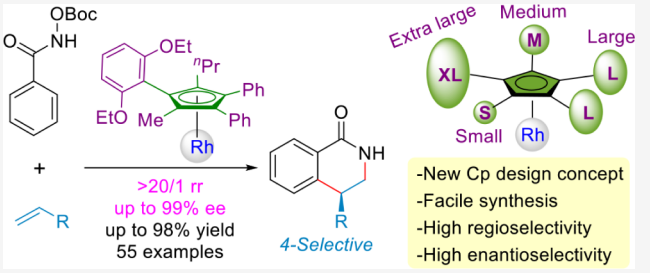
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
pubs.acs.org/JACS
Article

Highly Regio- and Enantioselective Synthesis of 4-Substituted Dihydroisoquinolones Catalyzed by a Planar-Chiral Rhodium(III) Catalyst Bearing a Penta-Substituted Prochiral Cyclopentadienyl Ligand

Chunhui Zhang,[#] Gan-Lu Qian,[#] Junlian Ji, Ji-Jun Jiang, Xin Hong,* and Jun Wang*

Cite This: https://doi.org/10.1021/jacs.5c16993
Read Online
ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A class of rationally designed planar-chiral rhodium(III) catalysts featuring prochiral 1,3,4-triaryl-2,5-dialkyl cyclopentadienyl ligands has been developed. By a modular synthetic strategy that enables rapid diversification, the prochiral cyclopentadienyl ligands can be readily prepared in only three steps. Resolution of the planar-chiral complexes is efficiently achieved by flash column chromatography assisted by a chiral diene ligand. The catalyst could enable highly regio- and enantioselective asymmetric C−H activation of phenylhydroxamic acids with unactivated terminal alkenes, affording 4-substituted dihydroisoquinolones with high efficiency (55 examples, >20:1 rr, up to 98% yield, up to 99% ee). This transformation well addressed a long-standing and notoriously challenging problem in asymmetric synthesis. This reaction tolerates a wide range of functional groups in reactants, such as halogen, hydroxy, acetyl, alkoxy, amido, and cyano groups. Synthetic utilities of this methodology are showcased, such as the concise syntheses of 4-*n*-butyl and 4-benzyl tetrahydroisoquinolines. Mechanistic studies have been conducted, including H/D exchange, kinetic isotope effect (KIE), and capture of the metallacyclic intermediate. The 1,3,4-triaryl-2,5-dialkyl cyclopentadienyl moiety proves to be the key structural feature for achieving high regioselectivity. The cyclopentadienyl ligand adopts a well-defined conformation in the metallacycle intermediate formed during C−H activation. Density functional theory (DFT) calculations revealed that the migratory insertion of olefin was irreversible, constituting the stereo- and regioselectivity-determining event.



INTRODUCTION

3,4-Dihydroisoquinolin-1(2*H*)-ones widely exist in natural products and bioactive molecules.[1] Being one of the most straightforward synthetic methods, the [4 + 2] annulation reaction of phenylhydroxamic acid derivatives with alkenes through transition metal catalyzed C−H activation has drawn much interest of chemists.[1,2] It was first reported by Fagnou[3] and Glorius[4] in 2011. It should be noted that reactions with terminal alkenes may give two regioisomeric products. In general, for terminal olefins with electronically activating groups such as aryl,[3−5] vinyl[6] and carbonyl,[5c,i,6,7] 3-substituted dihydroisoquinolones were produced in high regioselectivity. In contrast, for vinylsilanes[8] and potassium vinyltrifluoroborates,[5a,g,9] 4-substituted dihydroisoquinolones were generated in high regioselectivity. However, for alkyl substituted terminal alkenes, the regioselectivity issue is quite complicated. 3-Substituted dihydroisoquinolones could be smoothly prepared in high regioselectivity with cobalt,[5b,f,i,m,10] palladium,[11] ruthenium[12] and rhodium[5c,7b,13] catalysts and in high enantioselectivity with cobalt catalysts[5i,m]. In contrast, 4-substituted dihydroisoquinolones were generated in poor regioselectivities (typically 1:1 ∼ 3:1 rr)[3,5g,j,l,14] and poor enantioselectivities (<62% ee), except for intramolecular reactions.[15] Interestingly, rhodium catalysts with sterically demanding cyclopentadienyl (Cp) ligands favored the formation of 4-substituted products.[5h,16] The most effective ones include $[(C_5H_3{}^tBu_2)RhCl_2]_2$ (**Rh-A**)[5h,16a,b,d,g,17] reported by Rovis (5:1 ∼ 19:1 rr) and $[(C_5H_2{}^tBu_2(CH^tBuR))RhCl_2]_2$ (**Rh−B**)[16e,h] by Perekalin (>15:1 rr). But, unfortunately, optically pure **Rh−B** only led to poor enantioselectivities (34−54% ee).[16f,i,18] In 2024, Cramer disclosed an elegant planar-chiral CpRh catalyst (**Rh−C**), which showed high enantioselectivity but low to moderate regioselectivity. Only three olefins were reported, including 1-hexene (7.5/1 rr, 86% ee), allyl benzene (5.3/1 rr, 90% ee) and allyl alcohol (1.7/1 rr, 90% ee).[5n] Thus, a catalyst capable of delivering both high regioselectivity and enantioselectivity across a broad substrate

Received: September 26, 2025
Revised: October 24, 2025
Accepted: October 27, 2025

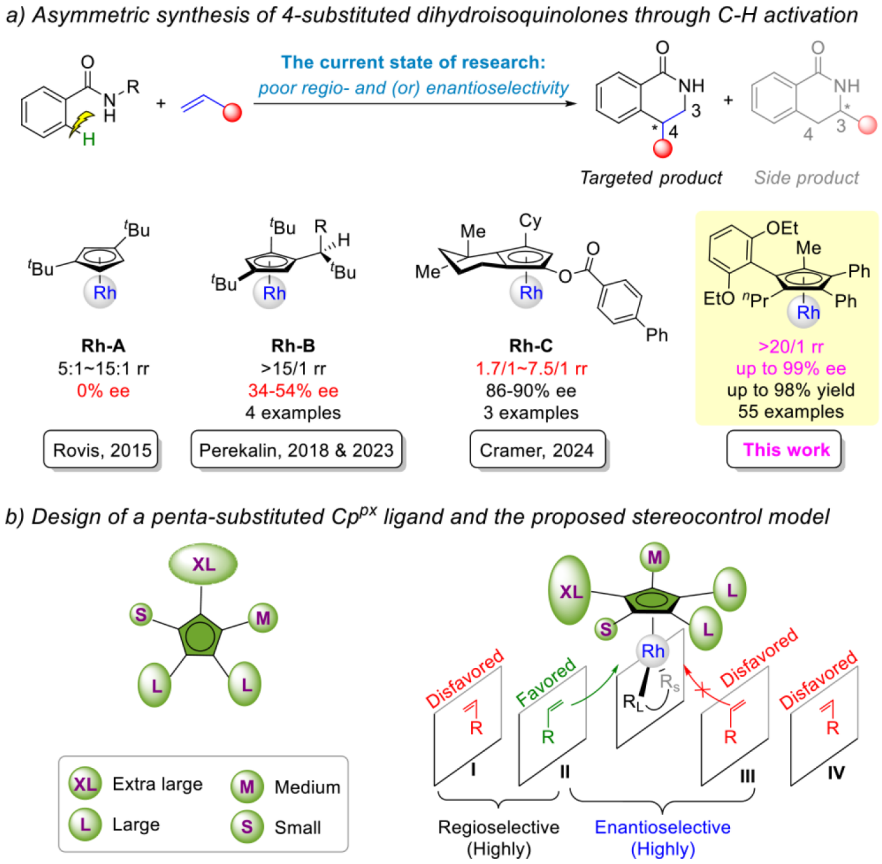


Figure 1. Research background and ligand design.

scope remains lacking. For the collection of previously reported data, please see Section 2 in Supporting Information. Herein, we present a class of tailor-made planar-chiral rhodium(III) catalyst bearing a penta-substituted prochiral cyclopentadienyl ligand (Cp^{px}, the superscript "px" denotes prochiral), which can efficiently catalyze this reaction in both high regio- and enantioselectivity (>20/1 rr, up to 99% ee, and up to 98% yield) with a broad substrate scope (55 examples) (Figure 1a).

