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Expanding the C_1-Symmetric Bicyclo[2.2.1]heptadiene Ligand Family: Highly Enantioselective Synthesis of Cyclic β-Aryl-Substituted Carbonyl Compounds

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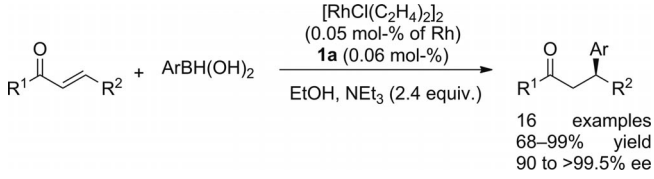
The efficient preparation of highly enantioenriched cyclic β-aryl-substituted carbonyl compounds has been achieved through the Rh^I-catalyzed asymmetric 1,4-addition of an array of arylboronic acids to cyclic α,β-unsaturated carbonyl compounds. In the presence of 0.1 or 0.5 mol-% of the Rh^I/**1g** complex, the products of conjugate addition were isolated in 89 to 98 % *ee* and in good to excellent yield.

Introduction

Enantioselective carbon–carbon bond formation is crucial to the synthesis of complex organic molecules. As a consequence, the development of efficient and highly stereoselective asymmetric C–C bond-forming processes is absolutely critical to the practice of modern-day synthetic organic chemistry. The transition-metal-catalyzed asymmetric conjugate addition of carbon-based nucleophiles to α,β-unsaturated carbonyl compounds is one of the most important reactions presently used in the preparation of chiral β-substituted carbonyl compounds, which, in turn, can often be converted into many biologically active compounds or natural products of great value.[1] Chiral rhodium(I) catalysts have proven especially versatile and useful and allow various organoboron reagents to be employed as nucleophiles. The advantages of using such methodology are derived from the high stability and ready availability of many organoboron reagents and their high degree of compatibility with a wide range of functional groups.[2] Recent developments in this area have included the utilization of novel chiral dienes as new chiral ligands for rhodium.[3] Their primary advantage stems from their greater catalytic activity in these reactions and in the higher degree of enantioselectivity they often impart to many asymmetric rhodium-catalyzed 1,4-addition reactions when compared with their chiral phosphane counterparts. Hence, significant effort has gone into the design, synthesis, and study of new chiral diene ligands for such asymmetric transformations.[4–7] In this connection, we recently described the synthesis of a new set of chiral diene ligands **1** for Rh that possess a 2,5-substituted bicyclo[2.2.1]heptadiene skeleton, and significantly, we also observed that these are highly efficient for mediating various Rh-catalyzed asymmetric 1,4-conjugate addition processes.

With an overall catalyst loading as low as 0.05 mol-%, reactions of a variety of arylboronic acids with acyclic α,β-unsaturated ketones and esters provided 1,4-adducts with high enantioselectivities (90→99.5 %*ee*) at ambient temperatures (Scheme 1).[8] However, cyclic α,β-unsaturated carbonyl compounds proved unsuitable substrates under these reaction conditions, with none of the desired product being observed after 48 h in the reaction between 2-cyclohexenone and phenylboronic acid. This limitation led us to study the synthesis of optically active 3-arylindanones through multistep manipulations from acyclic substrates.[8]



Scheme 1. Asymmetric conjugate addition of various arylboronic acids to acyclic α,β-unsaturated carbonyl compounds.

Motivated by an interest in preparing chiral cyclic β-substituted carbonyl compounds as intermediates for the synthesis of various natural products and biologically active compounds and given that a family of 2,5-disubstitued bicyclo[2.2.1] chiral diene ligands **1** were now at hand, the Rh^I-catalyzed 1,4-addition of different cyclic enones was studied. This report now presents the results of exploiting ligand **1** in the enantioselective addition of arylboronic acids to cyclic α,β-unsaturated carbonyl compounds.

