lactone furan-2(5*H*)-one with **5k** and **5a**, respectively, was also tested and afforded corresponding addition products in high yields, but unsatisfactory enantioselectivity (22 and 16% ee, respectively).

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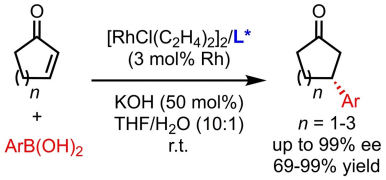

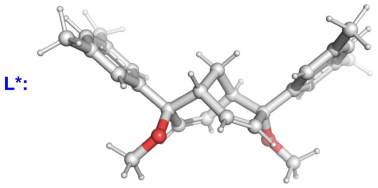

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Fine-Tuning the Bicyclo[3.3.1] nona-2,6-diene Ligands: Second Generation 4,8-Substituted Dienes for Rh-Catalyzed Asymmetric 1,4-Addition Reactions

Asymmetric catalysis: Room temperature asymmetric Rh-catalyzed arylation of cyclic enones with boronic acids in the presence of the second generation C_2-symmetric 4,8-*endo,endo*-bis(alkoxy) bicyclo[3.3.1] nona-2,6-diene ligands affords corresponding 1,4-addition products in 69–99% yields and enantioselectivities up to 99% ee. Bulky 4,8-*exo,exo* groups in such tetrasubstituted bicyclo[3.3.1] nona-2,6-dienes provide a further element for fine-tuning of the ligand structure.