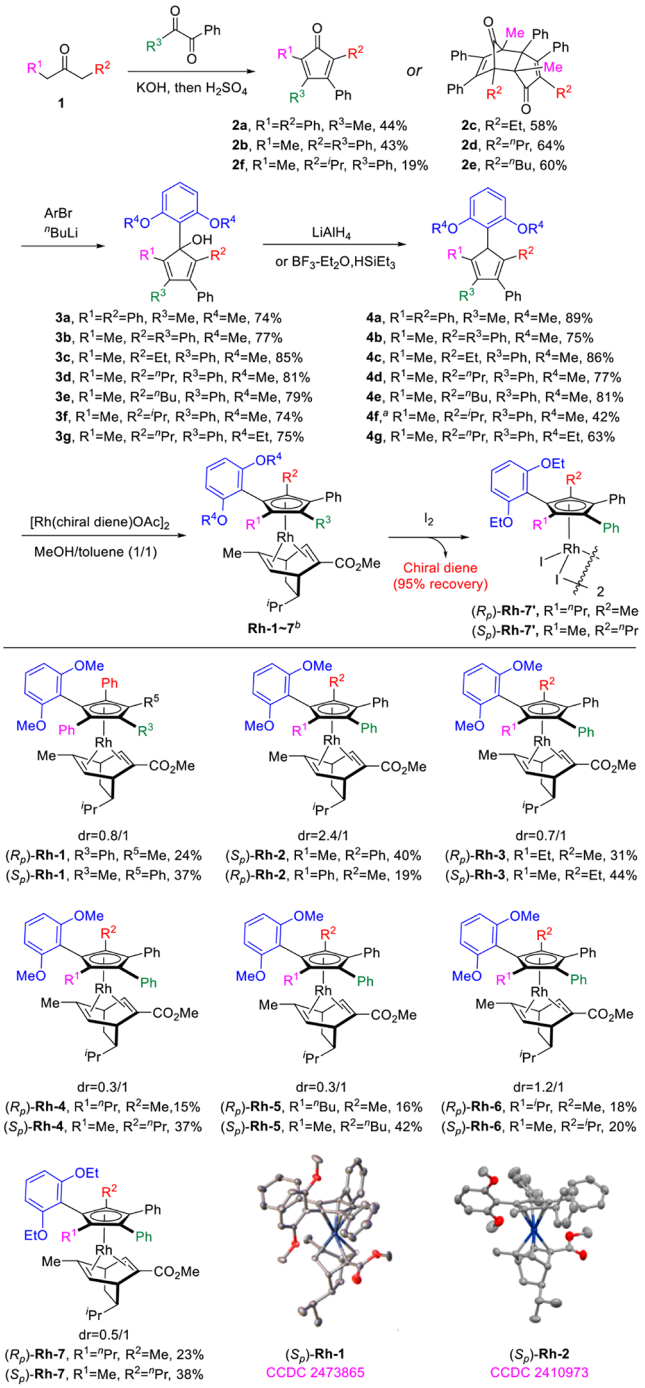
Whereas $Cp^{x}M$ catalysts made from chiral Cp ligands[5a,e,j,l,7a,14b,15d,19] have been well established for asymmetric C–H activation[20] since the seminal work of Cramer,[5a] Ward and Rovis,[7a] the use of planar-chiral $Cp^{px}M$ catalysts[20f,21] bearing prochiral Cp ligands remains rare[5n,14a 16f,i,18,22] since Perekalin's pioneering work[16f]. Its most attractive advantage lies in the vast structural tunability of the Cp^{px} ligand, which could enable facile and flexible tuning of the catalysts' electronic and steric properties. However, the development of this promising class of catalysts has been largely hindered by the lack of established design guidelines and efficient synthetic methodologies. In an attempt to address this problem, we introduced a Cp^{px} design concept in 2023,[14a] which led to the development of a class of planar-chiral $Cp^{px}Rh$ catalysts (Cp^{px} = C_5HMe_2PhAr). While these catalysts performed well in various reactions, they proved ineffective for the aforementioned regio- and enantioselective preparation of 4-alkyl substituted dihydroisoquinolones (SI, page 4, entries 3–4). As part of our ongoing efforts in designing and synthesizing planar-chiral $Cp^{px}M$ catalysts,[14a,22a] we herein present another design concept for the development of such catalysts. As illustrated in Figure 1b, the periphery of the cyclopentadienyl ring was adorned by five achiral substituents in four different sizes, namely, extra-large (XL), large (L), medium (M), and small (S). Upon C–H activation, the substrate is assumed to be in favor of embedding itself into the catalyst's groove shaped properly by the extra-large substituent XL and two large substituents L, meanwhile heading its large segment toward the site of the small substituent S. There are four possible ways (**I**, **II**, **III** and **IV**) for a terminal olefin to approach the rhodium. Owning to the large steric hindrance of substituents XL and L, the approaching ways **I**, **III** and **IV** are blocked, which would lead to high regio- and enantioselectivity.

RESULTS AND DISCUSSION

By a modular synthetic strategy that enables rapid diversification, the designed penta-substituted $Cp^{px}H$ could be facilely synthesized via three steps from readily available starting materials (Scheme 1). First, the condensation of 1,3-disubstituted ketone **1** with 1,2-diketone gave tetrasubstituted cyclopentadienones **2**.[23] Notably, **2c–e** were isolated as dissociable dimers thanks to the less sterically bulky alkyl substituents in both 2- and 5-positions.[23a,24] Reacting **2** with 2,6-dialkoxyaryl lithium gave alcohol **3**, which was then reduced to $Cp^{px}H$ **4** (generally as a isomeric mixture). It was reacted with $[Rh^{I}(\text{chiral diene})OAc]_2$ to provide the $Cp^{px}Rh^{I}$(chiral diene) complex as a mixture of two diastereomers (1.2:1 to 3.3:1 dr), which could be separated by silica gel flash column chromatography.[14a] The exact structures of (S_p)-**Rh-1** and (S_p)-**Rh-2** were determined by single crystal X-ray crystallography. The absolute configurations of the planar chirality of diastereomeric **Rh-3** to **Rh-7** were assigned according to the single-crystal structure of **14b**

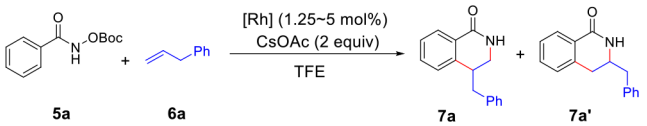
https://doi.org/10.1021/jacs.5c16993
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Scheme 1. Synthesis of Planar-Chiral $Cp^{px}Rh$ Catalysts



[a]By BF_3•Et_2O and $HSiEt_3$. [b]The dr values were determined by NMR.

Table 1. Catalyst Screening for the Reaction of *O*-Boc Hydroxamic Acid and Allyl Benzene[a]



5a 6a 7a 7a'

entry	[Rh]	yield (%)	ee (%)	7a/7a'[b]
1	(R_p)-**Rh-1**	32	23	>20/1
2	(S_p)-**Rh-2**	91	53	>20/1
3	(R_p)-**Rh-3**	94	87	>20/1
4	(R_p)-**Rh-4**	98	88	>20/1
5	(R_p)-**Rh-5**	96	87	>20/1
6	(R_p)-**Rh-6**	97	88	>20/1
7	(R_p)-**Rh-7**	98	90	>20/1
8[c]	(R_p)-**Rh-7**	98	94	>20/1
9[d]	(R_p)-**Rh-7'**	97	94	>20/1
10[d,e]	(R_p)-**Rh-7'**	97	92	>20/1

[a]Under N_2, **5a** (0.1 mmol), **6a** (0.2 mmol), [Rh] (5 mol %), $(BzO)_2$ (10 mol %), CsOAc (2 equiv), TFE (1 mL), 0 °C, 18 h. Isolated yields are given. The ee values were determined by HPLC. [b]Determined by NMR. [c]At −20 °C. [d](R_p)-**Rh-7'** (1.25 mol %), $AgNTf_2$ (5 mol %), TFE (0.2 M), −20 °C, 24 h. [e]With MeOH as the solvent.

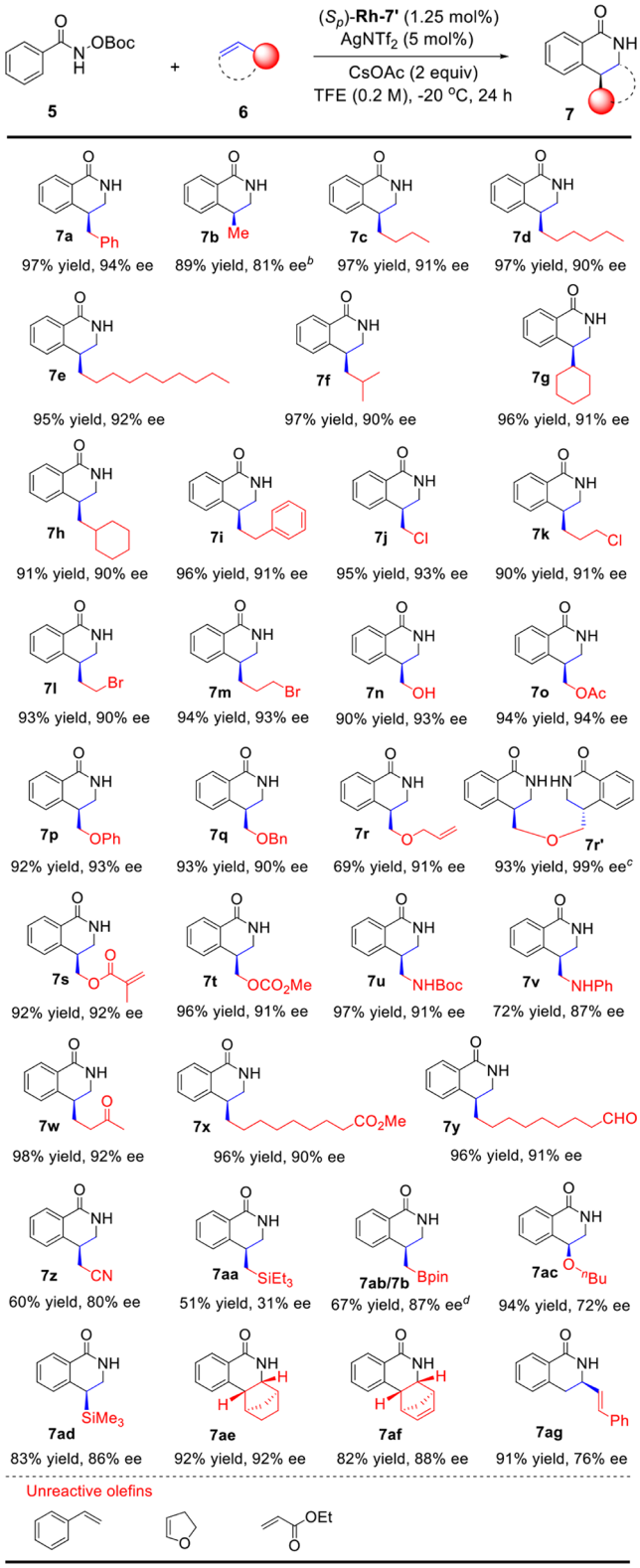
in Figure 2c and circular dichroism (CD) spectra (Supporting Information, Section 8). It should be noted that the $[Cp^{px}RhI_2]_2$ complex (R_p)-**Rh-7'** could be facilely prepared by treating the corresponding $Cp^{px}Rh^{I}$(chiral diene) complex (R_p)-**Rh-7** with iodine. Meanwhile, the chiral diene could be recovered in 95% yield.

