Asymmetric Catalysis

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Rhodium-Catalyzed Asymmetric Arylative Cyclization of *meso*-1,6-Dienynes Leading to Enantioenriched *cis*-Hydrobenzofurans**

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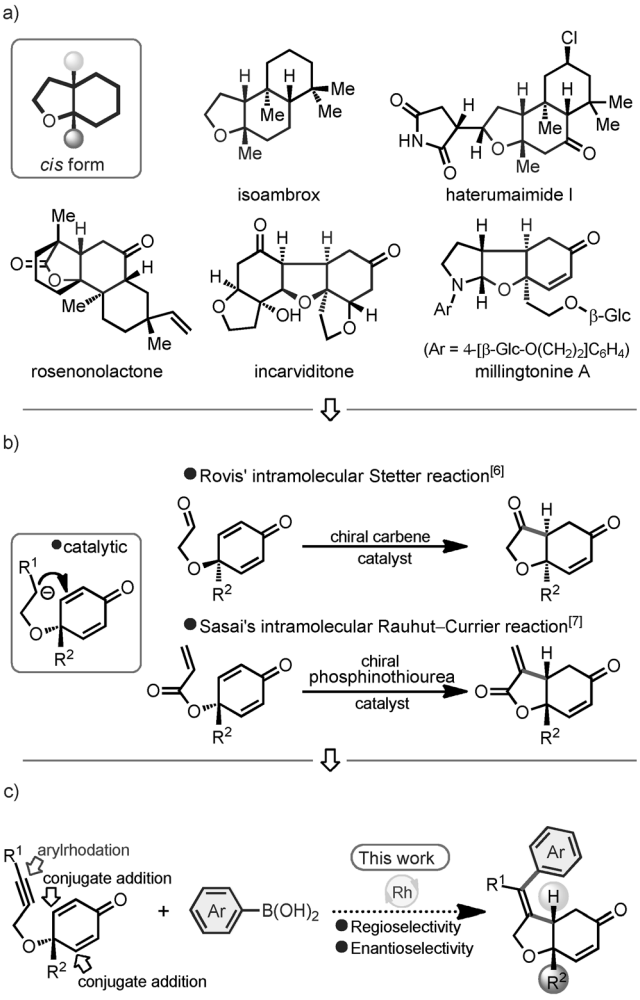
In memory of Wei-Shan Zhou

Chiral *cis*-hydrobenzofurans represent a unique motif existing in numerous natural products, for instance, isoambrox,[1] haterumaimide I,[2] rosenonolactone,[3] incarviditone,[4] and millingtonine A[5] (Scheme 1 a). Owing to their diverse biological activities,[1–5] a great deal of attention has been paid to the development of efficient methods toward their enantioselective syntheses. One of the most straightforward and powerful ways to construct such a framework is the catalytic asymmetric desymmetrization of cyclohexadienones (Scheme 1 b). In recent elegant reports, Rovis and co-workers demonstrated the feasibility of using chiral-NHC-catalyzed intramolecular Stetter reactions for the asymmetric desymmetrization of cyclohexadienones to prepare chiral *cis*-hydrobenzofuranones.[6] Very recently, Sasai and co-workers described the use of bifunctional chiral phosphinothiourea catalysts in a intramolecular Rauhut–Currier reaction for the enantioselective discrimination of cyclohexadienones.[7] Although these protocols[6–8] proved to be highly effective, their efforts were mainly focused on the application of chiral organocatalysts in intramolecular reactions with a limited substrate scope. Moreover, transition metal catalyzed asymmetric desymmetrization of cyclohexadienones is quite scarce.[9]

During our continuous efforts in exploring rhodium/chiral diene-catalyzed asymmetric arylation,[10] we envisioned that a rhodium-catalyzed tandem arylrhodation/conjugate addition reaction of cyclohexadienone-containing[13,14] 1,6-dienynes,[11,12] which are accessible from dearomatization of corresponding phenols,[15] would provide a novel approach to these enantioenriched *cis*-hydrobenzofurans (Scheme 1 c). However, two major concerns need to be addressed in this rhodium-catalyzed asymmetric desymmetrization process.



