# Chiral Cyclopentadienyls: Enabling Ligands for Asymmetric Rh(III)-Catalyzed C−H Functionalizations

Baihua Ye and Nicolai Cramer*

Laboratory of Asymmetric Catalysis and Synthesis, Institute of Chemical Sciences and Engineering, Ecole Polytechnique Fédérale de Lausanne (EPFL), SB-ISIC, BCH4305, 1015 Lausanne, Switzerland

CONSPECTUS: Transition-metal catalyzed C−H functionalizations became a complementary and efficient bond-forming strategy over the past decade. In this respect, Cp*Rh(III) complexes have emerged as powerful catalysts for a broad spectrum of reactions giving access to synthetically versatile building blocks. Despite their high potential, the corresponding catalytic enantioselective transformations largely lag behind. The targeted transformations require all the remaining three coordination sites of the central rhodium atom of the catalyst. In consequence, the chiral information on a competent catalyst can only by stored in the cyclopentadienyl unit. The lack of suitable enabling chiral cyclopentadienyl (Cp^x) ligands is the key hurdle preventing the development of such asymmetric versions. In this respect, an efficient set of chiral Cp^x ligands useable with a broad variety of different transition-metals can unlock substantial application potential. This Account provides a description of our developments of two complementary classes of C_2-symmetric Cp^x derivatives. We have introduced a side- and back-wall concept to enforce chirality transfer onto the central metal atom. The first generation consists of a fused cyclohexane unit having pseudo axial methyl groups as chiral selectors and a rigidifying acetal moiety. The second ligand generation derives from an atrop-chiral biaryl-backbone and which possesses adjustable substituents at its 3,3′-positions. Both ligand families can be modulated in their respective steric bulk to adjust for the specific needs of the targeted application. The cyclopentadienes can be metalated under standard conditions. The corresponding chiral rhodium(I) ethylene complexes are relatively air and moisture and represent storable stable precatalysts for the targeted asymmetric Rh(III)-catalyzed C−H functionalizations. These complexes are then conveniently oxidized in situ by dibenzoyl peroxide to give the reactive Cp^xRh(III)(OBz)$_2$ species. For instance, this catalyst is used for directed C−H activations of aryl hydroxamates and the subsequent enantioselective trapping with olefins, providing dihydroisoquinolones in very high enantioselectivities. In addition, we have established highly selective intramolecular trapping reactions with tethered higher substituted alkenes giving dihydrobenzofurans with quaternary stereogenic centers. Concerning intermolecular reactions, allene coupling partners allow for an enantioselective hydroarylation yielding substituted allylated compounds. A trapping process of the cyclometalated intermediate with diazo reactants enables the enantioselective construction of isoindolinones. Moreover, the catalysts can be used for the construction of atrophchiral biaryl motives using a dehydrogenative Heck-type reaction. The development of flexibly adjustable chiral Cp^x ligands is described in this Account showcasing their applicability for a variety of Rh(III) catalyzed C−H functionalization reactions. These Cp^x derivatives hold promise as powerful steering ligands for further transition-metals used in asymmetric catalysis.
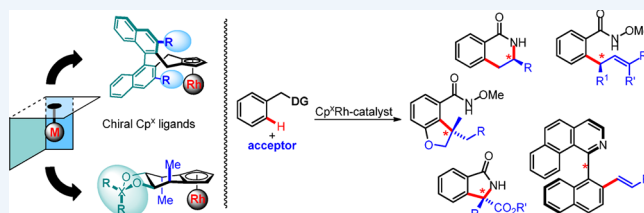
1. INTRODUCTION

Since the discovery of ferrocene in 1951,[1] cyclopentadienyl (Cp) or pentamethylcyclopentadienyl (Cp*) became a dominant class of anionic ancillary ligands for a wide range with different transition metals.[2] The robust nature of the metal complexes prompted strong interest for their use in catalysis. For applications in asymmetric catalysis, the underlying Cp metal complexes can be categorized in several different classes. On one hand, metallocenes have emerged as rigid and versatile backbone for chiral bidentate phosphine ligands such as Josiphos (**1**)[3] and chiral ansa-metallocenes (**2**)[4] which are powerful catalysts for several asymmetric reactions (Figure 1).[5] On the other hand, half-sandwich metal complexes having one single Cp ligand derivative as stabilizing structure in addition to additional chiral ligands on the metal atom (**3**) are used for a broad range of enantioselective transformations. For example, these can include chiral diamines,[6] diols,[7] and phosphines.[8] Moreover,
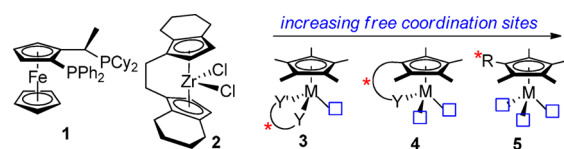