With a library of catalysts in hand, the reaction of *O*-Boc phenylhydroxamic acid **5a** with allyl benzene **6a** was investigated as the model reaction (Table 1). Both $Cp^{px}Rh^{I}$(chiral diene) and $[Cp^{px}RhI_2]_2$ complexes can be used in catalysis. However, it is important to add $(BzO)_2$ to oxidize $Cp^{px}Rh^{I}$(chiral diene) or $AgNTf_2$ to abstract iodide from $[Cp^{px}RhI_2]_2$ to generate the catalytically active species. To our delight, in all the cases, 4-substituted dihydroisoquinolone **7a** was generated in high regioselectivity (>20:1). Compared to **Rh-1**, the catalyst **Rh-2** provided higher enantioselectivity (53% ee vs 23% ee) and yield (91% vs 32%) (entries 1−2). When the substituent R^2 in **Rh-2** was altered from phenyl to the less bulky ethyl (**Rh-3**), the enantioselectivity of the reaction was further enhanced without affecting the yield (entry 3, 94% yield, 87% ee), emphasizing the well-shaped groove of Cp^{px} ligand by the extra-large substituent (2,6-dimethoxyphenyl) and two large substituents (phenyl) played a crucial role. Further tuning of steric hindrance of the alkyl substituent R^1 (**Rh-3** to **Rh-6**) could not improve enantioselectivity (entries 3−6). Increasing the steric hindrance on the alkoxy substituents of 2,6-dialkoxyphenyl by replacing methoxy to ethoxy (**Rh-7**) resulted in higher enantioselectivity of 90% ee (entry 7). When the reaction temperature was lowered down from 0 °C to −20 °C, the enantioselectivity was improved to 94% ee (entry 8). The $[Cp^{px}RhI_2]_2$ complex **Rh-7'** provided the same reaction outcome as **Rh-7**, and the catalyst loading could be decreased to 1.25 mol % (entry 9). It is also possible to run the reaction in methanol, though slightly decreased enantioselectivity was observed (entry 10).

Under the optimized reaction conditions, an array of alkenes was examined (Table 2). Uniformly high regioselectivities were observed (>20:1 dr). Of note, the 1-propene gas (in a balloon) could be used as reactant, giving the product **7b** in 89% yield with 81% ee. Moreover, other aliphatic terminal alkenes with linear or branched chains also reacted smoothly to give the corresponding products in good yields with high enantioselectivity (**7c-i**, 91−97% yield, 90−92% ee). Allyl chloride was a good reactant (**7j**, 95% yield, 93% ee), which was problematic in Perekalin's work.[16e,h] Other chloro- and bromo-substituted terminal alkenes were also applicable (**7k−m**, 90−94% yield, 90−93% ee). Allyl alcohol (**7n**) is a notoriously challenging reactant, which has been extensively studied.[3,5n,14a,16f] But

https://doi.org/10.1021/jacs.5c16993
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 2. Scope of Alkenes[a]



[a]Under N_2, **5** (0.1 mmol), **6** (0.2 mmol), (S_p)-**Rh-7'** (1.25 mol %), $AgNTf_2$ (5 mol %), CsOAc (2 equiv), TFE (0.5 mL), −20 °C, 24 h. The regioselectivities for all reactions were determined to be >20:1 dr by NMR. Isolated yields are given. The ee values were determined by HPLC. [b]At 0 °C. [c]**5** (0.2 mmol), **6** (0.1 mmol), (S_p)-**Rh-7'** (2.5 mol %), and $AgNTf_2$ (10 mol %). [d]The product **7ab** was not detected, which decomposed into **7b** in the reaction.

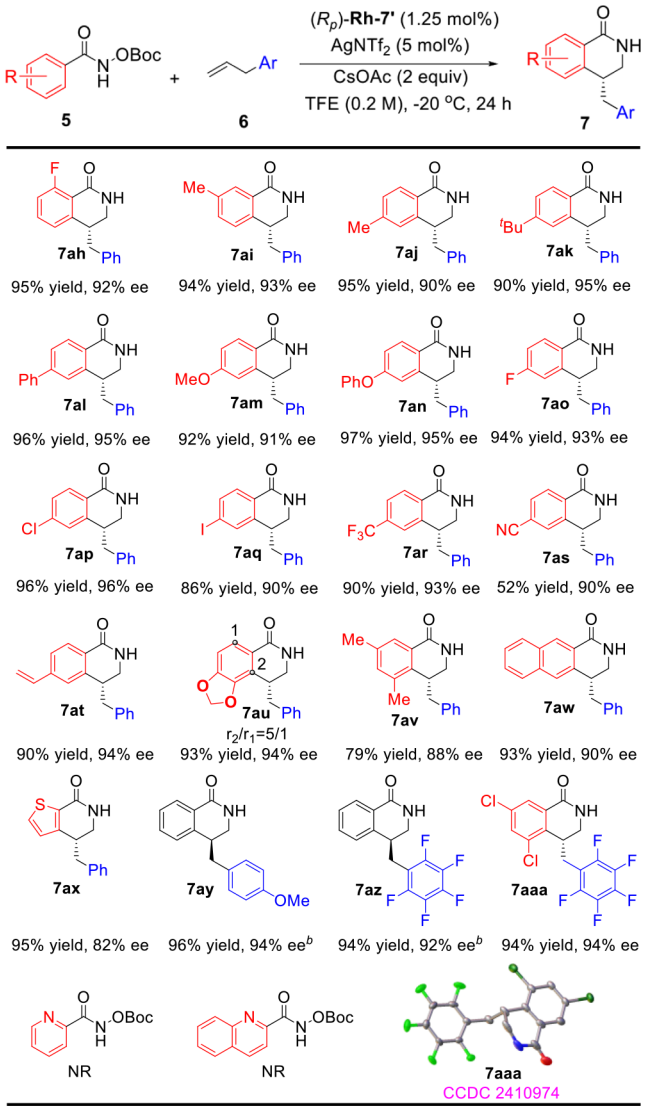
either poor regioselectivity or poor enantioselectivity was observed. With our catalyst, the targeted product **7n** was obtained in 90% yield with 93% ee, which is the best result ever achieved so far. Allyl acetate (**7o**) and allyl ethers (**7p**−**q**) reacted smoothly as well (92−94% yield, 90−94% ee). Diallyl ether could react with one or two double bonds depending on the dosage of the amide **5**, affording monodihydroisoquinolone **7r** (69% yield, 91% ee) or bis- dihydroisoquinolone **7r'** (93% yield, 99% ee). For allyl methacrylate, the reaction selectively occurred at the allyl double bond (**7s**, 92% yield, 92% ee). Allyl methyl carbonate reacted smoothly too (**7t**, 96% yield, 91% ee). Allyl amine derivatives could also be used (**7u**−**v**, 72−97% yield, 87−91% ee). Alkenes containing ketone (**7w**), ester (**7x**), aldehyde (**7y**), and nitrile (**7z**) functionalities were tolerated (60−98% yield, 80−92% ee). Allyl silane gave moderate yield and low enantioselectivity (**7aa,** 51% yield, 31% ee). Allyl boronic ester was tested. It was found the expected product **7ab** decomposed into **7b** in the reaction (67% yield, 87% ee). Vinyl ether and vinyl silane could be respectively converted to the products **7ac** and **7ad** (83−94% yield, 72−86% ee). Norbornene (**7ae,** 92% yield, 92% ee) and norbornadiene (**7af,** 82% yield, 88% ee) were good coupling partners as well. Interestingly, the diene (*E*)-1-phenyl-1,3-butadiene reacted smoothly to give the 3-substituted product **7ag** (91% yield, 76% ee) with the reversed regioselectivity. In this case, the electronic effects should dominate the regioselectivity during the migratory insertion of the olefin. However, styrene, dihydrofuran and acrylic ester were nonreactive in this reaction. In these cases, *O*-Boc phenylhydroxamic acid was almost quantitatively recovered.

Subsequently, the scope of *O*-Boc phenylhydroxamic acids was explored (Table 3). Both *ortho*-fluoro and *meta*-methyl substituted substrates gave the products in high yields and enantioselectivities (**7ah**-**7ai**, 94−95% yield, 92−93% ee). *Para*-substituted *O*-Boc phenylhydroxamic acids with a wide range of functionalities (alkyl, Ph, MeO, PhO, halogen, CF_3, CN) were well tolerated, providing products generally in high yields and high enantioselectivities (**7aj**-**7as**, 52−97% yield, 90−96% ee). The relatively low yield of **7as** could be due to the poisoning effect of cyano group on the catalyst. This correlates with the lower yield of **7z** in the case of allyl cyanide. The *para*-vinyl *O*-Boc phenylhydroxamic acid reacted well, leaving the vinyl intact (**7at**, 90% yield, 94% ee). *O*-Boc phenylhydroxamic acids derived from piperic acid, 3,5-dimethylbenzoic acid and 2-naphthoic acid were suitable substrates (**7au**−**7aw,** 79−93% yield, 88−94% ee). Thienyl amide was converted to the product **7ax** in 95% yield with 82% ee. Besides allyl benzenes, 4-allyl anisole and allyl pentafluorobenzene were also suitable coupling partners (**7ay**−**7aaa**, 94−96% yield, 92−94% ee). The absolute configuration of the major enantiomer of product **7aaa** was determined to be *R* by single-crystal X-ray crystallography. We examined benzamides bearing N-containing heteroatomatics, such as 2-picolinamide and 2-quinolinamide. Unfortunately, no products were obtained and the substrates were recovered in high yields. The strong coordinating effect of the basic nitrogens of substrates should poison the catalyst.