Scheme 1. Catalytic asymmetric desymmetrization of cyclohexadienones for preparing chiral *cis*-hydrobenzofurans. a) *cis*-Hydrobenzofurans as structural motifs in natural products. b) Organocatalytic asymmetric desymmetrization of cyclohexadienones. c) Our approach to enantioenriched *cis*-hydrobenzofurans.

One is the competitive reaction between the arylrhodation of the carbon–carbon triple bond and two conjugate addition reactions of the cyclohexadienone with the arylboronic acid. The other is whether the chiral ligand coordinating to rhodium could efficiently discriminate between the *meso*-cyclohexadienones in the cyclization step.

With this in mind, several varieties of chiral ligands (Scheme 2) were evaluated for this rhodium-catalyzed asymmetric tandem arylrhodation/conjugate addition of (4-

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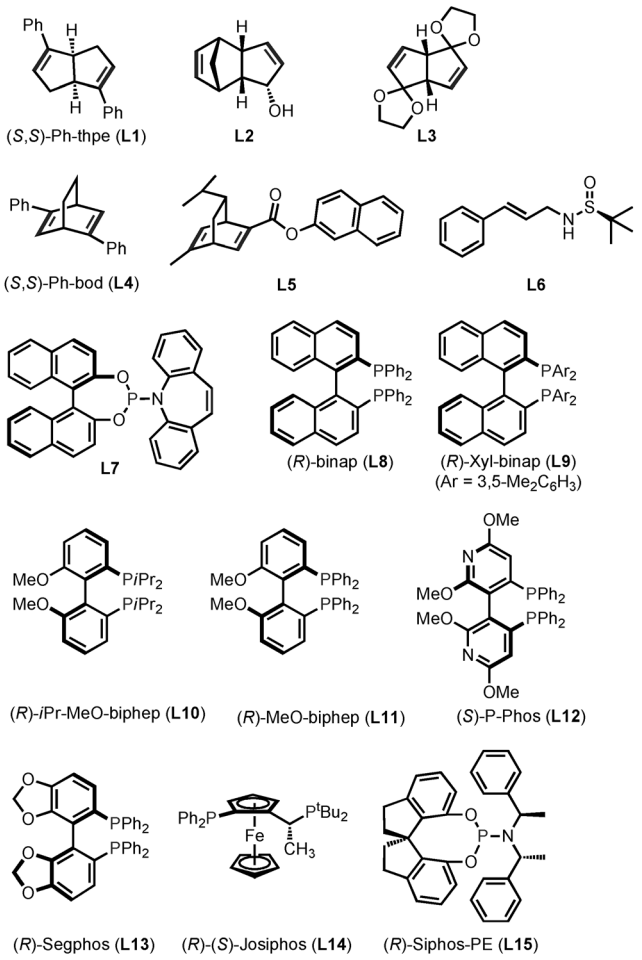
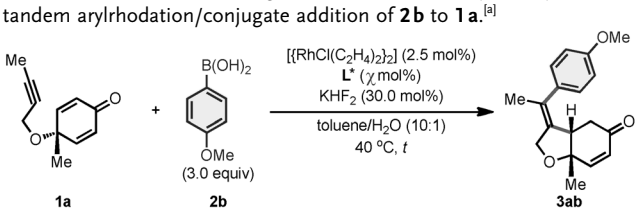


Scheme 2. Structures of chiral ligands.

Table 1: Evaluation of chiral ligands for rhodium-catalyzed asymmetric tandem arylrhodation/conjugate addition of **2b** to **1a**.[a]