Results and Discussion

At the outset of our work, the model reaction of 2-cyclohexenone (**2a**) and phenylboronic acid (**3a**) was examined

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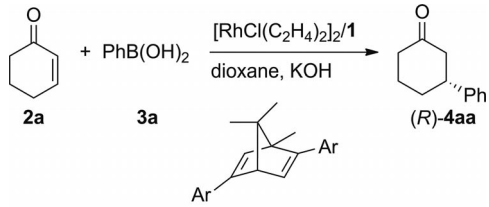
to study the effect of the loading of ligand **1a** on both yield and *ee* by using aqueous potassium hydroxide as a base and dioxane as a solvent. In the presence of 1 mol-% of the Rh^I/**1a** catalyst prepared in situ, desired adduct **4aa** was isolated in 78% yield with an unsatisfactory *ee* (60%), whereas when 3 mol-% of the complex was used, this resulted in a similar level of enantioinduction but a better yield (Table 1, Entries 1 and 2). Next, the catalytic reactions of ligands **1b**–**g** were examined. Whereas 2,5-diphenyl-substituted chiral diene ligand **1b** has been demonstrated in the addition reaction, completed within 1 h, to give (*R*)-**4aa** in 94% yield and 91%*ee* (Table 1, Entry 3),[8] the catalytic reaction that exploited **1c** as a ligand (which bears 4-tolyl substituents on the diene functionality) yielded the desired adduct with high *ee* (Table 1, Entry 4), and 4-*tert*-butylphenyl-substituted diene ligand **1d** detrimentally affected the enantioselectivity (Table 1, Entry 5). High asymmetric induction also occurred when ligands with electron-withdrawing groups on the benzene rings were adopted (i.e., **1e** and **1f**); these gave rise to compound **4aa** with 91 and 92%*ee* (Table 1, Entries 6 and 7, respectively). Given these observations, it was assumed that diene ligand **1g**, with highly electron-withdrawing 4-nitrophenyl substituents, would provide the 1,4-adduct with better enantioselectivity. Accordingly, ligand **1g** was synthesized by our reported method, which employs a Pd-catalyzed Suzuki cross-coupling reaction.[8] The asymmetric addition, in the presence of 3 mol-% of Rh/**1g**, thereafter yielded 1,4-adduct **4aa** with 93%*ee* and 92% yield (Table 1, Entry 8).

Table 1. Asymmetric 1,4-addition of phenylboronic acid (**3a**) to 2-cyclohexenone (**2a**).[a]



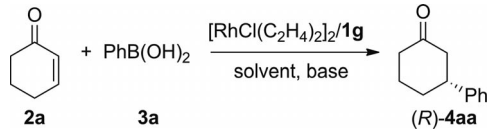
1a: Ar = 1-naphthyl; **1b**: C_6H_5; **1c**: Ar = 4-MeC_6H_4; **1d**: 4-*t*BuC_6H_4; **1e**: Ar = 4-FC_6H_4; **1f**: 4-ClC_6H_4; **1g**: Ar = 4-$NO_2C_6H_4$

Entry	Ligand	Yield [%][b]	*ee* [%][c]
1[d]	**1a**	78[e]	60
2	**1a**	95[e]	62
3	**1b**	94	91
4	**1c**	91	92
5	**1d**	87	64
6	**1e**	84	91
7	**1f**	89	92
8	**1g**	92	93

[a] Conditions: $[RhCl(C_2H_4)_2]_2$ (3 mol-% of Rh), **1** (3.6 mol-%), **2a** (0.2 mmol), **3a** (0.4 mmol). The reactions were carried out under an Ar atmosphere at 30 °C for 1 h. [b] Calibrated GC yields with the use of *n*-decane as an internal standard. [c] Determined by chiral HPLC, and the absolute configuration of **4aa** was determined by comparison of the sign of the specific rotation with that of the known sample; see the Supporting Information. [d] 1 mol-% of catalyst was used. [e] Isolated yield after 3 h.

Next, the general reaction conditions were optimized by screening different solvents and bases for the catalytic asymmetric addition of phenylboronic acid to 2-cyclohexenone by using ligand **1g** (Table 2).[9] In general, the optical induction of the conjugate addition reactions that were carried out in ethereal solvents was generally encouraging, yielding (*R*)-3-phenylcyclohexanone (**4aa**) with good to excellent levels of enantioselectivity (88–93%*ee*) and high chemical yields (Table 2, Entries 1–3). Similar results were also obtained when this reaction was carried out in alcohol as a solvent; the best yield (>99%) and *ee* (95%) were obtained in 2-propanol (Table 2, Entry 6).[10] Subsequently, a series of aqueous alkali metal hydroxide solution were examined as bases. Generally, the isolation of **4aa** in high yield along with a 92–94%*ee* was achieved (Table 2, Entries 7–9).[11] Substitution of KOH in 2-propanol for aqueous KOH had no positive effect on the reaction (Table 2, Entry 10). However, in parallel screenings aimed at identifying an optimal combination of a solvent and base, a slight increment in enantioselectivity (96%*ee*) was observed when potassium hydroxide in ethanol was used in ethanol as the solvent (Table 2, Entry 11).