Interestingly, when *O*-Boc hydroxamic acid **5a** was allowed to react with an equimolar olefin mixture of allyl benzene, styrene, 2-methylbut-2-ene, cyclopentadiene, dihydrofuran, and cyclohexene, 4-benzyl dihydroisoquinolone **7a** was obtained as the sole product in 96% yield with 94% ee (Scheme 2). It clearly demonstrated the remarkable chemo-

https://doi.org/10.1021/jacs.5c16993
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Table 3. Scope of *O*-Boc Phenylhydroxamic Acids[a]

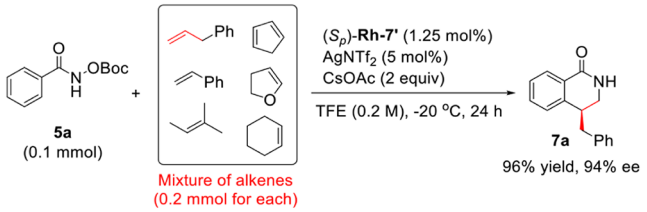


[a]Under N_2, **5** (0.1 mmol), **6** (0.2 mmol), (R_p)-**Rh-7'** (1.25 mol %), $AgNTf_2$ (5 mol %), CsOAc (2 equiv), TFE (0.5 mL), −20 °C, 24 h. The regioselectivities for all reactions were determined to be >20:1 dr by NMR. Isolated yields are given. The ee values were determined by HPLC. [b]With (S_p)-**Rh-7'**.

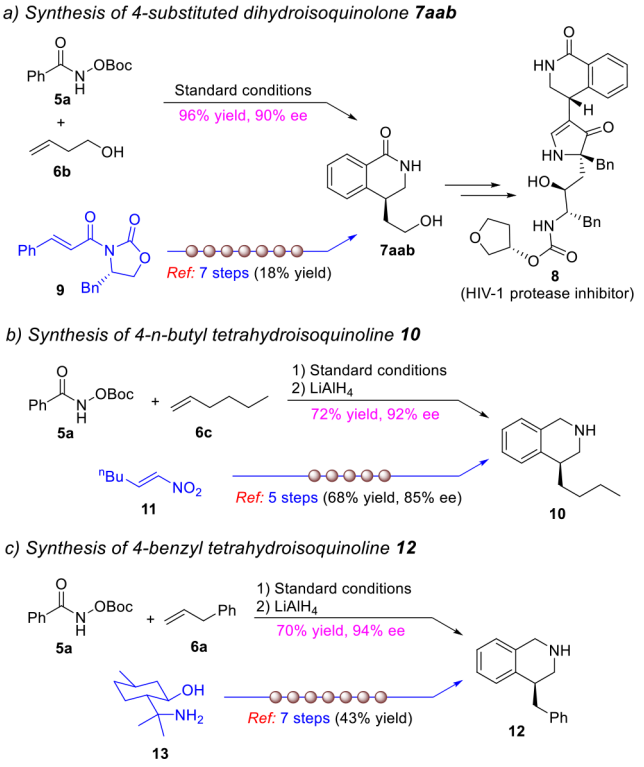
selectivity of this reaction, which favored unactivated terminal alkenes.

Then, synthetic utilities of this methodology are showcased (Scheme 3). First, dihydroisoquinolone **7aab** is the key intermediate for the preparation of HIV-1 protease inhibitor **8**.[25] It was previously prepared through seven steps from the chiral cinnamic acid derivative **9**.[25] With our protocol, in

Scheme 2. Competitive Experiments



Scheme 3. Synthetic Applications



contrast, its preparation only took one step (96% yield, 90% ee) by reacting **5a** with the readily available and cheap alkene 3-buten-1-ol (**6b**). Second, in a literature,[26] the 4-*n*-butyl tetrahydroisoquinoline **10** was synthesized from nitroalkene **11** via five steps in 68% yield with 85% ee. By our protocol, it could be concisely prepared by reduction of the product **7c** from the reaction of **5a** with 1-hexene (**6c**) in 72% overall yield with 92% ee. By the same way, 4-benzyl tetrahydroisoquinoline **12** could also be easily prepared in two steps with 70% overall yield and 94% ee, which was previously synthesized via seven steps from **13** in 43% overall yield.[27] The syntheses of **10** and **12** were also reported by Cramer by the same strategy.[5n]

To gain mechanistic insight into this reaction, several control experiments were carried out. First, deuterated *O*-Boc phenylhydroxamic acid **5a**-d_5 (>99% D) was subjected to the standard reaction condition in the absence or presence of alkene **6a**. It was found that no hydrogen incorporation occurred, suggesting that cleavage of C−H bond should be irreversible in the reaction (Figure 2a). Second, the primary kinetic isotope effect was studied and k_H/k_D was determined to be 1.2, indicating the cleavage of C−H bond was not the turnover-limiting step (Figure 2b). Third, stoichiometric reaction of *O*-Boc phenylhydroxamic acid **5a** with (S_p)-**Rh-7** in the presence of AgOAc followed by the addition of PMe_3 generated rhodacyclic compounds **14a** (18% yield) and **14b** (62% yield) in 0.3/1 dr. Of note, when PPh_3 was applied instead of PMe_3, the corresponding rhodacyclic product was low-yielding and not sufficiently stable to allow isolation, which could be attributed to the serious steric clashes between the sterically hindered Cp^{px} ligand and sterically demanding PPh_3 (Figure 2c). The three- dimensional structure of **14b** was revealed by single crystal X-ray diffraction, which hints stereocontrol event of the catalytic reaction. Interestingly, the ethyl moiety of *n*-propyl points upward, forcing the two

https://doi.org/10.1021/jacs.5c16993
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

adjacent benzene rings to tilt in opposite directions. Affected by the tilt of phenyl, the other phenyl also tilts accordingly. As a result, the space below the methyl group becomes less crowded, while the space below the propyl group becomes more crowded. As such, a well-defined chiral pocket is built up. In order to intuitively show the steric surroundings around rhodium, the steric map was generated for **14b** by the SambVca 2.1 tool[28] (Figure 2d). Consistent with our design concept, the groove of Cp^{px} along the north−south direction can be easily recognized (steric map A), which can perfectly accommodate phenylhydroxamic acid substrate (steric map B). Owing to the steric hindrance, alkene preferably approach rhodium from the southeast direction. To investigate the influence of substituents on the Cp ring on the control of the regioselectivity of reaction, four catalysts (**Rh-8** to **Rh-11**) were tested (Figure 2e). When **Rh-8** (with the *n*-butyl group on the Cp ring of **Rh-5** replaced by Me) was used, the regioselectivity remained unchanged at >20/1. When **Rh-9** (with both phenyl groups on the Cp ring of **Rh-8** replaced by two methyl groups) was employed, the regioselectivity decreased to 6/1. With **Rh-10** (where the 2,6-dimethoxyphenyl group on the Cp ring of **Rh-8** was replaced by a methyl group), the regioselectivity dropped to 10/1. When **Rh-11** (with both the 2,6-dimethoxyphenyl and the two phenyl groups on the Cp ring of **Rh-8** replaced by methyl groups) was used, the regioselectivity was further reduced to 1.4/1. These results identify the 1,3,4-triaryl-2,5-dialkyl cyclopentadienyl architecture as the critical determinant for achieving high regioselectivity.

To gain further insight into the mechanism and origins of selectivities, we performed DFT calculations at the ωB97X-D/def2-TZVPP-SMD(TFE)//B3LYP-D3(BJ)/def2-SVP level on the [4 + 2] annulation of phenylhydroxamic acid **5a** with allyl benzene **6a** catalyzed by (S_p)-**Rh-6** (Figure 3a). The computed free energy profile supports a Rh(III)/Rh(V) catalytic cycle. Starting from the C−H activation intermediate **Int1**, the olefin undergoes migratory insertion via **TS2** with a barrier of 10.6 kcal/mol to give the rhodacyclic intermediate **Int3**. This step is calculated to be irreversible and thus constitutes the stereo- and regioselectivity-determining event. Subsequent oxidative addition of the N−OBoc group generates the Rh(V) nitrene species **Int5**, followed by a facile reductive elimination through **TS6** to afford the stable Rh(III) intermediate **Int7**, which undergoes protonation to release the observed product **7a**. An alternative Rh(I)/Rh(III) pathway involving direct reductive elimination from **Int3** to **Int11** is energetically disfavored, consistent with previous mechanistic study by Lan, Houk and coworkers.[29] We note that the calculated energy of **TS6** is slightly lower than that of **Int5** due to the use of different levels of theory in geometry optimization and single-point energy calculation, but IRC analysis confirmed the validity of **TS6** and its proper connection to both **Int5** and **Int7** (Figure S6).

