

Chiral Pincer Carbodicarbene Ligands for Enantioselective Rhodium-Catalyzed Hydroarylation of Terminal and Internal 1,3-Dienes with Indoles

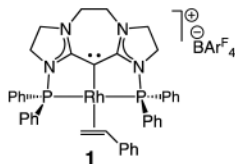
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Supporting Information

ABSTRACT: Catalytic enantioselective addition of N-heteroarenes to terminal and internal 1,3-dienes is reported. Reactions are promoted by 5 mol % of Rh catalyst supported by a new chiral pincer carbodicarbene ligand that delivers allylic substituted arenes in up to 95% yield and up to 98:2 er. Mechanistic and X-ray evidence is presented that supports that the reaction proceeds via a Rh(III)- η^3 -allyl.

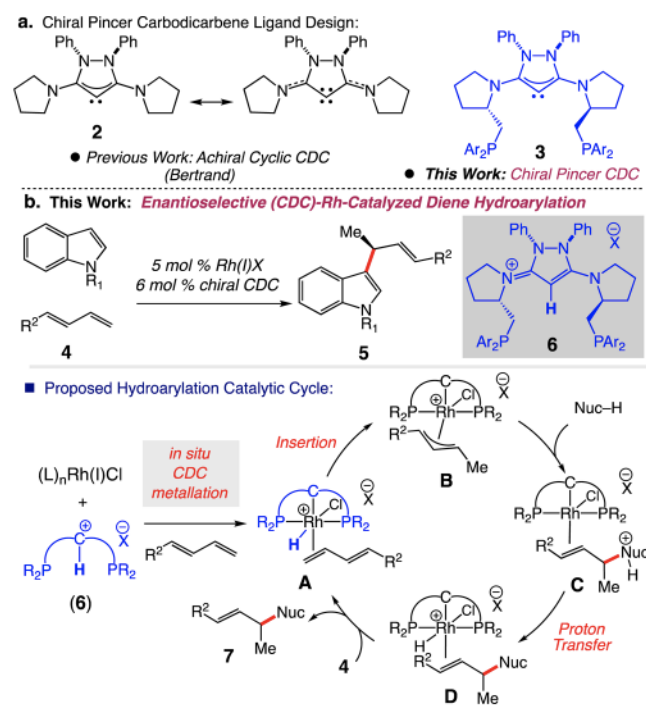
Metal-catalyzed olefin hydroarylation is an important, atom economical C–C bond forming strategy for the synthesis of functionalized arenes. Of particular significance is the development of chiral catalysts that render this process enantioselective. Enantioselective olefin hydroarylation methods are scarce (>95:5 er), and are generally limited to intramolecular variants or electron deficient alkenes.^{1,2}



We recently reported the site-selective addition of N-heteroarene nucleophiles to dienes catalyzed by pincer carbodicarbene (CDC) Rh complex **1** that operates with a Lewis acid cocatalyst.^{3,4} Carbodicarbenes belong to an emerging class of N-heterocyclic carbon(0) donor ligands for transition metal catalysis that also include cyclic bent-allenes (e.g., **2**),⁵ and carbodiphosphoranes (Scheme 1a).⁶ In light of these studies, related efforts in our laboratories have been in connection to the design, synthesis, and development of new chiral carbon(0) ligands and their ability to affect enantioselective olefin hydrofunctionalizations.^{3,6b} Herein, we describe the synthesis, structure, and activity of the first chiral, optically pure CDC ligands that can be used to efficiently promote enantio- and site-selective hydroarylation of terminal and internal 1,3-dienes in up to 98:2 er (Scheme 1b).⁷ Transformations are facilitated by an in situ generated (CDC)-Rh complex at 35–60 °C, and structural data indicates the importance of a tridentate CDC scaffold.