Table 2. Optimization of reaction conditions.[a]



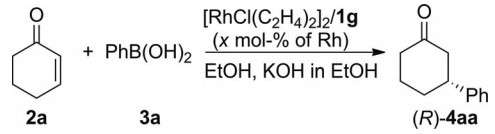
Entry	Solvent	Base	Yield [%][b]	*ee* [%][c]
1	dioxane	aq. KOH	92	93
2	THF	aq. KOH	72	88
3	glyme	aq. KOH	64	91
4	MeOH	aq. KOH	>99	92
5	EtOH	aq. KOH	92	93
6	2-propanol	aq. KOH	>99	95
7	2-propanol	aq. LiOH	>99	93
8	2-propanol	aq. NaOH	96	92
9	2-propanol	aq. CsOH	88	94
10	2-propanol	KOH in 2-propanol	96	94
11	EtOH	KOH in EtOH	97	96

[a] Conditions: $[RhCl(C_2H_4)_2]_2$ (3 mol-% of Rh), **1g** (3.6 mol-%), **2a** (0.2 mmol), **3a** (0.4 mmol). The reactions were carried out under an Ar atmosphere at 30 °C for 1 h. [b] Calibrated GC yields with the use of *n*-decane as an internal standard. [c] Determined by chiral HPLC; see the Supporting Information.

Because a high turnover number (TON)[8,12] for the catalyst is one of the key features associated with using chiral dienes for metal-catalyzed asymmetric transformations, the effect of the catalyst loading of Rh^I/**1g** on the reaction outcome under the conditions specified in Entry 11 in Table 2 was studied. High catalytic reactivity and enantioselectivity of ligand **1g** were anticipated as the loading of the catalyst was reduced. As shown in Table 3, in the presence of 2.0–0.1 mol-% of the catalyst, the conjugate addition of phenylboronic acid (**3a**) to 2-cyclohexenone (**2a**) generated desired adduct **4aa** without loss of high enantioselectivity and

yield (Table 3, Entries 1–5), although more time was required for the catalytic reaction to proceed with the use of 0.1 mol-% of the catalyst (Table 3, Entry 5). Notably, 0.05 mol-% of Rh^{I}/**1g** promoted the asymmetric transformation, forming the desired adduct with 96%*ee*, but in an unsatisfactory yield after 24 h, preventing the adoption of these conditions (Table 3, Entry 6).

Table 3. Optimization of ligand loading on the model reaction.[a]



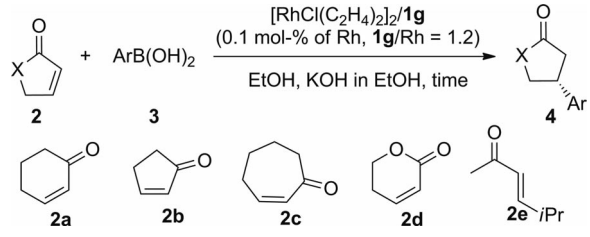
2a **3a** (*R*)-**4aa**

Entry	Rh [mol-%]	Yield [%][b]	*ee* [%][c]
1	2.0	91	95
2	1.5	98	93
3	1.0	>99	94
4	0.5	>99	95
5[d]	0.1	>99	95
6[e]	0.05	14	96

[a] The reactions were conducted with the use of [RhCl(C_2H_4)$_2$]$_2$ (0.003 mmol) and the required amount of reagents were added accordingly. All reactions were carried out under an Ar atmosphere at 30 °C for 1 h. [b] Calibrated GC yields with the use of *n*-decane as an internal standard. [c] Determined by chiral HPLC; see the Supporting Information. [d] The reaction was conducted for 8 h. [e] The reaction was conducted for 24 h.