The origins of enantioselectivity can be explained by comparing the favored transition state **TS2** with its enantiomeric counterpart **TS2-Minor** (Figure 3b), which is higher in free energy by 2.3 kcal/mol, in line with the experimentally observed 88% ee. In **TS2**, the bulky 2,6-dimethoxyphenyl substituent of the Cp ligand is positioned on the same side as the olefin, but the terminal unsubstituted carbon of the olefin points toward this substituent, minimizing steric repulsion. In contrast, in **TS2-Minor**, the substrate orientation forces the N−OBoc group to approach the same 2,6-dimethoxyphenyl substituent, introducing steric clash that

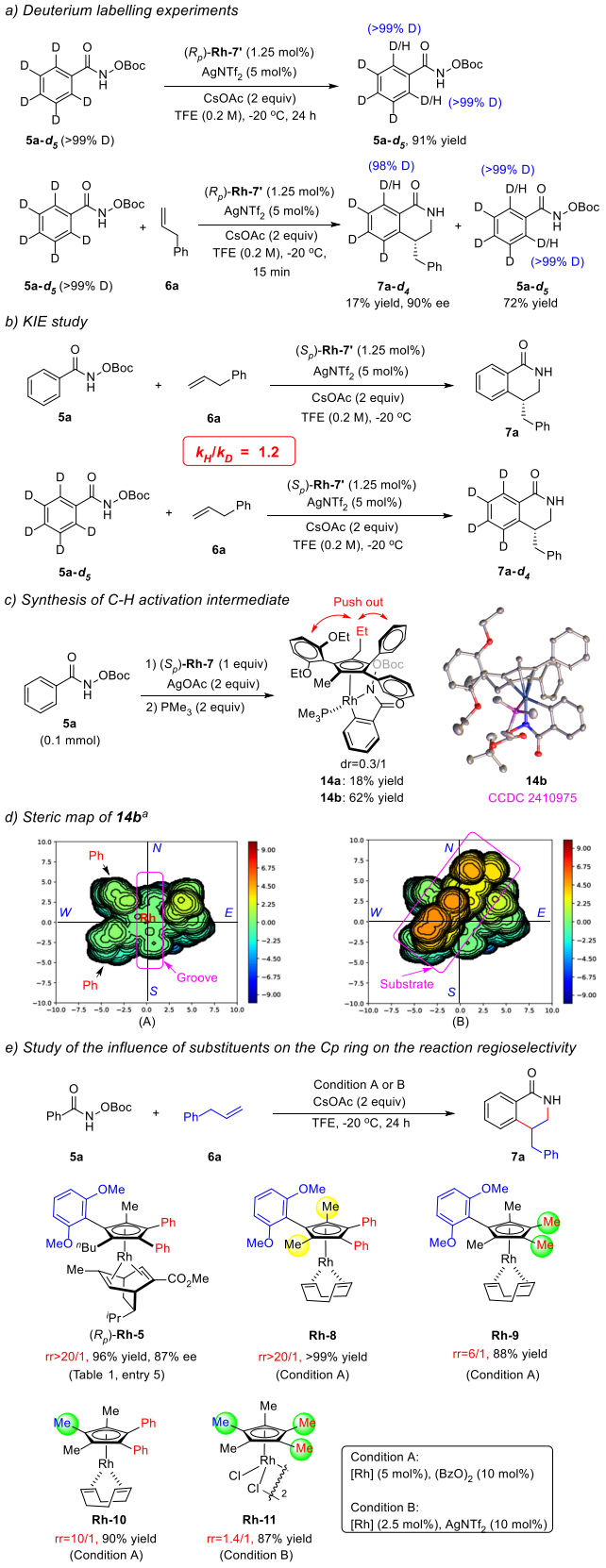


Figure 2. Mechanistic studies. [a]The steric map was generated by the SambVca 2.1 tool (bondi radii scaled by 1.17, sphere radius 10 Å, mesh spacing 0.1 Å). The red and blue zones indicate the more- and less-hindered zones, respectively. The axes indicate the distance away from the metal.

https://doi.org/10.1021/jacs.5c16993
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

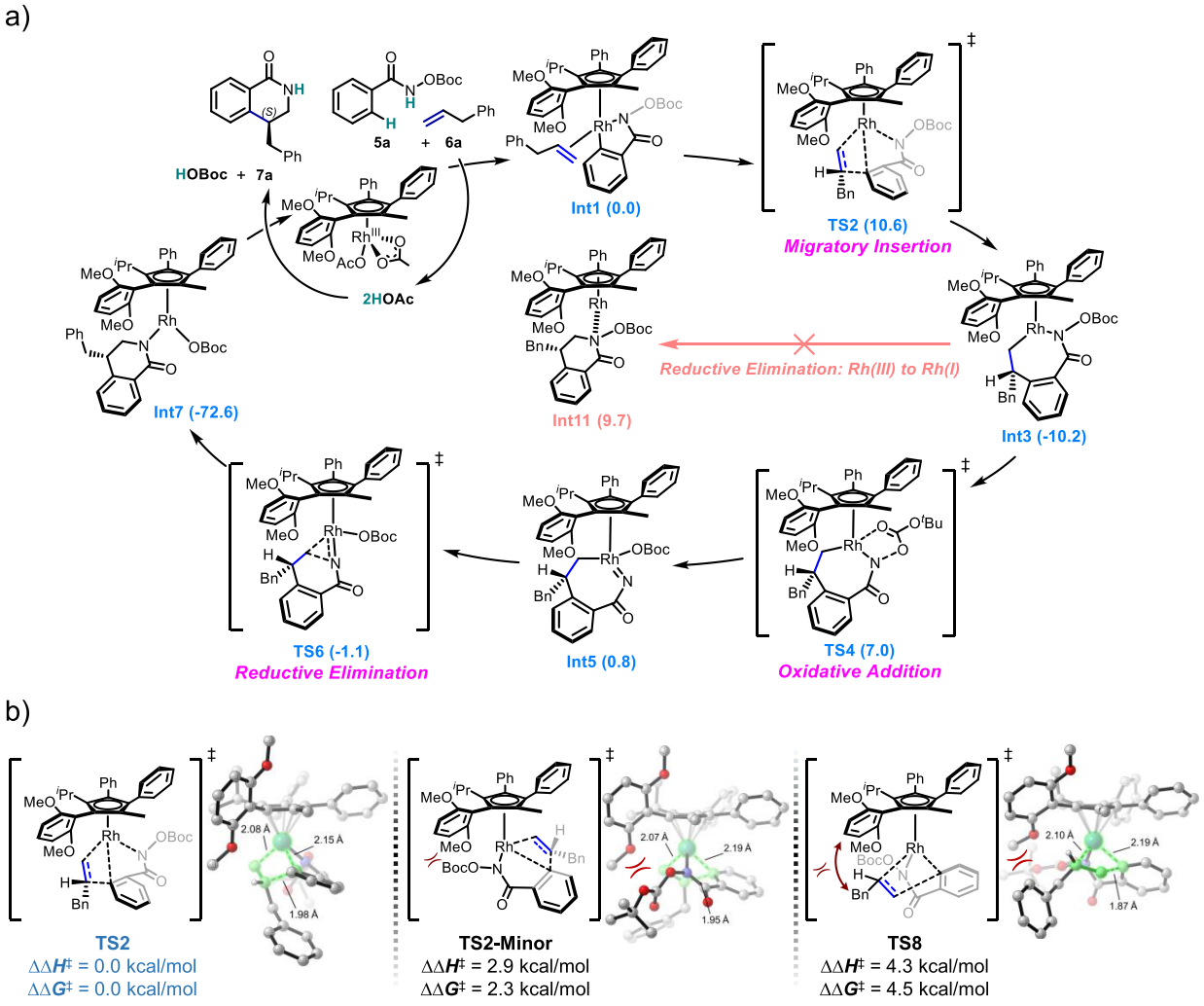


Figure 3. (a) DFT-computed free energy profile for the [4 + 2] annulation of **5a** with **6a** catalyzed by (S_p)-**Rh-6**; (b) Computed enantio- and regioselectivity of the migratory insertion step.

destabilizes this pathway and accounts for the enantioselectivity.

The regioselectivity is also governed by the migratory insertion step (Figure 3b). In **TS2**, the olefin inserts nearly perpendicular to the Cp plane, thereby avoiding steric congestion with the ligand. Reversing the insertion site would direct the benzyl-substituted olefinic carbon toward the sterically demanding 2,6-dimethoxyphenyl group, generating strong steric repulsion. As a result, the regioisomeric transition state **TS8** adopts an almost parallel orientation relative to the Cp ring, but this distortion renders it 4.5 kcal/mol higher in energy than **TS2**, in excellent agreement with the experimentally observed exclusive regioselectivity. Together, these results demonstrate that the unique steric environment of the 1,3,4-triaryl-2,5-dialkyl penta-substituted Cp ligand enforces the preferred insertion trajectory, thereby governing both enantio- and regioselectivity and validating migratory insertion as the key stereocontrolling step in this Rh(III)-catalyzed annulation.

CONCLUSIONS

In conclusion, we proposed a new design paradigm for Cp^{px} ligands and successfully developed a new category of planar-chiral rhodium(III) catalyst featuring a 1,3,4-triaryl-2,5-dialkyl penta-substituted Cp^{px} ligand. Notably, by a modular synthetic strategy that enables rapid diversification, the Cp^{px} ligands can be facilely prepared via three steps. Resolution of the planar-chiral complexes is efficiently achieved by flash column chromatography assisted by a chiral diene ligand. With this new catalyst, the regio- and enantioselectivity were simultaneously controlled for the asymmetric C−H activation of phenylhydroxamic acids with unactivated terminal alkenes. A series of 4-substituted dihydroisoquinolones were yielded in high regio- and enantioselectivity (55 examples, >20/1 rr, up to 99% ee). This method provides a highly straightforward route to prepare various synthetically important 4-substituted dihydroisoquinolones and 4-substituted tetrahydroisoquinolines with high optical purity. Mechanistic studies have been carried out, including H/D exchange, kinetic isotope effect (KIE), and capture of the metallacyclic intermediate. The deuterium labeling experiments identified that the irreversible C−H activation is not rate-limiting. The 1,3,4-triaryl-2,5-dialkyl cyclopentadienyl moiety proves to be the key structural feature for achieving high regioselectivity. The Cp^{px} ligand adopts a well-defined conformation in the metallacycle intermediate formed during C−H activation. DFT calculations revealed that the migratory insertion of olefin was irreversible, constituting the stereo- and regioselectivity-determining event.

https://doi.org/10.1021/jacs.5c16993
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

This new class of planar-chiral $Cp^{px}Rh$ catalysts is expected to offer opportunities to address other asymmetric C−H activation reactions with challenging selectivity issues. Moreover, these modular synthesized Cp^{px} ligands also hold great potential to generate other chiral metal complexes, broadening their utility in asymmetric catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.5c16993.