Selection of a chiral pyrazolium-based CDC pincer (**3**) over a chiral diazapyrenium-based CDC (e.g., **1**) was based on the idea that a pyrazolium ligand scaffold would offer increased conformational flexibility, while maintaining a well-defined chiral binding

Scheme 1. Chiral Pincer Carbodicarbene Ligands and Rh(III)–Hydride Catalyzed Diene Hydrofunctionalization



site, as well as render catalyst synthesis modular. Furthermore, as a design from our previous studies with CDC pincer ligands,^{6b} we hypothesized that in situ metallation of Rh(I) onto the pyrazolium **6** would furnish a (CDC)-Rh(III)–H (**A**) that could undergo migratory insertion to generate an electrophilic Rh(III)-(η^3 -allyl) intermediate (**B**) (Scheme 1c).⁸ Nucleophilic addition of indole to the Rh(III)-(η^3 -allyl) followed by oxidative protonation at Rh (**C** → **D**) regenerates the Rh(III)–H. Subsequent ligand substitution by diene **4** affords product **7** and regenerates (CDC)-Rh(III) complex **A**. Reports by a number of groups have demonstrated enantioselective Pd- and Rh-catalyzed hydroalkylations,⁹ hydroaminations,¹⁰ and hydroarylations¹¹ of 1,3-dienes through the intermediacy of an electrophilic metal-allyl species formed by metal–hydride migratory insertion.

We began our catalytic studies by examining the ability of chiral pyrazolium salts **L1–4** to promote enantioselective

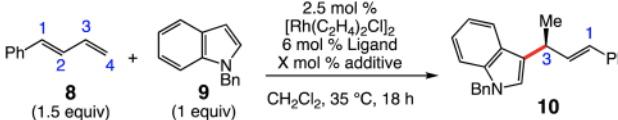
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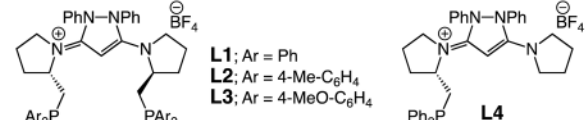


hydroarylations. Addition of *N*-Bn-indole to **8** (Table 1) to afford **10** served as the representative reaction. As shown in

Table 1. Initial Screening of Chiral (CDC)-Rh Complexes



entry	Ligand	additive (mol %)	conv (%) ^b	rr (3,4:1,4) ^b	er ^c
1	-	-	<2	-	-
2	L1	-	<2	-	-
3	L1	NaBARF ₄ (10)	83	8:1	90:10
4	L2	NaBARF ₄ (10)	>98	12:1	94:6
5	L3	NaBARF ₄ (10)	57	8:1	90:10
6	L4	NaBARF ₄ (10)	17	3:1	55:45
7	L2	LiBARF ₄ (10)	58	14:1	78:22
8	L2	KBARF ₄ (10)	25	>20:1	87:13
9	L2	NaBF ₄ (10)	<2	-	-
10	dpe-phos	NaBARF ₄ (10)	<2	-	n/a
11	xantphos	NaBARF ₄ (10)	<2	-	n/a
12	(<i>R</i>)-binap	NaBARF ₄ (10)	<2	-	-

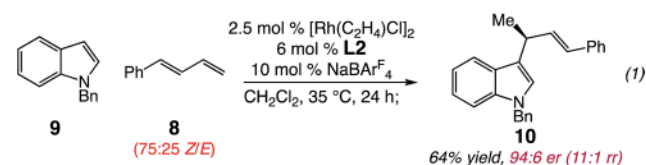


^aReactions performed under N₂ atmosphere. ^bConversion to **10** determined by analysis of 400 or 600 MHz ¹H NMR spectra of crude reactions with DMF as internal standard. ^cDetermined by HPLC analysis; see the Supporting Information for details.

entries 1–2 of Table 1, hydroarylation in the presence of 2.5 mol % [Rh(C₂H₄)₂Cl]₂ and **L1** in CH₂Cl₂ at 35 °C affords <2% conversion to **10**. When 10 mol % NaBARF₄ is used, reaction proceeds to 83% conversion and 90:10 er (entry 3).

The result in entry 4 shows that if the PPh₂ is replaced by P(*p*-tol)₂, conversion and er increases; treatment of **8** and **9** with 5 mol % Rh, 6 mol % **L2** affords **10** in >98% conversion and 94:6 er.¹² Changing the phosphine to P(*p*-MeOC₆H₄)₂ results in a decrease to 90:10 er (entry 5). The importance of a tridentate scaffold is highlighted by the inefficient hydroarylation promoted by bidentate CDC **L4**; **10** is generated in 17% conversion, 3:1 rr, and 55:45 er (entry 6). As the data in entries 7 and 8 indicate, 5 mol % LiBARF₄ and KBARF₄ as an additive, deliver **10** in 58% and 25% conversion but in diminished 78:22 er and 87:13 er, respectively. Use of NaBF₄, which contains a less dissociating counteranion, delivers <2% conv (entry 9). Control reactions employing representative bidentate phosphines also afforded <2% conversion to **10** (entries 10–12).