Entry	L	*x* (mol%)	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**L1**	5.0	17.0	14	10
2	**L2**	5.0	17.0	29	−24
3	**L3**	5.0	17.0	38	59
4	**L4**	5.0	17.0	27	−57
5	**L5**	5.0	17.5	29	57
6	**L6**	5.0	17.5	16	20
7	**L7**	5.0	17.0	65	−75
8	***L8***	*5.0*	*17.0*	*71*	*96*
9	**L9**	5.0	16.0	24	83
10	**L10**	5.0	22.0	< 5	–
11	**L11**	5.0	16.0	56	93
12	**L12**	5.0	22.0	54	−90
13	**L13**	5.0	16.0	36	93
14	**L14**	5.0	16.0	24	83
15	**L15**	5.0	22.0	38	−60
16	**L8**	6.0	17.0	71	96
17	**L8**	7.5	7.0	95	97
18	***L8***	*10.0*	*6.0*	*99*	*99*
19	**L8**	12.5	12.0	88	99

[a] The reaction was carried out with **1a** (0.1 mmol), **2b** (0.3 mmol), $[\{RhCl(C_2H_4)_2\}_2]$ (2.5 mol%), and chiral ligand (**L***, x mol%) in toluene/H_2O (10:1, 4 mL) at 40°C. [b] Yield of the isolated product. [c] Determined by HPLC analysis using a chiral stationary phase.

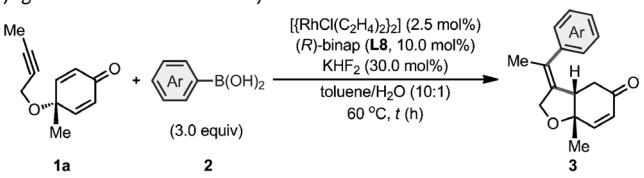
methoxyphenyl)boronic acid (**2b**) to the *meso*-1,6-dienyne substrate **1a**. The reaction was conducted in the presence of 2.5 mol% of $[\{RhCl(C_2H_4)_2\}_2]$ and 5 mol% of a chiral ligand, and the screening results are summarized in Table 1. We began with a representative set of chiral diene ligands (**L1**–**L5**;[16] entries 1–5, Table 1). The desired product **3ab** was obtained despite low yield and low to moderate *ee* values, which might result from the emulative coordination of **1a** and the chiral diene ligand to rhodium. The sulfoxide olefin hybrid ligand **L6**[17] and phosphine olefin hybrid ligand **L7**[18] were subsequently examined in this reaction (entries 6 and 7, Table 1). **L7** furnished the cyclization product with better enantioselectivity, thus indicating that the strong coordination of the phosphorus atom to rhodium played a role in achieving good enantioselectivity. Therefore the bisphosphine ligand (*R*)-binap (**L8**) was used in this catalytic tandem reaction. To our delight, both the reaction yield and the enantioselectivity were dramatically improved to 71% and 96% *ee*, respectively (entry 8, Table 1).

Next, various bisphosphine ligands (**L9**–**L14**) and the monophosphine ligand **L15** were investigated to further improve the enantioselectivity. Unfortunately, they lead to different levels of erosion in yields and *ee* values (entries 9–15, Table 1). Interestingly, almost no desired product was observed when **L10** was used, thus indicating that the π-acidic nature of the bisphosphine ligands play a decisive role in this tandem reaction. This observation is quite similar to the principle in the Hayashi–Miyaura reaction wherein a strong π-accepting ability can significantly accelerate the rate-determining transmetalation step and conjugate addition reaction.[19] From the above preliminary screening results, the chiral ligand (*R*)-binap (**L8**) was the best choice in this tandem reaction. Finally, the catalyst loading was optimized (entries 16–19, Table 1). By employing 10 mol% of (*R*)-binap, both nearly perfect yield (99%) and enantioselectivity (99% *ee*) were achieved.

With the optimal reaction conditions identified, the scope of various arylboronic acids **2** was investigated in this Rh/(*R*)-binap-catalyzed asymmetric tandem arylrhodation/conjugate addition to **1a**. All 4-substituted and 3-substituted arylboronic acids, regardless the electron-donating or electron-withdrawing ability of the substitutent at the phenyl ring, gave both excellent yields and enantioselectivities (entries 2–9, Table 2). As for the 3,5-disubstituted arylboronic acid **2j** and 2-naphthylboronic acid (**2k**), the reaction proceeded smoothly, thus providing the corresponding products with excellent yields and enantioselectivities (entries 10 and 11, Table 2).