> The data underlying this study are available in the published article and its Supporting Information. *si Supporting Information The Supporting Information is available free of charge at https://pubs.acs.org/doi/xxxxx Experimental details, characterization data, NMR spectra, crystal data, HPLC traces, CD spectra and DFT calculation data (PDF)

Accession Codes

Deposition Numbers 2410973−2410975 and 2473865 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service. www.ccdc.cam.ac.uk/data_request/cif

■ AUTHOR INFORMATION

Corresponding Authors

Jun Wang − *Key Laboratory of Bioinorganic and Synthetic Chemistry of Ministry of Education, School of Chemistry, and Guangdong Key Laboratory of Chiral Molecule and Drug Discovery, Sun Yat-Sen University, Guangzhou 510006, People's Republic of China;* orcid.org/0000-0002-4035-2786; Email: wangjun23@mail.sysu.edu.cn

Xin Hong − *Center of Chemistry for Frontier Technologies, Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China; School of Chemistry and Chemical Engineering, Henan Normal University, Xinxiang 453007, People's Republic of China*; Email: hxchem@zju.edu.cn

Authors

Chunhui Zhang − *Key Laboratory of Bioinorganic and Synthetic Chemistry of Ministry of Education, School of Chemistry, and Guangdong Key Laboratory of Chiral Molecule and Drug Discovery, Sun Yat-Sen University, Guangzhou 510006, People's Republic of China*

Gan-Lu Qian − *Center of Chemistry for Frontier Technologies, Department of Chemistry, Zhejiang University, Hangzhou 310027, People's Republic of China*

Junlian Ji − *Key Laboratory of Bioinorganic and Synthetic Chemistry of Ministry of Education, School of Chemistry, and Guangdong Key Laboratory of Chiral Molecule and Drug Discovery, Sun Yat-Sen University, Guangzhou 510006, People's Republic of China*

Ji-Jun Jiang − *Key Laboratory of Bioinorganic and Synthetic Chemistry of Ministry of Education, School of Chemistry, and Guangdong Key Laboratory of Chiral Molecule and Drug Discovery, Sun Yat-Sen University, Guangzhou 510006, People's Republic of China;* orcid.org/0000-0001-9483-6033

Complete contact information is available at: https://pubs.acs.org/10.1021/jacs.5c16993

Author Contributions

#C.Z. and G.-L.Q. contributed equally to this work.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the National Key R&D Program of China (2022YFA1504303, J. W.; 2022YFA1504301, X. H.), the National Natural Science Foundation of China (22371310, J. W.; 22122109, 22271253 and W2512004, X. H.) and GBRCE for Functional Molecular Engineering (J. W.) for financial support. New Generation Artificial Intelligence-National Science and Technology Major Project (2025ZD0121905, X. H.), the Starry Night Science Fund of Zhejiang University Shanghai Institute for Advanced Study (SN-ZJU-SIAS-006, X. H.), Fundamental Research Funds for the Central Universities (226-2022-00140, 226-2022-00224, 226-2023-00115 and 226-2024-00003, X. H), the State Key Laboratory of Physical Chemistry of Solid Surfaces (202210, X. H.), the Leading Innovation Team grant from Department of Science and Technology of Zhejiang Province (2022R01005, X. H.), Open Research Fund of School of Chemistry and Chemical Engineering of Henan Normal University (2024Z01, X. H.) are gratefully acknowledged. The AI-driven experiments, simulations and model training were performed on the robotic AI-Scientist platform of Chinese Academy of Sciences. We thank Hao Liang for assisting the manuscript preparation. This work is dedicated to Prof. Carsten Bolm on the occasion of his 65th birthday.

■ REFERENCES

(1) Kulkarni, M. R.; Gaikwad, N. D. Recent Advances in Synthesis of 3,4-Dihydroisoquinolin-1(2H)-one. *ChemistrySelect* **2020**, *5*, 8157.

(2) (a) Trifonova, E. A.; Perekalin, D. S. Rhodium Complexes with Chiral Cyclopentadienyl Ligands for Catalytic Synthesis of Dihydroisoquinolones from Aryl Hydroxamic Acids and Alkenes. *INEOS Open* **2019**, *2*, 124. (b) Liu, J.; Xiao, X.; Lai, Y.; Zhang, Z. Recent Advances in Transition Metal-Catalyzed Heteroannulative Difunctionalization of Alkenes via C−H Activation for the Synthesis of Heterocycles. *Org. Chem. Front.* **2022**, *9*, 2256.

(3) Guimond, N.; Gorelsky, S. I.; Fagnou, K. Rhodium(III)-Catalyzed Heterocycle Synthesis Using an Internal Oxidant: Improved Reactivity and Mechanistic Studies. *J. Am. Chem. Soc.* **2011**, *133*, 6449.

(4) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. Rh(III)-Catalyzed Directed C−H Olefination Using an Oxidizing Directing Group: Mild, Efficient, and Versatile. *J. Am. Chem. Soc.* **2011**, *133*, 2350.

(5) (a) Ye, B.; Cramer, N. Chiral Cyclopentadienyl Ligands as Stereocontrolling Element in Asymmetric C−H Functionalization. *Science* **2012**, *338*, 504. (b) Grigorjeva, L.; Daugulis, O. Cobalt-Catalyzed, Aminoquinoline-Directed Coupling of sp^2 C−H Bonds with Alkenes. *Org. Lett.* **2014**, *16*, 4684. (c) Liu, H.; An, Z.; He, J. Nanosheet-Enhanced Rhodium(III)-Catalysis in C−H Activation. *ACS Catal.* **2014**, *4*, 3543. (d) Wodrich, M. D.; Ye, B.; Gonthier, J. F.; Corminboeuf, C.; Cramer, N. Ligand-Controlled Regiodivergent Pathways of Rhodium(III)-Catalyzed Dihydroisoquinolone Synthesis: Experimental and Computational Studies of Different Cyclopentadienyl Ligands. *Chem. - Eur. J.* **2014**, *20*, 15409. (e) Jia, Z. J.; Merten, C.; Gontla, R.; Daniliuc, C. G.; Antonchick, A. P.; Waldmann, H. General Enantioselective C−H Activation with Efficiently Tunable Cyclopentadienyl Ligands. *Angew. Chem., Int. Ed.* **2017**, *56*, 2429. (f) Yu, X.; Chen, K.; Wang, Q.; Zhang, W.; Zhu, J. Co(III)-Catalyzed

N-Chloroamide-Directed C−H Activation for 3,4-Dihydroisoquinolone Synthesis. *Org. Chem. Front.* **2018**, *5*, 994. (g) Audic, B.; Wodrich, M. D.; Cramer, N. Mild Complexation Protocol for Chiral Cp^{x}Rh and Ir Complexes Suitable for in situ Catalysis. *Chem. Sci.* **2019**, *10*, 781. (h) Barber, J. S.; Scales, S.; Tran-Dubé, M.; Wang, F.; Sach, N. W.; Bernier, L.; Collins, M. R.; Zhu, J.; McAlpine, I. J.; Patman, R. L. Rhodium(III)-Catalyzed C−H Activation: Ligand-Controlled Regioselective Synthesis of 4-Methyl-Substituted Dihydroisoquinolones. *Org. Lett.* **2019**, *21*, 5689. (i) Ozols, K.; Jang, Y.-S.; Cramer, N. Chiral Cyclopentadienyl Cobalt(III) Complexes Enable Highly Enantioselective 3d-Metal-Catalyzed C−H Functionalizations. *J. Am. Chem. Soc.* **2019**, *141*, 5675. (j) Pototskiy, R. A.; Kolos, A. V.; Nelyubina, Y. V.; Perekalin, D. S. Rhodium Catalysts with a Chiral Cyclopentadienyl Ligand Derived from Natural R-Myrtenal. *Eur. J. Org. Chem.* **2020**, *2020*, 6019. (k) Wodrich, M. D.; Ye, B.; Gonthier, J. F.; Corminboeuf, C.; Cramer, N. Corrigendum: Ligand-Controlled Regio-divergent Pathways of Rhodium(III)-Catalyzed Dihydroisoquinolone Synthesis − Experimental and Computational Studies of Different Cyclopentadienyls. *Chem. - Eur. J.* **2020**, *26*, 7727. (l) Kharitonov, V. B.; Podyacheva, E.; Chusov, D.; Nelyubina, Y. V.; Muratov, D. V.; Loginov, D. A. Planar Chiral Rhodium Complex Based on the Tetrahydrofluorenyl Core for Enantioselective Catalysis. *Org. Lett.* **2023**, *25*, 8906. (m) Yao, Q.-J.; Huang, F.-R.; Chen, J.-H.; Zhong, M.-Y.; Shi, B.-F. Enantio- and Regioselective Electrooxidative Cobalt-Catalyzed C−H/N−H Annulation with Alkenes. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202218533. (n) Ye, Y. S.; Laverny, A.; Wodrich, M. D.; Laplaza, R.; Fadaei-Tirani, F.; Scopelliti, R.; Corminboeuf, C.; Cramer, N. Enantiospecific Synthesis of Planar Chiral Rhodium and Iridium Cyclopentadienyl Complexes: Enabling Streamlined and Computer-Guided Access to Highly Selective Catalysts for Asymmetric C−H Functionalizations. *J. Am. Chem. Soc.* **2024**, *146*, 34786.