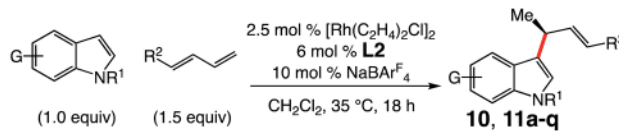
In seeking to understand what effect the isomeric *E/Z* purity of the 1,3-diene has on the enantioselectivity, we prepared and examined the hydroarylation reaction with diene **8** formed as an *E/Z* mixture favoring the *Z*-isomer (75:25, *Z/E*) (eq 1). With



5.0 mol % (**L2**)-Rh under standard conditions (see entry 4, Table 1), indole **10** is formed with similar efficiency (64% yield) and in the same enantioselectivity, 94:6 er (vs 94:6 er Table 1). Thus, the *E/Z* stereoisomeric purity of the diene does not noticeably affect er.

Data shown in Table 2 illustrates a brief scope of the (CDC)-Rh-catalyzed reaction with various terminal dienes and indoles. As shown in entries 1–8, treatment of **8** with a variety of

Table 2. Heteroarene Scope in Enantioselective Hydroarylation^a



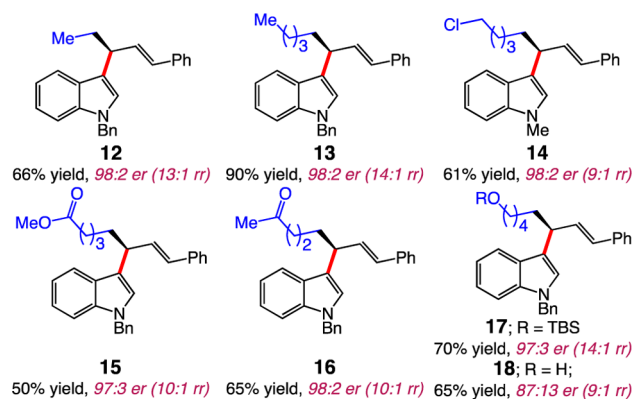
entry	arene	R ²	product; yield (%) ^b	er ^c	rr ^d
1	indole	Ph	11a ; 59	92:8	>20:1
2	<i>N</i> -Me-indole	Ph	11b ; 81	95:5	16:1
3	<i>N</i> -Et-indole	Ph	11c ; 94	94.5:5.5	17:1
4	5-OMe- <i>N</i> -Bn-indole	Ph	11d ; 63	94:6	14:1
5	5-OMe- <i>N</i> -Me-indole	Ph	11e ; 99	93:7	>20:1
6	5-B(pin)- <i>N</i> -Me-indole	Ph	11f ; 98	94.5:5.5	16:1
7	5-Br- <i>N</i> -Me-indole	Ph	11g ; 91	91:9	15:1
8 ^e	5-CO ₂ Me- <i>N</i> -Me-indole	Ph	11h ; 66	88:12	10:1
9	2-Me- <i>N</i> -Me-indole	Ph	11i ; 98	90:10	14:1
10	<i>N</i> -Bn-indole	Ph	10 ; 87	94:6	12:1
11	<i>N</i> -Bn-indole	4-FC ₆ H ₄	11j ; 78	93:7	5:1
12	<i>N</i> -Bn-indole	4-ClC ₆ H ₄	11k ; 83	96:4	9:1
13	<i>N</i> -Bn-indole	4-CF ₃ -C ₆ H ₄	11l ; 56	93:7	10:1
14	<i>N</i> -Bn-indole	3-ClC ₆ H ₄	11m ; 65	94:6	10:1
15	<i>N</i> -Bn-indole	3-OMeC ₆ H ₄	11n ; 54	96:4	10:1
16	<i>N</i> -Bn-indole	3-MeC ₆ H ₄	11o ; 84	90:10	7:1
17	<i>N</i> -Bn-indole	3-thiophene	11p ; 85	85:15	8:1
18	<i>N</i> -Et-indole	Cy	11q ; 85	72:28	7:1