The above process was extended to catalytic reactions of a series of cyclic α,β-unsaturated carbonyl compounds with various arylboronic acids under the optimized general conditions. Table 4 summarizes the results from which certain trends were identified. Both 2-cyclohexenone (**2a**) and 2-cyclopentenone (**2b**) proved to be favorable substrates in this study, with observed enantiomeric excess values for a number of arylboronic acids lying in the range of 90–98%, regardless of whether the nucleophiles bore electron-donating or electron-withdrawing substituents (Table 4, Entries 1–12). Whereas excellent *ee* values were generally observed, the use of sterically hindered 2-methylphenylboronic acid (Table 4, Entries 6 and 11) and 4-fluorophenylboronic acid (Table 4, Entries 7 and 12) required the use of 0.5 mol-% of the catalyst to produce a satisfactory yield. Similar results were also encountered when a α,β-unsaturated δ-lactone, 6-dihydro-2*H*-pyran-2-one (**2d**), was investigated as an acceptor. In the presence of 0.5 mol-% of the rhodium complex, addition reactions of phenylboronic acid (**3a**) and 4-methylphenylboronic acid (**3e**) to compound **2d** furnished the corresponding adducts **4da** and **4de** with 95 and 85%*ee*, respectively, but in unsatisfactory chemical yields, mainly because of the ring-opening side reaction (Table 4, Entries 15 and 16). Conducting the catalytic reactions in dioxane not only improved the chemical yields but also the enantioselectivities up to 97%*ee*. 2-Cycloheptenone (**2c**) was likewise found to be a good substrate for the present Rh complex, such that, in the presence of 0.5 mol-% of Rh/**1g**, the enantioselective addition of both arylboronic acids **3a** and **3e** gave (*R*)-3-phenylcycloheptanone (**4ca**) and (*R*)-3-*p*-tolylcycloheptanone (**4ce**) with high enantioselectivities (Table 4, Entries 13 and 14). This investigation was further expanded to include acyclic α,β-unsaturated ketone **2e** as a substrate. High yields (83–99%) and excellent enantioselectivity (93–97%) were noted in the catalytic reactions of **2e** with arylboronic acids in the presence of 0.1 mol-% of the catalyst (Table 4, Entries 17–19).[13]

Table 4. Asymmetric addition to cyclic α,β-unsaturated carbonyl compounds.[a]



2 **3** **4**

2a **2b** **2c** **2d** **2e**

Entry	**2**	Ar	Time [h]	Yield [%][b]	*ee* [%][c]
1	**2a**	Ph (**3a**)	8	93 (**4aa**)	95
2	**2a**	4-PhC_6H_4 (**3b**)	2.5	90 (**4ab**)	98
3	**2a**	4-MeOC_6H_4 (**3c**)	1	85 (**4ac**)	94
4	**2a**	2-MeOC_6H_4 (**3d**)	1	95 (**4ad**)	92
5	**2a**	4-MeC_6H_4 (**3e**)	1	>99 (**4ae**)	89
6[d]	**2a**	2-MeC_6H_4 (**3f**)	1	>99 (**4af**)	90
7[d]	**2a**	4-FC_6H_4 (**3g**)	1	>99 (**4ag**)	96
8	**2a**	3-$CF_3C_6H_4$ (**3h**)	1	96 (**4ah**)	96
9	**2b**	Ph (**3a**)	2	99 (**4ba**)	97
10	**2b**	4-MeOC_6H_4 (**3c**)	1	98 (**4bc**)	92
11[d]	**2b**	2-MeC_6H_4 (**3f**)	1	93 (**4bf**)	95
12[d]	**2b**	4-FC_6H_4 (**3g**)	1	88 (**4bg**)	96
13[d]	**2c**	Ph (**3a**)	1.5	>99 (**4ca**)	95
14[d]	**2c**	4-MeC_6H_4 (**3e**)	1.5	>99 (**4ce**)	89
15[d]	**2d**	Ph (**3a**)	2 (7)[e]	43 (59)[e] (**4da**)	95 (97)[e]
16[d]	**2d**	4-MeC_6H_4 (**3e**)	2 (7)[e]	38 (54)[e] (**4de**)	85 (92)[e]
17	**2e**	Ph (**3a**)	2	89 (**4ea**)	96
18	**2e**	4-MeOC_6H_4 (**3c**)	1	99 (**4ec**)	93
19	**2e**	2-MeC_6H_4 (**3f**)	8	83 (**4ef**)	97

[a] Reactions were carried out on a 6.0-mmol scale at 30 °C. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC; see the Supporting Information. [d] Reactions were carried out on a 1.2-mmol scale in the presence of 0.5 mol-% of the catalyst. [e] Results in the parentheses are from reactions conducted in dioxane.