(6) Sun, M.; Wu, H.; Xia, X.; Chen, W.; Wang, Z.; Yang, J. Asymmetric Palladium-Catalyzed C−H Functionalization Cascade for Synthesis of Chiral 3,4-Dihydroisoquinolones. *J. Org. Chem.* **2019**, *84*, 12835.

(7) (a) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. Biotinylated Rh(III) Complexes in Engineered Streptavidin for Accelerated Asymmetric C−H Activation. *Science* **2012**, *338*, 500. (b) Palmer, N.; Peakman, T. M.; Norton, D.; Rees, D. C. Design and Synthesis of Dihydroisoquinolones for Fragment-Based Drug Discovery (FBDD). *Org. Biomol. Chem.* **2016**, *14*, 1599.

(8) Presset, M.; Oehlrich, D.; Rombouts, F.; Molander, G. A. Complementary Regioselectivity in Rh(III)-Catalyzed Insertions of Potassium Vinyltrifluoroborate via C−H Activation: Preparation and Use of 4-Trifluoroboratotetrahydroisoquinolones. *Org. Lett.* **2013**, *15*, 1528.

(9) Ghosh, A.; Rana, T.; Bhaduri, N.; Pawar, A. B. Reverse Regioselective Cp*Co(III)-Catalyzed [4 + 2] C−H Annulation of N-Chloroamides with Vinylsilanes: Synthesis of 4-Silylated Isoquinolones and Their Synthetic Utilities. *Org. Lett.* **2023**, *25*, 7878.

(10) Yadav, S. K.; Jeganmohan, M. Cobalt(III)-Catalyzed Regioselective [4 + 2]-Annulation of N-Chlorobenzamides with Substituted Alkenes. *J. Org. Chem.* **2022**, *87*, 13073.

(11) Sun, M.; Chen, W.; Xia, X.; Shen, G.; Ma, Y.; Yang, J.; Ding, H.; Wang, Z. Palladium-Catalyzed Tandem Dehydrogenative [4 + 2] Annulation of Terminal Olefins with N-Sulfonyl Amides via C−H Activations. *Org. Lett.* **2020**, *22*, 3229.

(12) Kumar Giri, C.; Dana, S.; Baidya, M. Ruthenium(II)-Catalyzed (4 + 2) Annulative Difunctionalization of Non-conjugated Alkenyl Amides with Hydroxamic Acid Esters. *Chem.−Asian J.* **2022**, *17*, No. e202200861.

(13) Arsenov, M. A.; Stoletova, N. V.; Smol'yakov, A. F.; Savel'yeva, T. F.; Maleev, V. I.; Loginov, D. A.; Larionov, V. A. A Synthetic Route to Artificial Chiral α-Amino Acids Featuring a 3,4-Dihydroisoquinolone Core through a Rh(III)-Catalyzed Functionalization of Allyl Groups in Chiral Ni(II) Complexes. *Org. Biomol. Chem.* **2023**, *21*, 9143.

(14) (a) Zhang, C.; Jiang, J.; Huang, X.; Wang, J. Planar-Chiral Cyclopentadienyl Rhodium Catalysts: Design Concept, Chiral Resolution Strategy, and Applications. *ACS Catal.* **2023**, *13*, 10468. (b) Guo, W.; Jiang, J.; Wang, J. [2.2]Benzoindenophane-Based Chiral Indenyl Ligands: Design, Synthesis, and Applications in Asymmetric C−H Activation. *Angew. Chem., Int. Ed.* **2024**, *63*, No. e202400279.

(15) (a) Davis, T. A.; Hyster, T. K.; Rovis, T. Rhodium(III)-Catalyzed Intramolecular Hydroarylation, Amidoarylation, and Heck-type Reaction: Three Distinct Pathways Determined by an Amide Directing Group. *Angew. Chem., Int. Ed.* **2013**, *52*, 14181. (b) Shi, Z.; Boultadakis-Arapinis, M.; Koester, D. C.; Glorius, F. Rh(III)-Catalyzed Intramolecular Redox-Neutral Cyclization of Alkenes via C−H Activation. *Chem. Commun.* **2014**, *50*, 2650. (c) Ye, B.; Donets, P. A.; Cramer, N. Chiral Cp-Rhodium(III)-Catalyzed Asymmetric Hydroarylations of 1,1-Disubstituted Alkenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 507. (d) Liang, H.; Vasamsetty, L.; Li, T.; Jiang, J.; Pang, X.; Wang, J. A New Class of C_2-Symmetric Chiral Cyclopentadienyl Ligand Derived from Ferrocene Scaffold: Design, Synthesis and Application. *Chem. - Eur. J.* **2020**, *26*, 14546.

(16) (a) Hyster, T. K.; Dalton, D. M.; Rovis, T. Ligand Design for Rh(III)-Catalyzed C−H Activation: An Unsymmetrical Cyclopentadienyl Group Enables a Regioselective Synthesis of Dihydroisoquinolones. *Chem. Sci.* **2015**, *6*, 254. (b) Hyster, T. K.; Dalton, D. M.; Rovis, T. Correction: Ligand Design for Rh(III)-Catalyzed C−H Activation: An Unsymmetrical Cyclopentadienyl Group Enables a Regioselective Synthesis of Dihydroisoquinolones. *Chem. Sci.* **2017**, *8*, 1666. (c) Piou, T.; Romanov-Michailidis, F.; Romanova-Michaelides, M.; Jackson, K. E.; Semakul, N.; Taggart, T. D.; Newell, B. S.; Rithner, C. D.; Paton, R. S.; Rovis, T. Correlating Reactivity and Selectivity to Cyclopentadienyl Ligand Properties in Rh(III)-Catalyzed C−H Activation Reactions: An Experimental and Computational Study. *J. Am. Chem. Soc.* **2017**, *139*, 1296. (d) Hyster, T. K.; Dalton, D. M.; Rovis, T. Correction: Ligand Design for Rh(III)-Catalyzed C−H Activation: An Unsymmetrical Cyclopentadienyl Group Enables a Regioselective Synthesis of Dihydroisoquinolones. *Chem. Sci.* **2018**, *9*, 8024. (e) Trifonova, E. A.; Ankudinov, N. M.; Kozlov, M. V.; Sharipov, M. Y.; Nelyubina, Y. V.; Perekalin, D. S. Rhodium(III) Complex with a Bulky Cyclopentadienyl Ligand as a Catalyst for Regioselective Synthesis of Dihydroisoquinolones through C−H Activation of Arylhydroxamic Acids. *Chem. - Eur. J.* **2018**, *24*, 16570. (f) Trifonova, E. A.; Ankudinov, N. M.; Mikhaylov, A. A.; Chusov, D. A.; Nelyubina, Y. V.; Perekalin, D. S. A Planar-Chiral Rhodium(III) Catalyst with a Sterically Demanding Cyclopentadienyl Ligand and Its Application in the Enantioselective Synthesis of Dihydroisoquinolones. *Angew. Chem., Int. Ed.* **2018**, *57*, 7714. (g) Lee, S.; Semakul, N.; Rovis, T. Direct Regio- and Diastereoselective Synthesis of δ-Lactams from Acrylamides and Unactivated Alkenes Initiated by Rh^{III}-Catalyzed C−H Activation. *Angew. Chem., Int. Ed.* **2020**, *59*, 4965. (h) Trifonova, E. A.; Ankudinov, N. M.; Kozlov, M. V.; Sharipov, M. Y.; Nelyubina, Y. V.; Perekalin, D. S. Corrigendum: Rhodium(III) Complex with a Bulky Cyclopentadienyl Ligand as a Catalyst for Regioselective Synthesis of Dihydroisoquinolones through C−H Activation of Arylhydroxamic Acids. *Chem. - Eur. J.* **2021**, *27*, 3184. (i) Kolos, A. V.; Nelyubina, Y. V.; Podyacheva, E. S.; Perekalin, D. S. Rhodium Complexes with Planar-Chiral Cyclopentadienyl Ligands: Synthesis from tert -Butylacetylene and Catalytic Performance in C−H Activation of Arylhydroxamates. *Dalton Trans.* **2023**, *52*, 17005−17010. (j) Kolos, A. V.; Nelyubina, Y. V.; Godovikova, M. I.; Perekalin, D. S. Synthesis of Cyclopentadienyl Rhodium Catalysts by Co-Cyclization of Two Different Alkynes. *Chem. - Eur. J.* **2025**, *31*, No. e202501793.

(17) Kharitonov, V. B.; Antonova, A. S.; Muratov, D. V.; Navasardyan, M. A.; Loginov, D. A. Rhodium Catalysts Based on Polyphenyl-Substituted Cp Ligands for Regioselective Annulation of Aryl Hydroxamates with Terminal Alkenes. *Organometallics* **2025**, *44*, 2301.

(18) Kolos, A. V.; Nelyubina, Y. V.; Sundararaju, B.; Perekalin, D. S. Synthesis of Overloaded Cyclopentadienyl Rhodium(III) Complexes

https://doi.org/10.1021/jacs.5c16993
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

via Cyclotetramerization of tert-Butylacetylene. *Organometallics* **2021**, *40*, 3712.