^aReactions performed under N₂ atmosphere. ^bYield represents isolated yield of purified material and is an average of two experiments. ^cDetermined by HPLC or SFC analysis; see the Supporting Information for details. ^dDetermined by analysis of 400 or 600 MHz ¹H NMR spectra of crude reactions. ^e3.75 mol % [Rh(C₂H₄)₂Cl]₂ at 60 °C.

substituted indoles and 5.0 mol % Rh, 6 mol % **L2**, and 10 mol % NaBAR₄^F for 24 h at 35 °C in CH₂Cl₂ furnished hydroarylation products **11a–h** efficiently and in high enantioselectivity (88:12 to 95:5 er). In addition, we found transformation with the more sterically hindered 2-methyl-N-Me-indole also proceeded effectively generating **11i** in 98% yield and in slightly diminished 90:10 er. Accordingly, we also varied the aryl diene component. Hydroarylation of 1,3-dienes containing different aryl groups (halogens, CF₃, OMe, Me) was also efficient and enantioselective (entries 11–16). The catalytic method is also compatible with thiophene groups; for example, the formation of **11p** (entry 16) in 85% yield and 85:15 er, is representative. Catalytic hydroarylation also proceeds with alkyl-substituted dienes efficiently but with lower enantioselectivity; **11q** was furnished in 85% yield and 72:28 er. The reaction is also tolerant of pyrrole nucleophiles but results in lower er with **L2** compared indoles.¹³

Next, we set out to examine the ability of (CDC)-Rh complexes to promote catalytic C–H arylation with internal 1,4-disubstituted 1,3-dienes; in general, internal olefins represent significantly more challenging classes of substrates in catalytic hydrofunctionalizations methods. With the (CDC)-Rh catalyst derived from **L2**, reactions proceed efficiently with isomerically impure dienes, with some substrates requiring slightly elevated temperatures (60 °C), affording products in high er (>96:4 er). For example, treatment of 1-phenyl-4-methyl-butadiene and **9** with 5.0 mol % (**L2**)-Rh at 50 °C for 24 h furnished **12** in 66% isolated yield and 98:2 er (**Scheme 2**). Additionally, internal

Scheme 2. Enantioselective Hydroarylation of Internal 1,3-Dienes^{a–d}



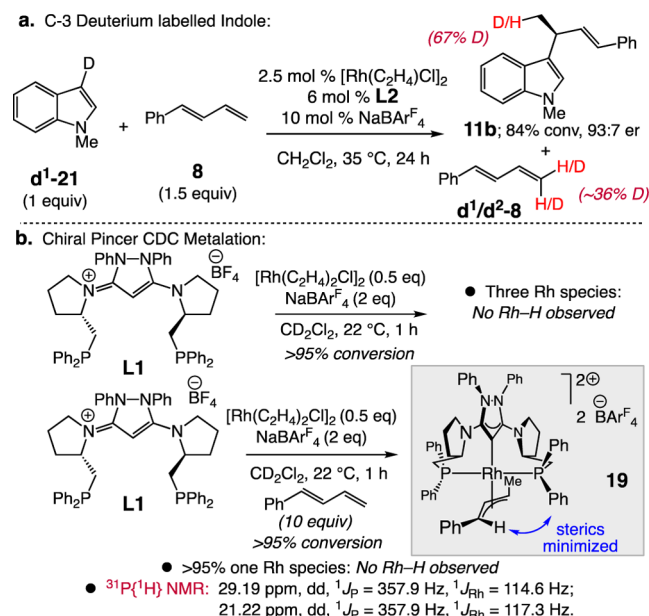
^{a–d}See Table 2.

dienes bearing alkyl, alkyl halide, ester, ketone, and silyl ether functional groups are tolerated furnishing products **13–17** in 50–90% yield, 97:3–98:2 er, and good site-selectivity. Notably, reaction of an internal diene bearing unprotected alcohol results in similar efficiency but lower er; the formation of **18** in 65% yield and 87:13 er, is representative.