Figure 1. Different chirality origins in Cp−metal complexes and available coordination sites for catalysis.

other complexes (**4**) comprise the combination of a Cp unit tethered to phosphines[9] or sulfoxides.[10]

All these designs categorically exclude transformations falling in the category "high coordination-sites demand" reactions. A myriad of synthetically attractive transformations catalyzed by

half-sandwich complexes of transition-metals, for example, Co(I),[11] Rh(I),[12] Rh(III),[13] Ir(III),[14] and Ru(II),[15] have been shown to require besides the Cp all remaining coordination sites (**5**) for catalytic activity. These coordination sites (often three) are required to bind substrates, reactants and to turn over the catalyst. Thus, for competent catalysts for these reaction classes, it is mandatory that the chirality generating substituents of Cp ligand are noncoordinating and do not reduce the number of available coordination sites. Pioneering investigations were performed by Vollhardt and co-workers,[16] Halterman and co-workers,[17] and others.[18] For instance, Vollhardt and Halterman reported a chiral C_2-symmetric Cp derivative[16c] in 1986 and used the corresponding Co(I) complex for a cyclotrimerizations with up to 45% ee.[19] Another example for a C_2-symmetric Cp ligand was reported by Halterman and Colletti in 1989.[17c] It consists of an atrop-chiral biaryl motif, and the corresponding half-sandwich and metallocene complexes[17a] were prepared, but with little to no use in catalysis. Notably, two reports from Erker et al. (Zr(IV)-catalyzed aldol reaction)[18b] as well as Gutnov et al. (Co(I)-catalyzed cyclotrimerization, indenyl ligand)[19] demonstrated the principal feasibility of high enantioselectivities with such chiral Cp ligands. However, the asymmetric inductions of the chiral Cp complexes of early transition metals were inferior to other popular and simpler ligand systems in benchmark transformations.[20] These struggles somewhat reduced for decades the interest in this approach. However, the rapid rise of late transition-metal catalyzed transformations and in particular the tremendous developments of C−H functionalizations with the Cp*Rh(III) fragment[13] renewed the demand for chiral Cp* surrogates. The lack of suitable solutions is pointing to a significant gap in the currently available chiral ligand weaponry. These shortcomings prompted us to develop modular chiral Cp ligand classes with the potential to be applied for several different transition metals.

2. DESIGN AND SYNTHESIS OF THE CHIRAL CYCLOPENTADIENYL LIGANDS

2.1. General Design Principles and Requirements

The shield and bulk design of the chiral Cp^x complexes is based on two main assumptions. First, the coordination of the third ligand **L3** to fluxional tricoordinated intermediate **6** would lead to the formation of pseudotetrahedral $[(\eta^5\text{-}C_5H_5)ML^SL^LL3]$ complexes **7** and *ent*-**7** having a stereogenic central metal atom (Figure 2). Second, we assumed that the configuration at the
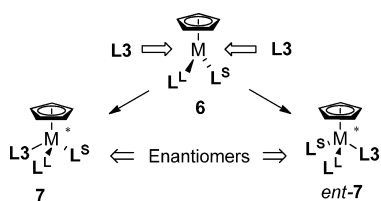
Figure 2. Generation of a stereogenic metal center by coordination of **L3**.

metal atom of this intermediate would translate with very high fidelity onto the formation of a single product enantiomer. The opposite configuration at the metal would form the opposite enantiomer of the product.

With these assumptions, a successful chiral catalyst would possess an element of chirality (planar or in the periphery), able to efficiently control the selective formation of a single diastereomer. Two cooperating design elements were required