(19) (a) Ye, B.; Cramer, N. A Tunable Class of Chiral Cp Ligands for Enantioselective Rhodium(III)-Catalyzed C−H Allylations of Benzamides. *J. Am. Chem. Soc.* **2013**, *135*, 636. (b) Zheng, J.; Cui, W. J.; Zheng, C.; You, S.-L. Synthesis and Application of Chiral Spiro Cp Ligands in Rhodium-Catalyzed Asymmetric Oxidative Coupling of Biaryl Compounds with Alkenes. *J. Am. Chem. Soc.* **2016**, *138*, 5242. (c) Sun, Y.; Cramer, N. Tailored Trisubstituted Chiral Cp^xRh^{III} Catalysts for Kinetic Resolutions of Phosphinic Amides. *Chem. Sci.* **2018**, *9*, 2981. (d) Wang, S. G.; Park, S. H.; Cramer, N. A Readily Accessible Class of Chiral Cp Ligands and their Application in Ru^{II}-Catalyzed Enantioselective Syntheses of Dihydrobenzoindoles. *Angew. Chem., Int. Ed.* **2018**, *57*, 5459. (e) Duchemin, C.; Smits, G.; Cramer, N. Rh^{I}, Ir^{III},and Co^{III} Complexes with Atropchiral Biaryl Cyclopentadienyl Ligands: Syntheses, Structures, and Catalytic Activities. *Organometallics* **2019**, *38*, 3939. (f) Cui, W.-J.; Wu, Z.-J.; Gu, Q.; You, S.-L. Divergent Synthesis of Tunable Cyclopentadienyl Ligands and Their Application in Rh-Catalyzed Enantioselective Synthesis of Isoindolinone. *J. Am. Chem. Soc.* **2020**, *142*, 7379. (g) Li, G.; Yan, X.; Jiang, J.; Liang, H.; Zhou, C.; Wang, J. Chiral Bicyclo[2.2.2]octane-Fused CpRh Complexes: Synthesis and Potential Use in Asymmetric C−H Activation. *Angew. Chem., Int. Ed.* **2020**, *59*, 22436. (h) Wang, S.-G.; Cramer, N. Asymmetric Cp^xRh(III)-Catalyzed Acrylic Acid C−H Functionalization with Allenes Provides Chiral γ-Lactones. *ACS Catal.* **2020**, *10*, 8231. (i) Pan, C.; Yin, S. Y.; Wang, S. B.; Gu, Q.; You, S. L. Oxygen-Linked Cyclopentadienyl Rhodium(III) Complexes-Catalyzed Asymmetric C−H Arylation of Benzo[h]quinolines with 1-Diazonaphthoquinones. *Angew. Chem., Int. Ed.* **2021**, *60*, 15510. (j) Guo, W.; Pang, X.; Jiang, J.; Wang, J. Chiral 3,3,3′,3′-Tetramethyl-1,1'-Spirobiindanyl Cyclopentadienyl (TMSCp) Ligands: Design, Synthesis, and Applications. *Org. Lett.* **2023**, *25*, 3823. (k) Yang, H.; Zhang, R.; Zhang, S.-Z.; Gu, Q.; You, S.-L. Synthesis of Hexamethyl-1,1′-spirobiindane-Based Chiral Spiro Cp Ligands and Their Application in Rhodium-Catalyzed Enantioselective Aryl C−H Addition to Nitroalkenes. *ACS Catal.* **2023**, *13*, 8838. (l) Edlová, T.; Rybáček, J.; Cattey, H.; Vacek, J.; Bednárová, L.; Gendre, P. L.; Normand, A. T.; Stará, I. G.; Starý, I. Stereocontrolled Synthesis of Chiral Helicene-Indenido ansa- and Half-Sandwich Metal Complexes and Their Use in Catalysis. *Angew. Chem., Int. Ed.* **2025**, *64*, No. e202414698.

(20) (a) Newton, C. G.; Wang, S.-G.; Oliveira, C. C.; Cramer, N. Catalytic Enantioselective Transformations Involving C−H Bond Cleavage by Transition-Metal Complexes. *Chem. Rev.* **2017**, *117*, 8908. (b) Shaaban, S.; Davies, C.; Waldmann, H. Applications of Chiral Cyclopentadienyl (Cp^x) Metal Complexes in Asymmetric Catalysis. *Eur. J. Org. Chem.* **2020**, *2020*, 6512. (c) Mas-Roselló, J.; Herraiz, A. G.; Audic, B.; Laverny, A.; Cramer, N. Chiral Cyclopentadienyl Ligands: Design, Syntheses, and Applications in Asymmetric Catalysis. *Angew. Chem., Int. Ed.* **2021**, *60*, 13198. (d) Wang, Q.; Liu, C.-X.; Gu, Q.; You, S.-L. Chiral Cp^xRh Complexes for C−H Functionalization Reactions. *Sci. Bull.* **2021**, *66*, 210. (e) Liu, C.-X.; Yin, S.-Y.; Zhao, F.; Yang, H.; Feng, Z.; Gu, Q.; You, S.-L. Rhodium-Catalyzed Asymmetric C−H Functionalization Reactions. *Chem. Rev.* **2023**, *123*, 10079. (f) Yan, X.; Wang, J. Advances in Exploring Cyclopentadienyl (Cp) Rhodium Catalysts Featuring Diastereotopic or Enantiotopic Cp Faces for Asymmetric C−H Activation. *Synthesis* **2023**, *55*, 1309.

(21) (a) Laws-III, D.; Poff, C. D.; Heyboer, E. M.; Blakey, S. B. Synthesis, Stereochemical Assignment, and Enantioselective Catalytic Activity of Late Transition Metal Planar Chiral Complexes. *Chem. Soc. Rev.* **2023**, *52*, 6003. (b) Zou, Y.; Guo, W.; Wang, J. Application of Planar Chiral Cyclopentadienyl Rhodium Catalysts without Chiral Substituents in Asymmetric C−H Activation. *Chin. J. Org. Chem.* **2025**, *45*, 466.

(22) (a) Yan, X.; Jiang, J.; Wang, J. A Class of Readily Tunable Planar-Chiral Cyclopentadienyl Rhodium(III) Catalysts for Asymmetric C−H Activation. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e202201522. (b) Farr, C. M. B.; Kazerouni, A. M.; Park, B.; Poff, C. D.; Won, J.; Sharp, K. R.; Baik, M.-H.; Blakey, S. B. Designing a Planar Chiral Rhodium Indenyl Catalyst for Regio- and Enantioselective Allylic C−H Amidation. *J. Am. Chem. Soc.* **2020**, *142*, 13996.

(23) (a) Allen, C. F. H.; VanAllan, J. A. Dimerization of Cyclopentadienones. *J. Am. Chem. Soc.* **1950**, *72*, 5165. (b) Dou, X.; Hayashi, T. Synthesis of Planar Chiral Shvo Catalysts for Asymmetric Transfer Hydrogenation. *Adv. Synth. Catal.* **2016**, *358*, 1054.

(24) (a) Fuchs, B.; Pasternak, M.; Pazhenchevsky, B. Photochemical Studies: Irradiation Induced Transformations of Reversibly Dissociating Cyclopentadienone-Dimers and Their Monomers. *Tetrahedron* **1980**, *36*, 3443. (b) Weiss, H. M. Steric Effects in the Dimerization of 2,5-Dialkyl-3,4-diphenylcyclopentadienones. *J. Chem. Soc., Perkin Trans. 2*, **1991**, 439. (c) Moore, J. E.; York, M.; Harrity, J. P. A. A Metal-Free Cycloaddition Approach to Highly Substituted Aromatic Boronic Esters. *Synlett* **2005**, *2005*, 860.

(25) Smith III, A. B.; Cantin, L.-D.; Pasternak, A.; Guise-Zawacki, L.; Yao, W.; Charnley, A. K.; Barbosa, J.; Sprengeler, P. A.; Hirschmann, R.; Munshi, S.; Olsen, D. B.; Schleif, W. A.; Kuo, L. C. Design, Synthesis, and Biological Evaluation of Monopyrrolinone-Based HIV-1 Protease Inhibitors. *J. Med. Chem.* **2003**, *46*, 1831.

(26) Yamashita, M.; Yamada, K.-I.; Tomioka, K. Construction of Arene-Fused-Piperidine Motifs by Asymmetric Addition of 2-Trityloxymethylaryllithiums to Nitroalkenes: The Asymmetric Synthesis of a Dopamine D1 Full Agonist, A-86929. *J. Am. Chem. Soc.* **2004**, *126*, 1954.

(27) (a) Pedrosa, R.; Andrés, C.; Iglesias, J. M.; Obeso, M. A. Synthesis of Enantiopure Mono- and Disubstituted Tetrahydroisoquinolines by 6-exo Radical Cyclizations. *Tetrahedron* **2001**, *57*, 4005. (b) Pedrosa, R.; Andrés, C.; Iglesias, J. M.; Pérez-Encabo, A. Diastereoselective Tandem 6-exo Carbolithiation Intramolecular Ring Opening in (−)-8-Aminomenthol-Derived Perhydrobenzoxazines. A New Synthesis of Enantiopure 4-Substituted Tetrahydroisoquinolines and 2-Azabenzonorbornanes. *J. Am. Chem. Soc.* **2001**, *123*, 1817.

(28) (a) Falivene, L.; Credendino, R.; Poater, A.; Petta, A.; Serra, L.; Oliva, R.; Scarano, V.; Cavallo, L. SambVca 2. A Web Tool for Analyzing Catalytic Pockets with Topographic Steric Maps. *Organometallics* **2016**, *35*, 2286. (b) Falivene, L.; Cao, Z.; Petta, A.; Serra, L.; Poater, A.; Oliva, R.; Scarano, V.; Cavallo, L. Towards the Online Computer-Aided Design of Catalytic Pockets. *Nat. Chem.* **2019**, *11*, 872.

(29) Li, Y.; Chen, H.; Qu, L.-B.; Houk, K. N.; Lan, Y. Origin of Regiochemical Control in Rh(III)/Rh(V)-Catalyzed Reactions of Unsaturated Oximes and Alkenes to Form Pyrdines. *ACS Catal.* **2019**, *9*, 7154.

https://doi.org/10.1021/jacs.5c16993
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX