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A Tunable Class of Chiral Cp Ligands for Enantioselective Rhodium(III)-Catalyzed C−H Allylations of Benzamides

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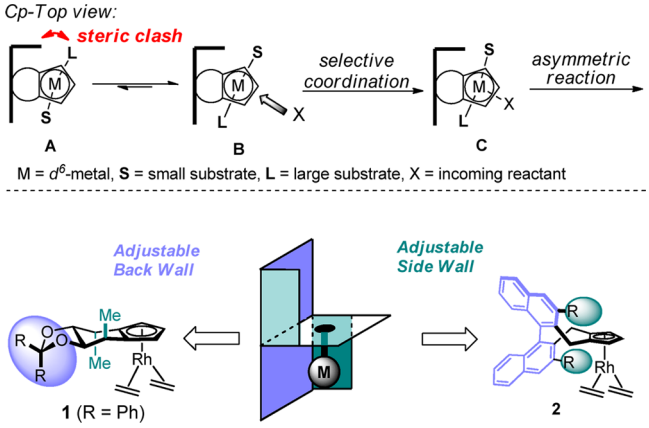
Supporting Information

ABSTRACT: The lack of robust and tunable chiral versions of cyclopentadienyl (Cp) ligands hampers progress in the development of catalytic asymmetric versions of a myriad of reactions catalyzed by this ubiquitous ligand. Herein, we describe of a class of chiral Cp ligands with tunable steric parameters. Coordinated to transition metals, the ligand creates a well-defined chiral pocket, able to imprint its chirality onto the metal. The corresponding Rh complexes are shown to be excellent catalysts for enantioselective allylation of *N*-methoxybenzamides via directed C−H functionalizations at very mild conditions. The obtained enantioselectivities are excellent and demonstrate the viability of chiral Cp complexes as selective transition metal catalysts.

Cyclopentadienyl ligands are among the most versatile and often used ligands to access robust and catalytically competent transition metal complexes.[1] Whereas most often the parent cyclopentadienyl itself (Cp) or pentamethylcyclopentadienyl (Cp*) is used, chiral versions enabling catalytic asymmetric reactions remain underdeveloped. Cp ligands combined with other ligands on the metal carrying chiral information,[2] *ansa*-metallocenes,[3] or multidentate Cp ligands with further coordinative groups[4] are established motifs in asymmetric catalysis. In stark contrast, few chiral Cp precursors and complexes were reported for catalytic reactions with Cp being the only permanent ligand on the metal and which require all remaining coordination sides of the metal for substrate and reactants binding or turnover.[5,6] We recently introduced a new class of Cp ligands and demonstrated their potential in Rh(III)-catalyzed enantioselective C−H functionalizations leading to chiral dihydroquinolones.[7,8] Despite the success of this ligand family, an expanded range of ligand scaffolds would be of high synthetic value. Along these lines, we seek to enlarge the available toolbox with ligands that have a complementary profile. Besides electronic and steric tuning of the Cp fragment itself, the reactivity and selectivity of chiral 1,2-disubstituted Cp ligands can be adjusted by manipulation of its chiral pocket. In a simplified view, this pocket consists of a back and a side wall (Scheme 1). Whereas the back wall forces an approach of the incoming reactant from the unsubstituted side, the side wall is responsible for aligning the three-coordinated intermediate to minimize steric interactions (**B** preferred over **A**). Once the ligand chirality is transferred to chirality-at-metal (**C**),[9] an asymmetric reaction can take place. Our previously

Scheme 1. Conceptual Design of the Chiral Cp Ligands



introduced cyclohexene-derived ligand family, with **1** as the most efficient member, has an adjustable back wall. We now report a class of tunable chiral Cp ligands from a common synthetic intermediate that allows us to modulate the **A**:**B** alignment by adapting the size of the side wall.

The envisaged ligand class **2** is based on the very successful C_2-symmetric atrop-chiral biaryl moiety, which was used by Halterman for the parent chiral Cp ligand architecture lacking its critical 3,3′ substituents.[5c−e] The synthesis started with **3**, used by Maruoka for the preparation of chiral phase-transfer catalysts.[10] Radical bromination followed by double alkylation of cyclopentadiene gave a mixture of ligand **5a** and the spiro product **4a** (Scheme 2). Cleavage of the methoxy groups provided phenol **4b**, which served as a common platform to introduce adjustable bulk in both *ortho* positions.