Given the highly enantioselective nature of this method, we investigated the addition of different 4-substituted arylboronic acids **2** to various *meso*-1,6-dienynes **1**. As for substrate **1b** (R^1 = Me, R^2 = Et), the tandem reactions with

Table 2: Rh/(*R*)-binap-catalyzed asymmetric tandem arylrhodation/conjugate addition of various arylboronic acids **2** to **1a**.[a]



Entry	**2** (Ar)	*t* [h]	**3**	Yield [%][b]	*ee* [%][c]
1[b]	**2a** (C_6H_5)	6.0	**3aa**	99	97
2[b]	**2b** (4-$MeOC_6H_4$)	6.0	**3ab**	99	99
3[b]	**2c** (4-MeC_6H_4)	18.0	**3ac**	99	98
4[b]	**2d** (4-*t*BuC_6H_4)	11.0	**3ad**	99	99
5	**2e** (4-FC_6H_4)	6.0	**3ae**	92	97
6	**2f** (4-ClC_6H_4)	8.0	**3af**	93	95
7	**2g** (4-BrC_6H_4)	8.0	**3ag**	92	97
8	**2h** (3-MeC_6H_4)	4.0	**3ah**	99	97
9[b]	**2i** (3-$MeOC_6H_4$)	18.0	**3ai**	85	96
10	**2j** (3,5-$Me_2C_6H_3$)	3.0	**3aj**	91	99
11[b]	**2k** (2-naphthyl)	15.0	**3ak**	94	98

[a] The reaction was carried out with **1a** (0.1 mmol), arylboronic acid **2** (0.3 mmol), [{$RhCl(C_2H_4)_2$}$_2$] (2.5 mol%), and (*R*)-binap (10.0 mol%) in toluene/H_2O (10:1, 4 mL) at 60°C, unless otherwise noted. [b] At 40°C. [c] Yield of the isolated product. [d] Determined by HPLC analysis using a chiral stationary phase.

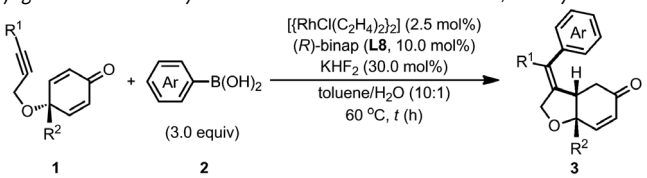
several electronically different 4-substituted arylboronic acids (**2b**, **2d**, **2e** and **2g**) provided excellent yields and enantioselectivities (entries 1–4, Table 3). Despite bulky R^2 or R^1 substituents in **1c**, **1d**, and **1e**, the reaction still performed uniformly with outstanding yields and enantioselectivities (entries 5–13, Table 3). With a heteroatom (O and N) as part of R^2 in substrate **1**, the reaction yields and *ee* values remained high (entries 14 and 15, Table 3).

The absolute configurations of two newly formed chiral centers in **3ag** were unambiguously assigned as *S* and *S* by X-ray crystal crystallography (see the Supporting Information).[20] The absolute configuration of other products could be determined as *S* and *S* by chemical correlation with (*S*,*S*)-**3ag**.

On the basis of the above results, a plausible mechanism is proposed in Scheme 3. Initiation of the reaction through the transmetalation of an aryl group from boron to the hydroxyrhodium **A** generates the aryl rhodium **B**, which subsequently undergoes *syn* addition to the carbon–carbon triple bond in **1** to afford the vinyl rhodium intermediate **C**. The favorable six-membered chair having an axial H atom and equatorial R^2 group in **C** enabled *syn*-migratory insertion of the vinyl rhodium across the carbon–carbon double bond in cyclohexadienone, thus forming the oxa-π-allylrhodium intermediate **D**, which is readily hydrolyzed under protic conditions to regenerate **A** and liberate the product **3**. Throughout the whole catalytic cycle, rhodium maintains an oxidation state of +1.

To check the practical applicability of this tandem reaction, a half-gram scale reaction of **1a** was carried out, and the excellent yield and *ee* value were maintained (Scheme 4). The cyclization products could be further converted into useful core structures related to natural products.

