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Synthesis of Hexamethyl-1,1′-spirobiindane-Based Chiral Spiro Cp Ligands and Their Application in Rhodium-Catalyzed Enantioselective Aryl C−H Addition to Nitroalkenes

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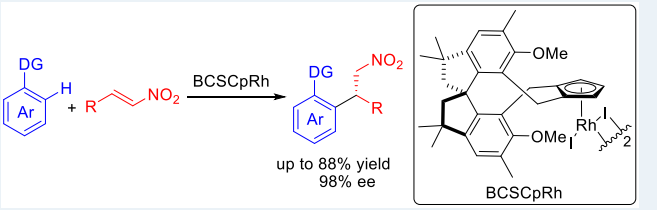
ABSTRACT: Spiro cyclopentadienyl rhodium (SCpRh) complexes are powerful catalysts for promoting asymmetric C−H functionalization reactions. However, the application of chiral SCp ligands is limited due to tedious synthetic procedures and expensive starting materials. Herein, we have developed a series of chiral spiro ligands (BCSCp) with 6−7 steps from commercially available and cheap Bisphenol C. Their corresponding rhodium complexes have been prepared and successfully applied in enantioselective aryl C−H addition to nitroalkenes, affording a series of C−H adducts in up to 88% yield with up to 98% ee.



KEYWORDS: *asymmetric catalysis, C−H functionalization, C−H addition, chiral cyclopentadienyl, rhodium catalysis*

Transition-metal-catalyzed asymmetric C−H functionalization has received considerable interest as an increasingly important strategy to access versatile chiral molecules.[1−10] Notably, chiral cyclopentadienyl metal complexes have been developed as one of the most efficient catalysts to realize asymmetric C−H bond functionalization.[11−20] Since the pioneering works by Cramer[21] and Ward and Rovis,[22] diverse chiral cyclopentadienyl ligands have been revealed,[23−39] such as binaphthyl-derived Cp **I**,[23−30] piperidine-fused Cp **II**,[31] cyclopentane-fused Cp **III**,[32] and bicyclo[2,2,2]octane-fused Cp **IV**,[33] as well as planar prochiral Cp ligands[34−37] and others[38,39] (Figure 1). Despite these advances, it remains essential to develop a concise synthetic approach for novel chiral ligands to meet the ever-growing demands of the rapid development of asymmetric C−H functionalization reactions.

1,1′-Spirobiindane has been recognized as a privileged chiral scaffold to provide an excellent platform for chiral ligand and catalyst diversification since the pioneering work of Zhou.[40−46] In 2016, our group designed and synthesized a series of 1,1′-spirobiindane-derived Cp (SCp) ligands and successfully applied their Rh complexes in an asymmetric oxidative coupling reaction.[47] Since then, application of SCpRh in versatile catalytic asymmetric C−H functionalization reactions has been well demonstrated.[48−60] Despite their successful applications in challenging C−H functionalization reactions, these SCp ligands are synthetically less practical due to the tedious synthesis and relatively expensive SPINOL starting material. Therefore, the design of novel SCp ligands with practical synthesis is of great significance and in high demand.

Transition-metal-catalyzed direct C−H addition to polar unsaturated bonds C═X (X = C, N, O) such as electron-deficient alkenes, aldehydes, and ketones has emerged as a