For instance, several alkyl and silyl groups were introduced (**5b**−**5d**). Alternatively, conversion to the corresponding triflate allowed for cross-couplings to access aryl-substituted dienes such as **5e**. Thermal rearrangement yielded the cyclopentadiene ligand progenitors **6a**−**6f** (Scheme 3). Subsequent complexation with $\{[Rh(C_2H_4)Cl]_2\}$ led to the chiral Cp**Rh(I) complexes **2a**−**2f**.

A representative X-ray crystal structure analysis of **2a** shows the structural characteristics of this complex family (Figure 1).[11] The lower naphthyl portion mainly acts as the back wall, preventing any coordination approach from this face. The top-view ORTEP representation illustrates the importance of the

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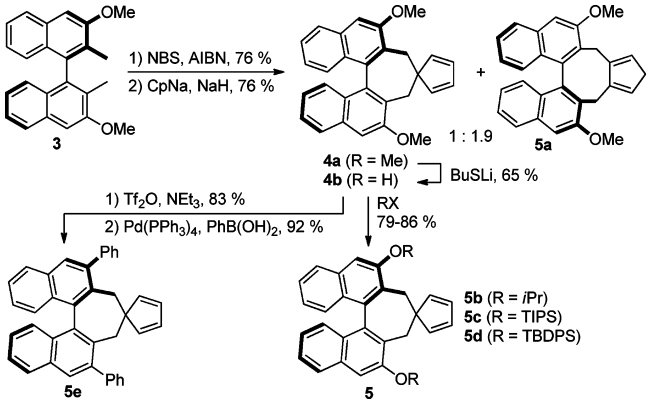
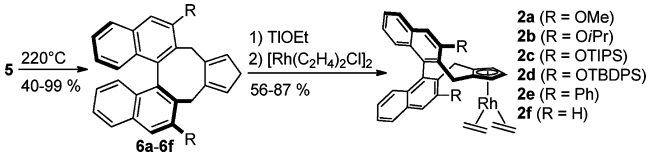
Scheme 2. Synthesis of the Spiro Precursors 5



Scheme 3. Synthesis of the Cp Rh(I) Complexes 2**



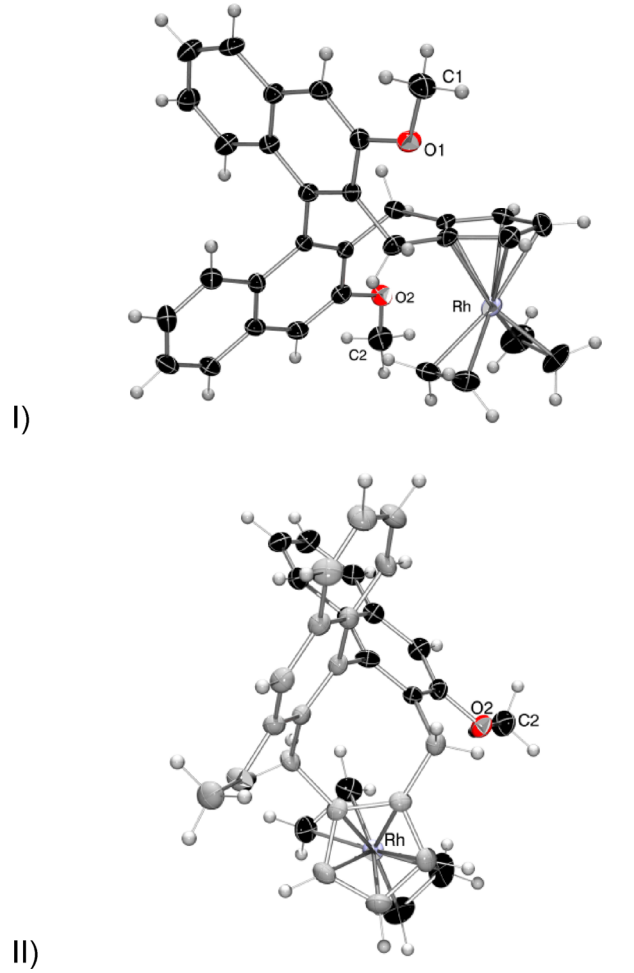
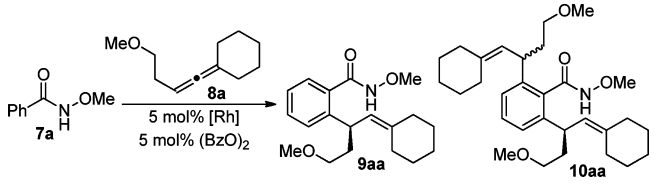