Deuterium labeling experiments to probe the fidelity of proton transfer from the C-3 position on indole to the product were undertaken (**Scheme 3a**). Reaction of **d**¹-**21** with **8** in the presence of (**L2**)-Rh affords **d**¹-**11b** with 67% deuterium in the methyl group. Furthermore, analysis of the reaction mixture revealed the presence of **d**¹/**d**²-**8**; 36% deuterium incorporation into the terminal diene. This data indicates Rh(III)–hydride insertion is rapid and reversible.

To gain insight into the structure of the metalated ligand and verify that a (CDC)-Rh(III)–H is generated, which leads to

Scheme 3. Catalyst Structure and Mechanism Experiments



a (CDC)-Rh(III)-allyl, we studied the catalyst formation. Following the catalytic method, treatment of [Rh(C₂H₄)₂Cl]₂ and **L1** with NaBAR₄^F in CD₂Cl₂ at 22 °C for 1 h results in the formation of three new Rh species by ³¹P NMR; however, no Rh-hydride is observed. Performing the same reaction but with the addition of diene **8** (10 equiv), affords a dark red/purple solution that contains a single species by ³¹P NMR. Again, no Rh-hydride is observed.

After careful experimentation, the X-ray crystal structure of dicationic [(**L1**)-Rh(III)-η³-allyl]₂BAR₄^F complex **19** was obtained, and is depicted in **Figure 1**.¹⁴ As indicated by the ORTEP diagram,

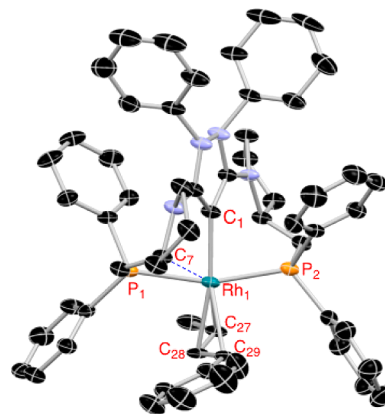


Figure 1. X-ray Structure of **19**. Two BAR₄^F ions omitted for clarity. Selected bond lengths for **19** (Å): Rh₁–C₁, 2.081(5); Rh₁–P₁, 2.3948(14); Rh₁–P₂, 2.3454(16); Rh₁–C₂₇, 2.181(5); Rh₁–C₂₈, 2.166(5); Rh₁–C₂₉, 2.281(5); C₂₇–C₂₈, 1.404(8); C₂₈–C₂₉, 1.390(8); Rh₁–C₇, 3.108(6).

the pincer (**L1**)-Rh(III) complex has a pseudotrigonal bipyramidal geometry. Of note, the C₇ methine proton resides ~2.5 Å from the Rh center, potentially providing additional stabilization for the observed dicationic (CDC)-Rh(III) complex. Analysis of the π-allyl fragment shows the Rh–C distance to the Ph-substituted allylic terminus (2.281(5)) is 0.10 Å longer than the corresponding distance to the Me-substituted terminus

(2.181(5)). These values are inconsistent with similar allyl $C_{27}-C_{28}/C_{28}-C_{29}$ bond lengths, suggesting the distortion is caused by sterics of the phenyl group. Also, the resulting observed major (S)-enantiomer formed in the catalytic reactions must occur via addition of indole to the least hindered allyl terminus.

Control reactions confirmed catalytic diene hydroarylation in the presence of 5 mol % **19** and 5 mol % $NaBAR^F_4$ results in >98% conv to **10** in 8:1 rr and 89:11 er. Notably, without $NaBAR^F_4$ **10** is formed in 6:1 rr, and 85:15 er, demonstrating the additive effect of Na salts in obtaining high rr and er. Furthermore, the stoichiometric reaction between **19** and **9** at 35 °C in CH_2Cl_2 results in <2% conv to **10**.¹⁵

In summary, we have developed the first chiral CDC ligand that promotes enantioselective Rh-catalyzed hydroarylation of terminal and internal 1,3-dienes. Further studies of other (CDC)-Rh-catalyzed enantioselective hydrofunctionalizations are in progress.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b08575.

Experimental procedures and spectral and analytical data for all products (PDF)

Data for $C_{59}H_{59}N_4P_2Rh$, $2(C_{32}H_{12}BF_4)$ (CIF)

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Notes

The authors declare no competing financial interest.

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