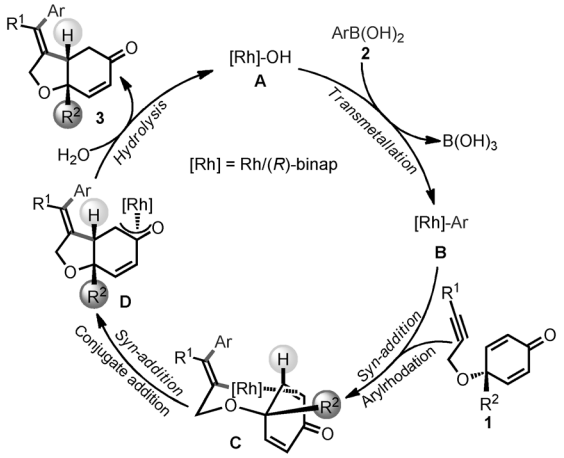
Table 3: Rh/(*R*)-binap-catalyzed asymmetric tandem arylrhodation/conjugate addition of arylboronic Acids **2** to various *meso*-1,6-dienynes **1**.[a]



1b: R^1 = Me, R^2 = Et **1c**: R^1 = Me, R^2 = *i*Pr
1d: R^1 = Me, R^2 = Ph **1e**: R^1 = *n*Bu, R^2 = Me
1f: R^1 = Me, R^2 = $AcO(CH_2)_2$ **1g**: R^1 = Me, R^2 = $BocNH(CH_2)_2$

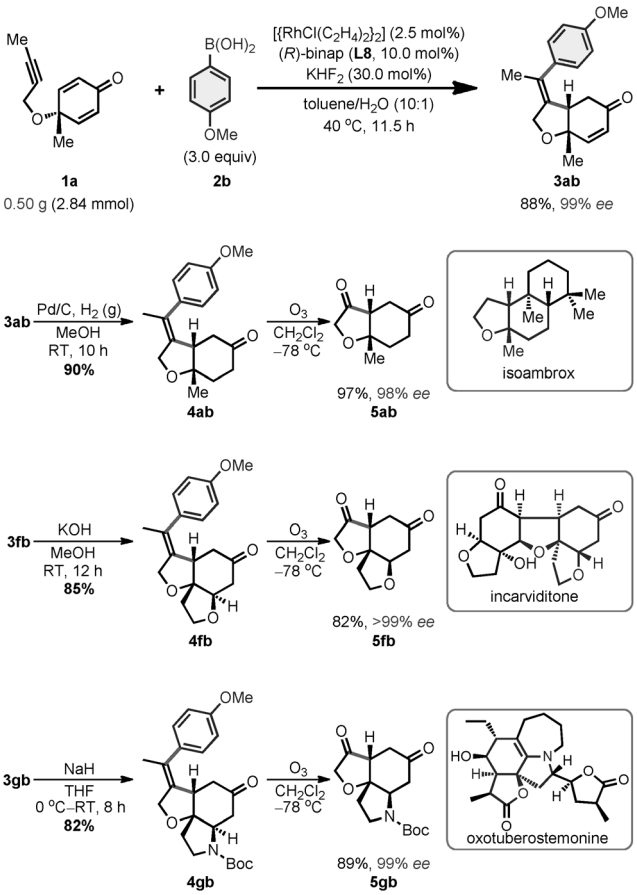
Entry	**1**	**2**	*t* [h]	**3**	Yield [%][e]	*ee* [%][f]
1[b]	**1b**	**2b**	13.0	**3bb**	91	97
2	**1b**	**2d**	2.0	**3bd**	90	98
3	**1b**	**2e**	17.0	**3be**	95	97
4[c]	**1b**	**2g**	17.0	**3bg**	92	95
5[b]	**1c**	**2b**	5.0	**3cb**	97	97
6	**1c**	**2d**	1.0	**3cd**	85	99
7[c]	**1c**	**2g**	20.0	**3cg**	90	97
8[b]	**1d**	**2b**	25.0	**3db**	99	99
9	**1d**	**2d**	3.0	**3dd**	84	98
10[c]	**1d**	**2g**	20.0	**3dg**	88	97
11	**1e**	**2b**	2.0	**3eb**	81	98
12	**1e**	**2d**	1.0	**3ed**	85	98
13[c]	**1e**	**2g**	1.0	**3eg**	84	95
14[d]	**1f**	**2b**	17.0	**3fb**	81	98
15[c]	**1g**	**2b**	17.0	**3gb**	80	98