Figure 1. (I) X-ray crystal structure of Rh(I) complex **2a**. (II) Top-view of **2a** showing the important modulation of the chiral space around O2 and C2.

ortho substitution of the naphthyl group (the OMe groups for **2a**). Variability in this position modulates the chiral pocket and hence is expected to strongly influence the ratio of the two three-coordinated intermediates **A** and **B**.

Given our longstanding interest in enantioselective C−H functionalizations[12] and allenes,[13] we selected as a challenging model reaction a directed aromatic C−H allylation[14] based on the Cp*Rh(III)-catalyzed process recently reported by Ma and co-workers.[15−17] With our developed chiral rhodium complexes, this process allows for the first time for a directed enantioselective aromatic C(sp^2)−H allylation. Based on our previous findings, *in situ* oxidation of the Rh(I) olefin complexes **2** with dibenzoyl peroxide provides direct access to the catalytically competent Rh(III) carboxylate species, avoiding the use of any basic carboxylate additive.[18] The reaction of methyl hydroxamate **7a** and trisubstituted allene **8a** was first explored with our cyclohexene-derived catalyst **1**. The low selectivity for the monoallylated product **9aa** underscores the needs for additional ligand scaffolds (Table 1, entry 1).

Table 1. Optimization of the Rh-Catalyzed Allylation[a]



entry	[Rh]	solvent	T (°C)	**9aa**:**10aa**[b]	yield[c] (%)	er of **9aa**[d]
1	**1**	MeOH	0	2:1	62	61:39
2	**2f**	MeOH	0	3.5:1	71	67.5:32.5
3	**2a**	MeOH	0	2.5:1	60	77.5:22.5
4	**2b**	MeOH	0	3:1	80	84.5:15.5
5	**2c**	MeOH	0	3.2:1	63	90:10
6	**2d**	CH_2Cl_2	0	5.4:1	70	94:6
7	**2e**	MeOH	0	2:1	40	72:28
8	**2c**	CH_2Cl_2	0	5.8:1	82	94.5:5.5
9	**2c**	acetone	0	2.3:1	42	90:10
10	**2c**	toluene	0	6:1	67	94.5:5.5
11[e]	**2c**	CH_2Cl_2	−20	30:1	90	96.5:3.5
12[e,f]	**2c**	CH_2Cl_2	0	6.9:1	76	92:8
13	**2c**	CH_2Cl_2	−20	10:1	80	96.5:3.5

[a]Conditions: 0.05 mmol **7a**, 0.05 mmol **8a**, 5 mol% [Rh], 5 mol% $(BzO)_2$, 0.2 M in solvent, 18 h. [b]Determined by ^{1}H NMR. [c]Isolated yields of **9a**. [d]Determined by HPLC with a chiral stationary phase. [e]0.05 mmol **7a**, 0.075 mmol **8a**, 2 mol% [Rh], and 2 mol% $(BzO)_2$.

Complex **2f**, with unsubstituted *ortho* positions of the Cp ligand,[5c] catalyzed the reaction well, albeit in moderate enantiomeric ratio of 67.5:32.5 and with significant amounts of the double allylation product **10aa** (entry 2). The selectivity was significantly better with **2a**, having two methoxy substituents (entry 3). Larger *ortho* groups improved the selectivity further (entries 4−6), the best obtained with **2c**, having large OTIPS moieties (entry 5). Phenyl substitution of the ligand (**2e**) was not successful for this reaction (entry 7). A solvent switch to dichloromethane and reduction of the ratio **7a**:**8a** to 1:1.5 mitigated competing double allylation and further improved the selectivity (entry 11). With 2 mol% catalyst loading, a slightly lower selectivity was observed (entry 12). Conducting the reaction at −20 °C improved the enantiomeric ratio further, providing **9a** with 96.5:3.5 er in 80% isolated yield at a **7a**:**8a** ratio of 1:1 (entry 13).