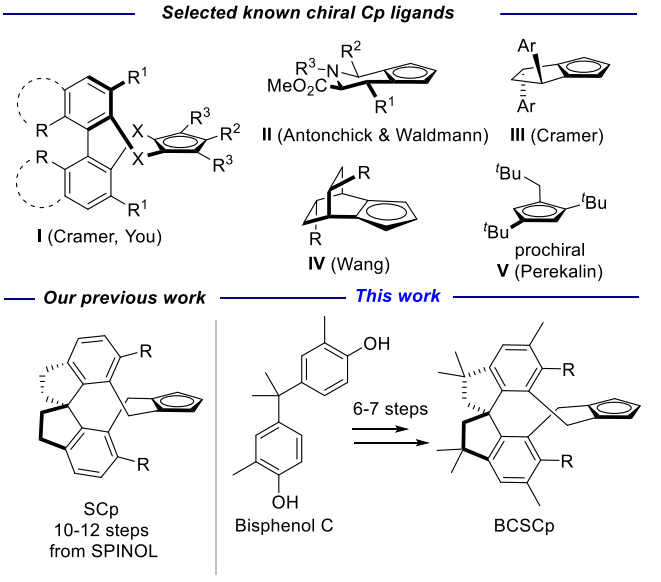


Figure 1. Previously and newly developed chiral cyclopentadienyl ligands.

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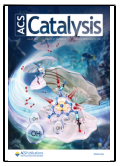

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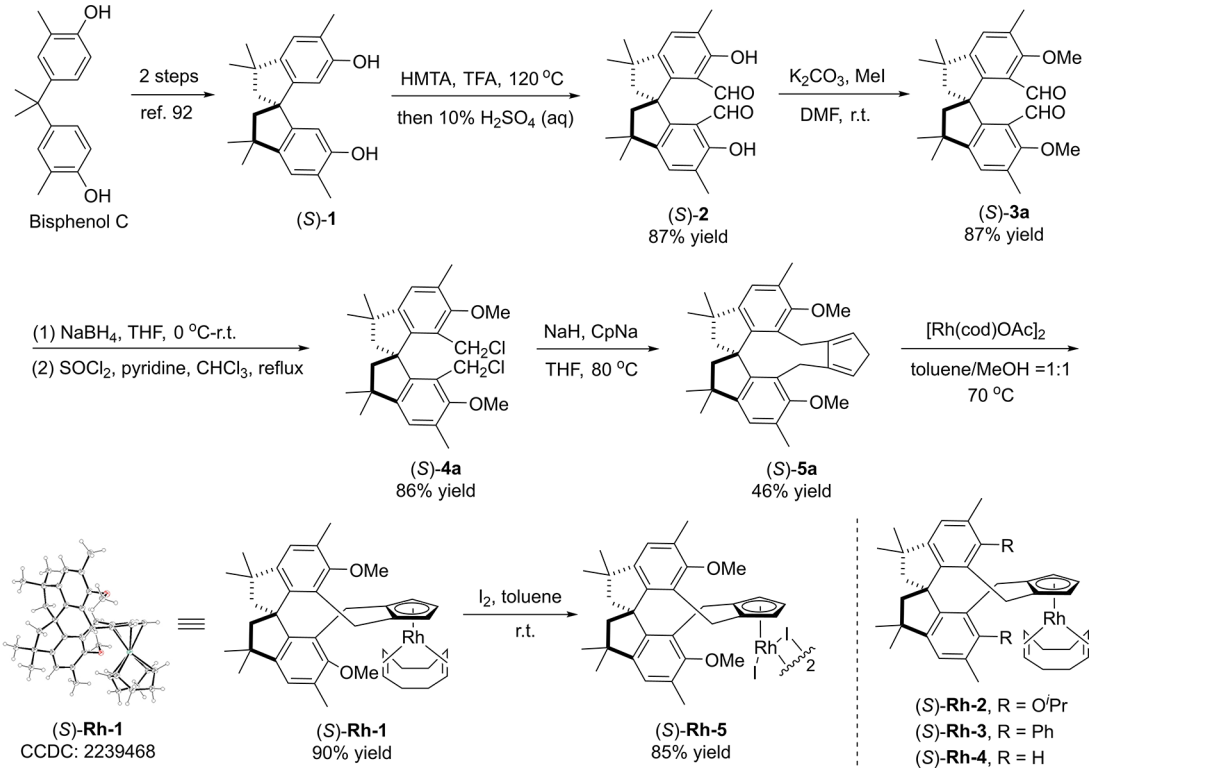
Scheme 1. Synthesis of Hexamethyl-1,1′-spirobiindane Cp Ligands and Their Rhodium Complexes.