Conclusions

In summary, a highly enantioselective rhodium-catalyzed conjugate addition of various arylboronic acids to cyclic α,β-unsaturated carbonyl compounds has been developed. Chiral diene **1g** is a ligand that exhibits excellent catalytic reactivity and enantioselectivities toward cyclic and acyclic enones and lactones. In the presence of 0.1 or 0.5 mol-% of the Rh^{I}/**1g** catalyst, generated in situ, the corresponding adducts were isolated with 89 to 98%*ee* and in good to excellent chemical yields. Future work in the authors' labo-

ratory will focus on the employment of chiral diene ligands **1** in challenging metal-catalyzed asymmetric transformations.

Experimental Section

General Procedure for the Synthesis of Chiral Diene Ligand 1g: To a solution of corresponding bistriflate (0.6 mmol), $Pd(PPh_3)_4$ (0.06 mmol), and 4-nitrophenylboronic acid (2.35 mmol) in toluene (9.5 mL) was added EtOH (2.4 mL) and sat. aqueous Na_2CO_3 (4.9 mL) at room temperature under an atmosphere of argon, and the resulting mixture was stirred at reflux. After 90 min, sat. aqueous NH_4Cl was added, and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layer was washed with brine and dried with Na_2SO_4, filtered, and evaporated to give the crude product, which was purified by column chromatography over silica gel to give ligand **1g** (104 mg, 46%) as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.20–8.18 (m, 4 H), 7.53–7.52 (m, 2 H), 7.39–7.37 (m, 2 H), 7.00 (d, J = 1.3 Hz, 1 H), 6.93 (d, J = 3.5 Hz, 1 H), 3.65 (dd, J = 3.5, 1.3 Hz, 1 H), 1.34 (s, 3 H), 1.20 (s, 3 H), 1.16 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.8, 154.0, 146.7, 146.7, 144.6, 144.1, 142.3, 140.7, 126.7 (2 CH), 125.1 (2 CH), 124.1 (2 CH), 123.7 (2 CH), 82.9, 66.6, 61.3, 21.4, 21.2, 11.0 ppm.

General Procedure for Rhodium-Catalyzed 1,4-Addition: A mixture of $[RhCl(C_2H_4)]_2$ (1.2 mg, 0.003 mmol), chiral diene ligand **1g** (2.7 mg, 0.0072 mmol), and phenylboronic acid (1.46 g, 12 mmol) in EtOH (20 mL) was stirred for 20 min at 30 °C. 2-Cyclohexen-1-one (**2a**; 577 mg, 6 mmol) was then added. After stirring for another 20 min, 1.5 M KOH in EtOH (2.0 mL) was added. After completion of the reaction, the solvent was removed under reduced pressure to give the crude product, which was purified by column chromatography over silica gel (hexane/ethyl acetate, 19:1) to furnish 3-phenylcyclohexanone (**4aa**, 971 mg, 93%) as a colorless oil. The *ee* was determined with a Daicel Chiralcel IA column with hexanes/2-propanol = 99:1, flow rate = 1.0 mL/min, retention times: 12.05 min [(*S*)-enantiomer], 13.57 min [(*R*)-enantiomer]; 95%*ee*. $[\alpha]_D^{19}$ = +24.1 (c = 0.92 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.33 (m, 2 H), 7.29–7.23 (m, 3 H), 3.04 (tt, J = 11.8, 4.0 Hz, 1 H), 2.67–2.35 (m, 4 H), 2.23–2.07 (m, 2 H), 1.95–1.74 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.9, 144.3, 128.7 (2 CH), 126.7, 126.5 (2 CH), 48.9, 44.7, 41.2, 32.8, 25.5 ppm.

Supporting Information (see footnote on the first page of this article): Experimental procedures, HPLC traces, and copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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[9] Ligand **1g** was chosen for the remaining studies after intensive parallel screenings of ligands with the reaction parameters shown in Tables 2 and 3.

[10] When other solvents such as CH_3CN, DMF, toluene, and DCM were studied, the addition product was obtained with *ee* values ranging from 89 to 94% in 13–77% yield.

[11] When organic bases such as Et_3N and DIPA (diisopropylamine) were tested in the asymmetric reaction, high enantioselectivities (92–94% *ee*) of the corresponding product were observed but with unsatisfactory chemical yields (2–66%).
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[13] In studies of compound **2e** as a substrate, attempts to utilize 0.05 mol-% of the catalyst failed to produce the adduct in good yields after 2 d.

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