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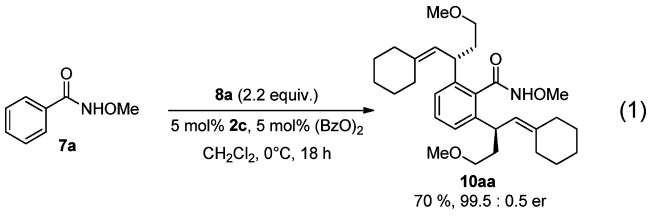
When the allylation reaction was carried out with 2.2 equiv of allene **8a** at 0 °C, the double allylated product **10a** became dominant and was isolated in excellent enantioselectivity of 99.5:0.5 er (eq 1).

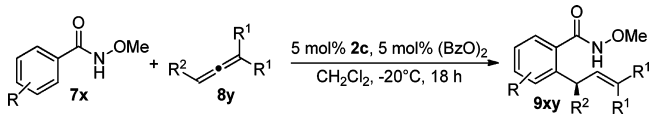


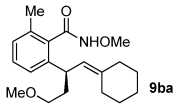
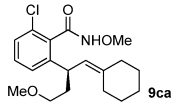
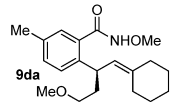
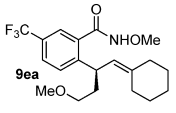
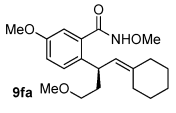
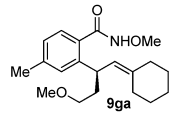
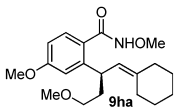
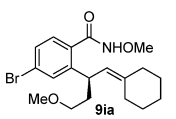
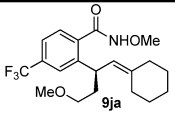
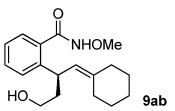
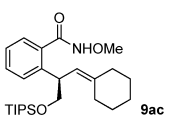
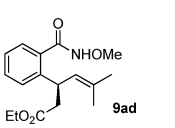
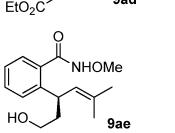
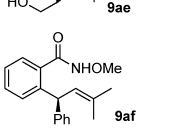
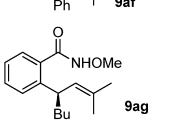
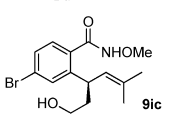
(1)

With the optimized conditions of Table 1, we next evaluated the scope of the enantioselective allylation. The reaction is largely independent of the substitution patterns of the benzamide. No double allylation was observed with *ortho*- or *meta*-substituted substrates **7** (Table 2, entries 1−5). Electron-withdrawing and -donating substituents generally have little influence on the reactivity and selectivity of the allylation (entries 1−9). Only for **7j**, with a *p*-CF_3 group, is a somewhat reduced selectivity observed (entry 9), whereas a *m*-CF_3 substituent behaves normally (entry 4). The allene component **8** can be varied over a wide range of trisubstituted allenes (entries 10−17). For instance, protected or free hydroxyl groups and esters at various distances from the allene can be used. Simple unfunctionalized allenes like **8g** provide similar selectivity (entry 15), leading to the conclusion that the selectivity is by and large determined by the steric difference between the H and R^2 substituents of allene **8**. The conditions are very mild, and even delicate products, such as **9af** with a rather acidic stereogenic center, are accessed in good selectivity (entry 14).

The absolute configuration of the allylated products was unambiguously established by X-ray crystallographic analysis of **9ic** to be (*R*) (Figure 2).[11] The selectivity leading to this isomer can be well realized with the stereochemical model. The allene coordinates with the lesser substituted double bond to the cyclometalated intermediate **C**, and the R^2 group points away from the Cp moiety.[19] With respect to the ligand backbone, the hydroxamate section of the substrate is preferentially oriented

Table 2. Scope of the Rh-Catalyzed Allylation[a]



entry	7x	8y	9xy	yield (%)[b]	er[c]
1[d]	**7b**	**8a**	 **9ba**	87	93 : 7
2[d]	**7c**	**8a**	 **9ca**	80	94.5 : 5.5
3[d]	**7d**	**8a**	 **9da**	83	96 : 4
4[d]	**7e**	**8a**	 **9ea**	71	95 : 5
5[d]	**7f**	**8a**	 **9fa**	88	96 : 4
6	**7g**	**8a**	 **9ga**	77	97 : 3
7	**7h**	**8a**	 **9ha**	83	96 : 4
8	**7i**	**8a**	 **9ia**	72	97.5 : 2.5
9	**7j**	**8a**	 **9ja**	91	82 : 18
10	**7a**	**8b**	 **9ab**	69	97.5 : 2.5
11	**7a**	**8c**	 **9ac**	86	95.5 : 4.5
12	**7a**	**8d**	 **9ad**	72	95 : 5
13	**7a**	**8e**	 **9ae**	84	97.5 : 2.5
14	**7a**	**8f**	 **9af**	69	92.5 : 7.5
15	**7a**	**8g**	 **9ag**	87	96 : 4
16	**7i**	**8c**	 **9ic**	66	99 : 1

[a]Conditions: 0.12 mmol **7x**, 0.10 mmol **8y**, 5 mol% **2c**, 5 mol% $(BzO)_2$, 0.2 M in CH_2Cl_2, −20 °C, 18 h. [b]Isolated yields. [c]Determined by HPLC with a chiral stationary phase. [d]0.10 mmol **7**, 0.12 mmol **8y**.

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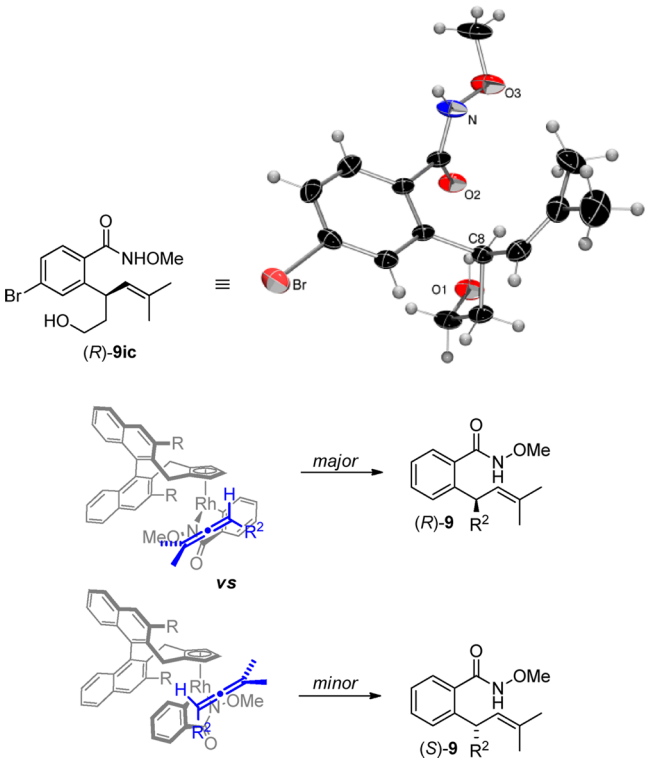

Figure 2. X-ray crystal structure of **9ic** and stereochemical model of the chiral-at-metal complex **C** accounting for the observed selectivity (R = OTIPS).

in an antiparallel fashion, pointing away from the bulky OTIPS group.

In summary, we have reported a class of chiral Cp ligand precursors and their corresponding Rh(I) complexes, based on a sterically adjustable biaryl backbone. They are excellent scaffolds for enantioselective Rh(III)-catalyzed C−H allylations. This process proceeds with excellent selectivity and is characterized by its mildness and good functional group compatibility. Further work focuses on expanding the chiral Cp ligand platform to other transition metals and transformations.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic procedures, characterization data for all new compounds, HPLC traces of the allylation products, and crystallographic data (CIF) for **2a** and **9ic**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Crystallographic data for **2a** and **9ic** are available as Supporting Information or as CCDC 914717 and 914718. 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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