powerful approach for the formation of C−C bonds.[61−68] The most significant feature of these reactions is that the crucial nucleophilic C−M species are generated catalytically *in situ via* C−H activation. In recent years, considerable studies on enantioselective C−H direct addition reactions have been successfully developed by Shibata,[69−72] Cramer,[30,73] Matsunaga,[74−77] and others.[78−83] Driven by our continuous interests in developing new chiral cyclopentadienyl ligands and asymmetric C−H functionalization,[84−90] we synthesized a novel class of chiral spiro (BCSCp) ligands from Bisphenol C in 6−7 steps. In addition, these Rh^{III} complexes of BCSCps were found to be highly efficient for a challenging asymmetric C−H addition of aryl amides to nitroalkenes, affording a series of C−H adducts in excellent yields and enantioselectivities. Herein, we report the details of this study. Recently, the Wang group also reported the synthesis and application of this class of ligands during the submission of our manuscript.[91]

As shown in Scheme 1, chiral Cp ligands **5** could be conveniently synthesized from Bisphenol C. The preparation of enantiopure hexamethyl-1,1′-spirobiindane-6,6′-diol **1** (6,6′-HMSIOL) was carried out according to the known procedure from commercially available Bisphenol C.[92] The Duff reaction of (*S*)-**1** with hexamethylenetetramine (HMTA) afforded dialdehyde (*S*)-**2** in 87% yield on a 10 g scale. *O*-Alkylation of (*S*)-**2** with MeI in the presence of potassium carbonate gave (*S*)-**3a** in an 87% yield. Then, dialdehyde (*S*)-**3a** was further transformed to the corresponding dichloride (*S*)-**4a** in 86% yield over two steps by $NaBH_4$ reduction, followed by chlorination with $SOCl_2$. Double alkylation of CpNa with (*S*)-**4a** gave substituted cyclopentadiene (*S*)-**5a** in 46% yield. The chiral $CpRh^{I}$ complex (*S*)-**Rh-1** was smoothly prepared by reaction with $[Rh(COD)OAc]_2$ in toluene/methanol at 70 °C under argon. At the same time, the corresponding $CpRh^{I}$ complexes (*S*)-**Rh-2** to (*S*)-**Rh-4** were prepared by a similar strategy (see the Supporting Information for details). Finally, upon oxidation of the $CpRh^{I}$ complex with iodine, the $CpRh^{III}$ complex (*S*)-**Rh-5** was obtained in 85% yield. The structure of (*S*)-**Rh-1** was confirmed unambiguously by X-ray crystallographic analysis.

Then, the utility of these newly developed BCSCpRh complexes in asymmetric C−H functionalization was explored. Recently, we reported a Rh-catalyzed enantioselective direct addition of aryl C−H bond to nitroalkenes,[53] and the highest enantioselectivity for the reaction of pyrrolidine benzamide **6a** with nitrostyrene **7a** could only reach 86% ee in the presence of the optimized catalyst **Rh-9**. Furthermore, the ee values of the products are generally lower than 90%. To our delight, with the newly developed BCSCpRh complex **Rh-1**, the reaction proceeded with excellent enantioselectivity to give **8aa**, albeit in a poor yield (Table 1, entry 1, 21% NMR yield, 92% ee). The existence of the 3,3,3′,3′-tetramethyl groups might affect the dihedral angle of two indanyls, leading to a better chiral induction environment. When catalysts **Rh-2**, **Rh-3**, and **Rh-4** were employed, inferior results were given (see the Supporting Information for details). Gratifyingly, **Rh-5** led to a remarkable improvement in catalytic efficiency, giving **8aa** in 64% NMR yield with 92% ee (entry 2). In contrast, the utilization of **Rh-6** or **Rh-7** gave a lower efficiency and enantioselectivity (entries 3 and 4). In addition, the desired product **8aa** was obtained in 78% yield with only 23% ee when **Rh-8** was used, probably due to the decreased steric hindrance (entry 5). Therefore, **Rh-5** was identified as the optimized catalyst for further optimizations. Screening of additives indicated that NaOAc was beneficial, giving the product in 82% NMR yield with 94% ee (entries 6−8). As expected, both excellent enantioselectivity and good yield were maintained when the additive loading was reduced to 0.4 equiv (entry 9, 81% yield, 93% ee). Further reducing the amount of the additive to 0.2 equiv resulted in a measurable decrease in yield (entry 10, 72% yield, 93% ee). For comparison, **Rh-9** and