for this task and 1,2-disubstituted cyclopentadienyl ligands were chosen as the most promising candidates. By these means, the Cp can be divided in half: a bulky side carrying the substitutions and an unsubstituted side (Figure 3). Both ligands of the metal
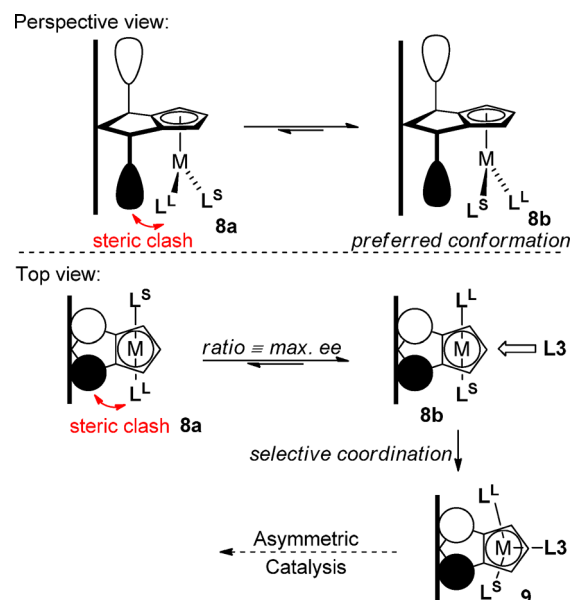
Figure 3. Schematic concept for the chiral Cp^x metal complexes.

atom L^L and L^S should orient in a more or less parallel fashion to the back shield avoiding steric congestion. In this orientation, one approach trajectory for **L3** is blocked, leaving as only possibility the coordination via the unsubstituted site of the Cp. As a controlling unit for the relative orientation of L^L and L^S with respect to the 1,2-substitution of the Cp, an additional element of bulk, the sidewall, resides at the carbon adjacent to the Cp ring. This group favors an orientation of the larger residue (L^L in this case) away from the more demanding group. The better this control works—or the bigger differences between L^S and L^L are—the more favorable the population ratio between **8a** and **8b** will be, enabling an efficient enantioselective transformation. With the general requirements for stereoselectivity discussed, four specific criteria for the design of chiral Cp ligands can be summarized:

(a) A bulky substituent one side of the Cp perpendicular to the Cp plane shields the metal so that only one trajectory of an incoming reagent (**L3**) is possible.

(b) The substituent on the sidewall creates a repulsion which would push the large component L^L preferentially to the less hindered position.

(c) The parent cyclopentadienyl anion should be C_2-symmetric. This avoids dealing with a diastereoselective complexation reactions with the transition-metal precursor since both faces of the Cp anion are equivalent. Otherwise, separation of often sensitive diastereomeric product mixtures could be tedious.

(d) The scaffold should be easily sterically and electronically modifiable, preferably at a late stage of the synthesis, enabling an adaptation to the reactivity and selectivity requirements of the envisioned reaction.

2.2. Synthesis of Two Chiral Cp Ligand Families and Their Rhodium(I) Complexes

We opted for two different chiral carbon scaffolds to access two independent and complementary ligand classes which are either
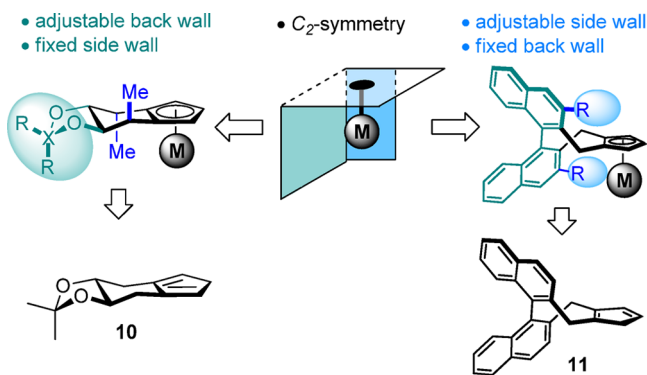
Figure 4. Parent carbon scaffolds used for C_2-symmetric chiral Cp^x ligands.

more amenable toward a modification of the back shield (1st generation)[21] or at the sidewalls (2nd generation)[22] (Figure 4). The first generation builds on the skeleton **10** reported by Vollhardt and Halterman in 1986.[16c] An additional methyl substituent should enable a better chiral microenvironment around the metal atom. The acetal moiety enables a modular adjustment of the size and nature of the back wall. The second generation of ligands uses the atropchiral scaffold **11** disclosed by Halterman and Colletti in 1989.[17c] While the naphthyl portion represents a fixed back wall, the variability of the ligand properties is achieved by the introductions of *ortho*-substituents, enabling a broad range of modulations of the side wall by sterics as well as auxiliary substrate coordinating groups.

The first ligand generation derives from the chiral pool using D-mannitol as starting material to access cyclic sulfate **12** (Scheme 1). Alkylation of sodium cyclopentadienide with **12**

Scheme 1. Synthesis of the First Generation of Chiral Cp^x Ligands and Their Rh(I) Complexes
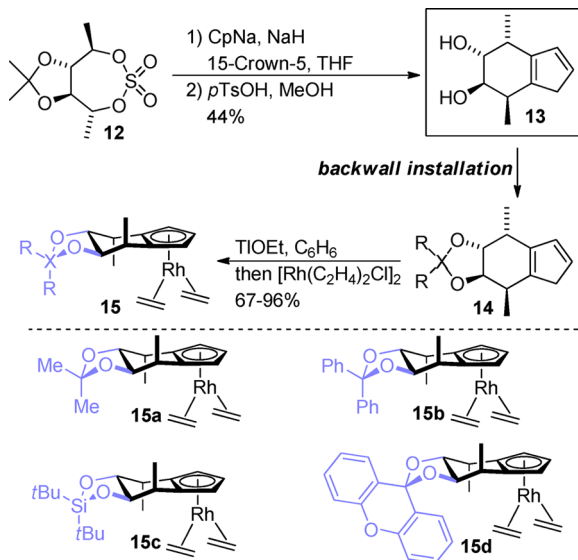

and subsequent ketal cleavage provided diol **13** as platform intermediate. The individual ligand members **14** were accessed by introduction of sterically different ketals and cyclic silylethers. The corresponding cyclopentadienyl anions were obtained by deprotonation with thallium ethoxide. Subsequent complexation with rhodium(I) ethylene chloride as metal source gave chiral Cp^{x}Rh(I) complexes **15a−15d** in high yields (other Cp

anions gave inferior results in the complexation step). These complexes proved to be fairly air stable, easy to handle and conveniently soluble in most organic solvents. Moreover, application in catalysis using either Rh(I) or with a suitable oxidant, Rh(III), can be envisioned.
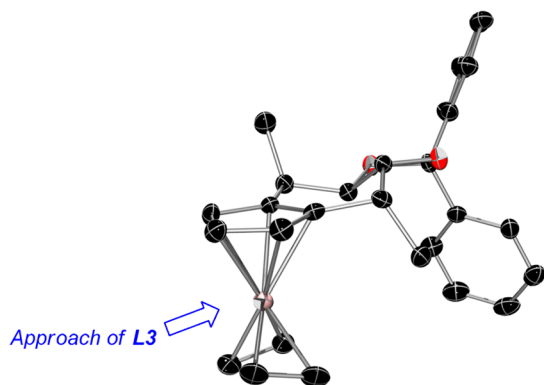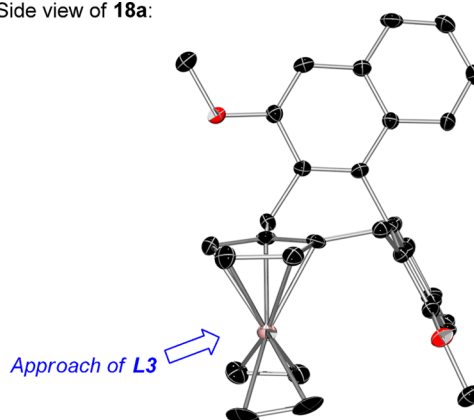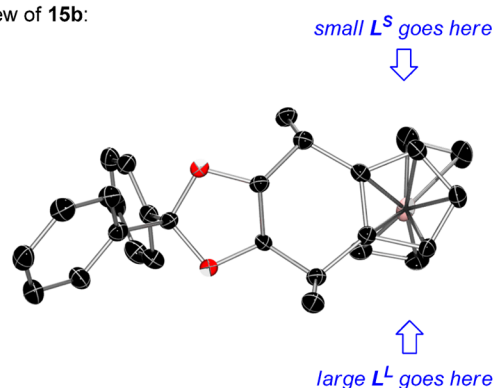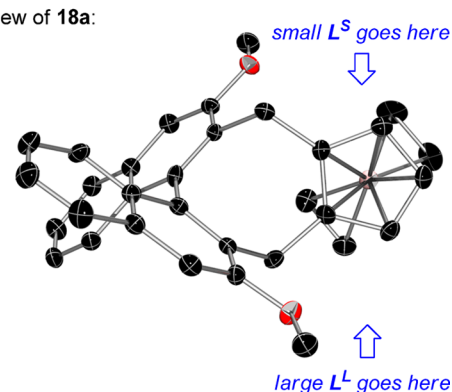
Complementary to this ligand family, the second generation of chiral Cp derivatives draws its chirality from an atrop-chiral biaryl backbone, originating from Binol. Binol is elaborated in a straightforward manner to the double electrophile **16** following Maruoka's protocol.[23] The alkylation of sodium cyclopentadienide with **16** afforded a mixture of the 1,2-disubstituted cyclopentadiene and spirocyclic diene (Scheme 2). Independently, both can be