[a] The reaction was carried out with **1** (0.1 mmol), arylboronic acid **2** (0.3 mmol), [{$RhCl(C_2H_4)_2$}$_2$] (2.5 mol%), and (*R*)-binap (10.0 mol%) in toluene/H_2O (10:1, 4 mL) at 60°C, unless otherwise noted. [b] At 40°C. [c] At 80°C. [d] [{$RhCl(C_2H_4)_2$}$_2$] (3.5 mol%) and (*R*)-binap (14.0 mol%) were used. [e] Yield of the isolated product. [f] Determined by HPLC analysis using a chiral stationary phase. Boc = *tert*-butoxycarbonyl.



Scheme 3. Proposed mechanism for this tandem reaction.

As for **3ab**, the α,β-unsaturated double bond was selectively reduced by hydrogenation, and subsequently the tetrasubstituted double bond was cleaved by ozonolysis to afford the optically pure tetrahydrobenzofurandione **5ab**, which is the core structure of isoambrox.[1] The oxygen and nitrogen atoms in **3fb** and **3gb**, respectively, provided a handle to construct tricyclic skeletons through Michael additions. After removing the acetyl group in **3fb** under basic conditions, an oxa-Michael addition reaction occurred in situ in a *syn* fashion to



Scheme 4. Half-gram scale reaction and transformations of the cyclization products. THF = tetrahydrofuran.

give **4fb**. Similarly, upon treatment of **3gb** with NaH, an aza-Michael addition reaction also proceeded equally well in a *syn* fashion to deliver the octahydrofuro[2,3-d]indolone **4gb**. Subsequent cleavage of the carbon–carbon double bond in **4fb** and **4gb** produced the corresponding optically pure tricyclic structures **5fb** and **5gb**, thus serving as the architecture units of incarviditone[4] and oxotuberostemonine,[21] respectively.

In summary, through tandem arylrhodation/conjugate addition reaction, rhodium-catalyzed asymmetric arylative cyclization of cyclohexadienone-containing *meso*-1,6-dienynes has been developed with high efficiency, thus providing optically pure *cis*-hydrobenzofurans with high to excellent yields (80–99%) and excellent enantioselectivities (95–99% *ee*). The cyclization products were transformed to interesting chiral frameworks of some natural products, thus demonstrating the utility of the products. Further studies on the applications of the cyclohexadienone-containing *meso*-1,6-dienynes are in progress in our laboratories and will be reported in due course.

Experimental Section

3ab: A dried Schlenk flask was charged with (4-methoxyphenyl)boronic acid **2b** (45.6 mg, 0.3 mmol, 3.0 equiv), $[\{RhCl(C_2H_4)_2\}_2]$ (1.0 mg, 0.0025 mmol, 2.5 mol%), (*R*)-binap (**L8**, 6.2 mg, 0.01 mmol, 10.0 mol%), KHF_2 (2.3 mg, 0.03 mmol, 30 mol%), and 2.0 mL of anhydrous toluene under argon. The resulting mixture was stirred at room temperature for 30 min. The 1,6-dienyne substrate **1a** (17.6 mg, 0.1 mmol) in anhydrous toluene (2.0 mL) was added, and then 0.4 mL of degassed water was added. After stirring at 40 °C for 6.0 h, the reaction mixture was quenched with saturated aqueous NH_4Cl (20 mL), extracted with ethyl acetate (30 mL × 3), and the combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (EtOAc/hexanes 1:10) to afford **3ab** (28.4 mg, 99% yield, 99% *ee*) as a colorless oil.

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[20] CCDC 916597 (**3ag**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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