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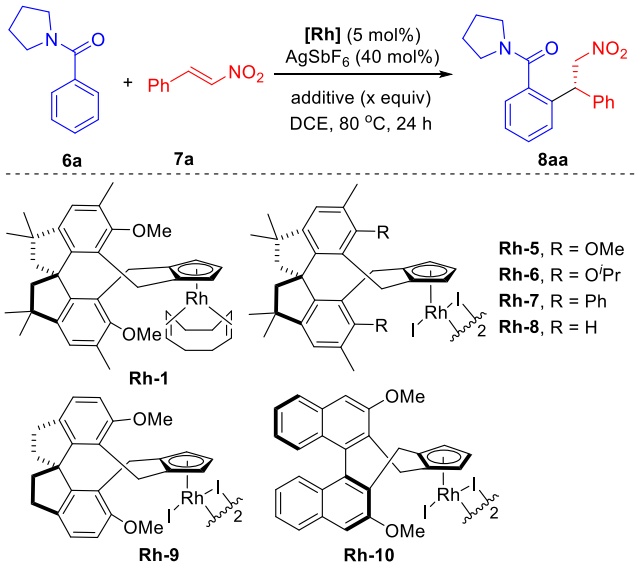
Table 1. Optimization of Reaction Conditions[a]



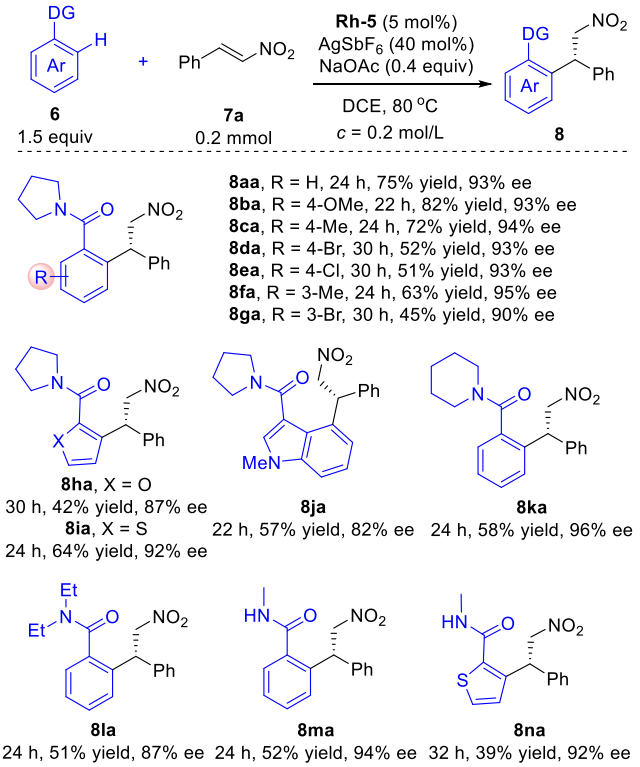
entry	[Rh]	additive (equiv)	yield (%)[b]	ee (%)[c]
1[d]	**Rh-1**	BPO (0.05)	21	92
2	**Rh-5**		64	92
3	**Rh-6**		45	87
4	**Rh-7**		46	84
5	**Rh-8**		78	23
6	**Rh-5**	NaOAc (1.0)	82	94
7	**Rh-5**	KOAc (1.0)	30	92
8	**Rh-5**	$Zn(OAc)_2$ (1.0)	54	94
9	**Rh-5**	NaOAc (0.4)	81	93
10	**Rh-5**	NaOAc (0.2)	72	93
11	**Rh-9**	NaOAc (0.4)	78	88
12	**Rh-10**	NaOAc (0.4)	56	84

[a]Reaction conditions unless specified otherwise: **6a** (0.15 mmol), **7a** (0.1 mmol), [**Rh**] (5 mol%), $AgSbF_6$ (40 mol%), and additive in DCE (0.5 mL) at 80 °C for 24 h under an argon atmosphere. [b]Determined by ^1H NMR analysis of the crude reaction mixture using CH_2Br_2 as an internal standard. [c]The ee values of **8aa** were determined by HPLC analysis on a chiral stationary phase. [d]Absence of $AgSbF_6$.

Rh-10 were also tested under identical reaction conditions (entries 11 and 12). However, lower enantioselectivity was observed in both cases (88% and 84% ee, respectively). Finally, the optimized reaction conditions were obtained as the following: **6a** (1.5 equiv), **7a** (1.0 equiv), **Rh-5** (5 mol%), $AgSbF_6$ (40 mol%), and NaOAc (0.4 equiv) under argon in DCE at 80 °C (entry 9).

With the optimized conditions in hand, we first explored the reaction scope with a variety of aryl amides **6** with nitrostyrene **7a** (Table 2). Pyrrolidine benzamides bearing a series of *para* electron-donating and electron-withdrawing substituents all reacted with good efficiency with excellent enantioselectivity (**8aa**−**ea**, 51−82% yields, 93−94% ee). Arenes bearing a 3-methyl or 3-bromo group were also compatible (**8fa**,**ga**), and the C−H activation took place at the less hindered *ortho* C−H site in excellent enantioselectivity (90−95% ee). Heteroaromatic substrates such as furan-, thiophene-, and indole-derived amides afforded their corresponding adducts **8ha**−**ja** in reasonable yields with good to excellent enantioselectivity (42−64% yields, 82−92% ee). In addition to pyrrolidine benzamide, other amide directing groups such as piperidine benzamide and *N*,*N*-diethylbenzamide were also successful in this transformation

Table 2. Substrate Scope for Benzamides[a]



[a]Reaction conditions: **6** (0.3 mmol), **7a** (0.2 mmol), **Rh-5** (5 mol%), $AgSbF_6$ (40 mol%), and additive in DCE (1.0 mL) at 80 °C under an argon atmosphere. Isolated yields of **8** are given. The ee values of **8** were determined by HPLC analysis on a chiral stationary phase.

(**8ka**,**la**, 51−58% yields, 87−96% ee). Notably, the *N*-methylbenzamide directing group was compatible with the reaction conditions, affording the product **8ma** in 52% yield with 94% ee. It is worth mentioning that an asymmetric reaction of such a substrate has not been realized previously. When the thiophene-derived amide **6n** was applied, product **8na** was obtained in 39% yield with 92% ee.

Next, the scope with respect to the nitroalkene was explored by reacting with benzamide **6b** as shown in Table 3. Aromatic rings bearing electron-donating or electron-withdrawing substituents were competent in this transformation, and products **8bb**−**bj** were obtained in moderate to good yields with excellent enantiocontrol (45−88% yields, 91−98% ee). When a 1-naphthyl-substituted nitroolefin was employed, product **8bk** was obtained in 86% yield with 95% ee. Furthermore, heteroaromatic substrates such as furan- and thiophene-derived nitroalkenes afforded products **8bl**,**bm** in acceptable yields with excellent enantioselectivity (70−74% yields, 90−93% ee). Notably, the reaction also worked well for alkyl nitroalkenes in moderate yields with good enantioselectivity (**8bn**−**bp**, 52−74% yields, 85−88% ee).

To demonstrate the practicality of this method, a 1.0 mmol scale reaction of **7a** was performed, and the desired product **8ba** was isolated in 79% yield with 93% ee (Scheme 2a). Moreover, 4-substituted dihydroisoquinolones **9ba**,**ia**,**bm** were obtained in good yields without erosion of enantioselectivity (Scheme 2b, 82−90% yields, 91−93% ee). Dihydroisoquinolone fragments are widely found in biologically active compounds and natural products.[93,94] The access to the 4-substituted product isomer is

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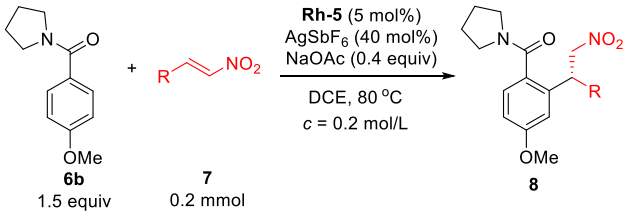
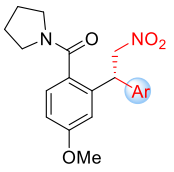
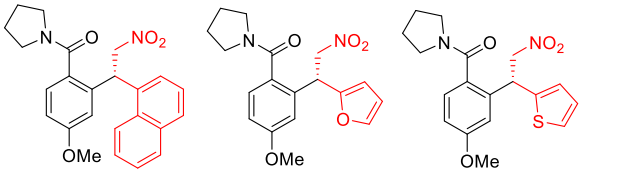
Table 3. Substrate Scope for Nitroolefins[a]

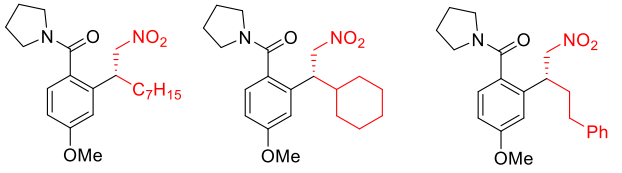




8bb, R = 4-F-C_6H_4, 22 h, 84% yield, 95% ee
8bc, R = 4-Cl-C_6H_4, 26 h, 63% yield, 95% ee
8bd, R = 4-Br-C_6H_4, 26 h, 68% yield, 95% ee
8be, R = 4-I-C_6H_4, 22 h, 88% yield, 95% ee
8bf, R = 4-OMe-C_6H_4, 20 h, 84% yield, 93% ee
8bg, R = 4-NO_2-C_6H_4, 20 h, 75% yield, 96% ee
8bh, R = 3-Br-C_6H_4, 20 h, 80% yield, 98% ee
8bi, R = 3-OMe-C_6H_4, 28 h, 62% yield, 94% ee
8bj, R = 2-Me-C_6H_4, 30 h, 45% yield, 91% ee



8bk 24 h, 86% yield, 95% ee | **8bl** 24 h, 70% yield, 90% ee | **8bm** 24 h, 74% yield, 93% ee



8bn 24 h, 64% yield, 87% ee | **8bo** 28 h, 52% yield, 88% ee | **8bp** 24 h, 74% yield, 85% ee

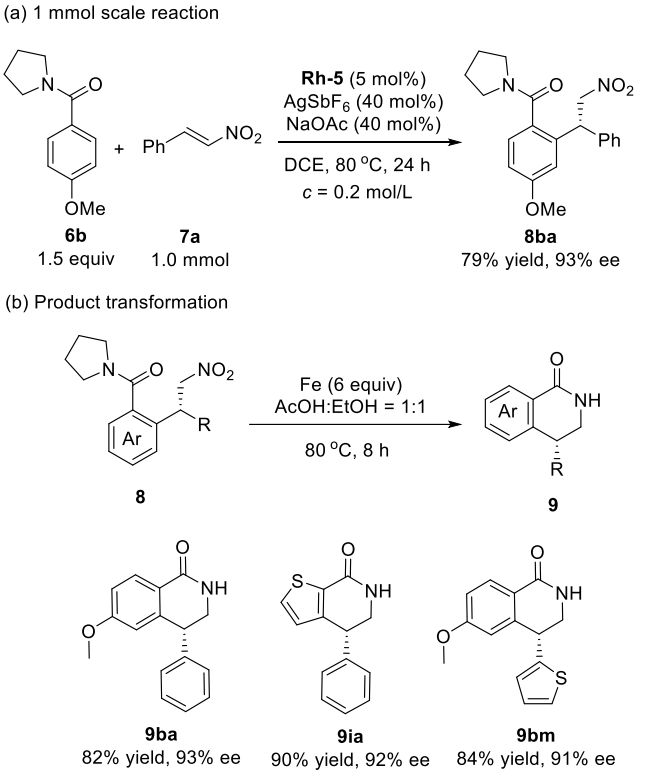
[a]Reaction conditions: **6b** (0.3 mmol), **7** (0.2 mmol), **Rh-5** (5 mol%), $AgSbF_6$ (40 mol%), and NaOAc (0.4 equiv) in DCE (1.0 mL) at 80 °C under an argon atmosphere. Isolated yields of **8** are given. The ee values of **8** were determined by HPLC analysis on a chiral stationary phase.

scarce by Rh(III)-catalyzed annulation of benzohydroxamic acid and styrene.[95,96]

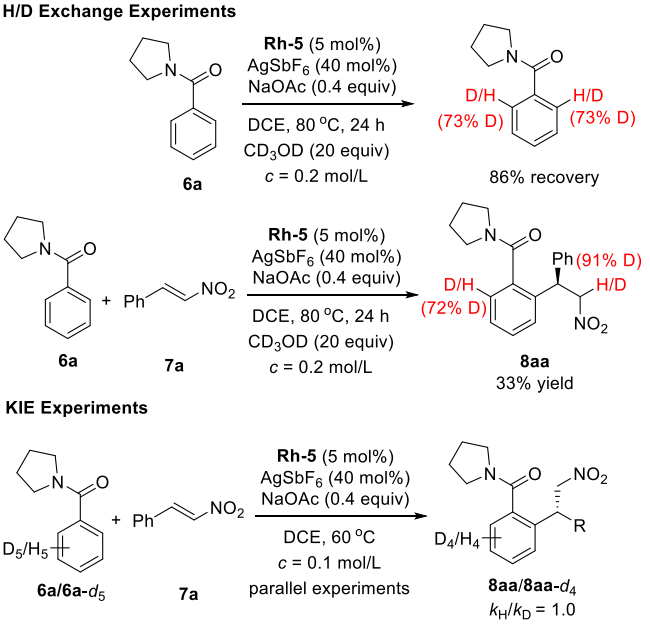
To shed light on the mechanism of this addition reaction, we carried out several experimental studies (Scheme 3). First, H/D exchange between **6a** and CD_3OD under the standard conditions in the presence or absence of nitrostyrene **7a** both gave significant deuteration at the *ortho* position of the benzene ring, suggesting the reversibility of the C−H cleavage. Two parallel reactions of **6a** and **6a**-d_5 with **7a** were performed to determined the kinetic isotope effect, and k_H/k_D = 1.0 was observed at a low conversion under the standard conditions. Overall, these results suggest that C−H bond cleavage is not involved in the rate-determining step.

In conclusion, we have developed a series of novel chiral cyclopentadienyl (BCSCp) ligands based on a hexamethyl-1,1′-spirobiindane scaffold, which are synthesized efficiently from commercially available Bisphenol C. The corresponding rhodium complexes were successfully applied to the asymmetric C−H addition of aryl amides to nitroalkenes. Excellent enantioselectivity and good yields were obtained for a wide range of substrates, including those which previously failed. Products could be converted to chiral 4-substituted dihydroisoquinolones in high yields without loss of enantiopurity. The preliminary mechanistic studies support the idea that C−H bond cleavage is reversible and is not involved in the rate-determining step. Further applications of these BCSCpRh complexes in asymmetric catalysis are part of ongoing research in our laboratory.

Scheme 2. (a) 1 mmol Scale Reaction and (b) Product Transformation



Scheme 3. Mechanistic Studies



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.3c02199.

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Experimental procedures and compound characterization data (PDF)

X-ray crystallographic data for compound (*S*)-**Rh-1** (CIF)

X-ray crystallographic data for compound **9ia** (CIF)

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Notes

The authors declare no competing financial interest.

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