Scheme 2. Synthesis of the Second Generation of Chiral Cp^x Ligands and Their Rh(I) Complexes
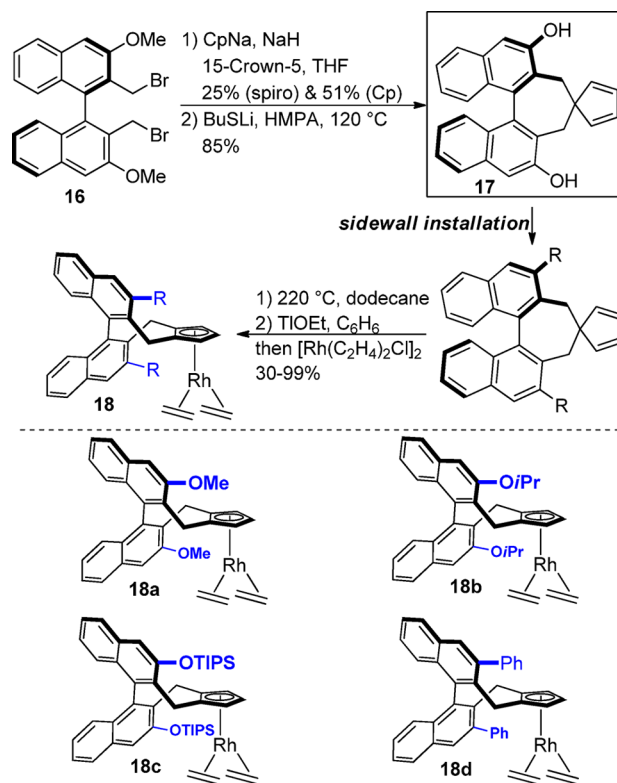
conveniently demethylated and represent the platform intermediates to access the different members of the second generation family. The robust spirocycle **17** tolerates a broader range of transformations; however, it must be thermally rearranged into the Cp^x ligand precursor. Ligands having a variety of ethers, silyl ethers, as well as alkyl and aryl substituents were prepared so far. Similar to the first generation complexes, deprotonation and salt metathesis delivered the corresponding Cp^{x}Rh(I) ethylene complexes **18** in good yields. As before, these are reasonably stable and can be purified by column chromatography or crystallization.

X-ray crystal structures of members from the first and second generation Cp ligands provide a good visualization of the anticipated orientations around the central metal atom (Figure 5).[21,22] Both complexes share a similar selection mechanism. In the side view, one can see that the approach of the third ligand/ reactant **L3** will proceed from the left for both ligand families and the alternative approach from the right side is blocked by the cyclic chiral selector group. The top view of the complexes allows visualization of the relative orientations of the presumed

Side view of **15b**:

Side view of **18a**:

Approach of L3

Approach of L3

Top view of **15b**:

small L^S goes here

Top view of **18a**:

small L^S goes here

large L^L goes here

large L^L goes here

Figure 5. X-ray crystal structures of the chiral Cp^xRh(I) complexes **15b** and **18a**.

three coordinated intermediate. The roughly parallel orientations of ethylene groups with respect to the steric bulk of the cyclic selector substituent in both complexes shows the favorite alignment for two ligands L^L and L^S. If they have different steric properties, the large ligand L^L occupies preferentially the position away from the bulky group and the small ligand L^S resides close to it.

## 3. APPLICATIONS OF THE CHIRAL Cp^x METAL COMPLEXES IN CATALYSIS

3.1. Asymmetric Cp^xRh(III)-Catalyzed Dihydroisoquinolone Synthesis

Transition-metal-catalyzed C−H functionalizations gained high importance over the past decade, including enantioselective transformations.[24] For instance, major advances have been made in the area of *ortho*-directed C_{sp2}−H functionalizations with Cp*Rh(III) catalysts.[13] Fagnou et al.[25] and Glorius et al.[26] in 2011 independently reported a Cp*Rh(III)-catalyzed reaction of aryl hydroxamates **19** and olefins **20** leading to dihydroisoquinolones **21** (eq 1).
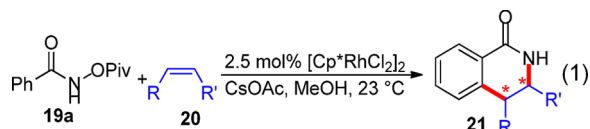
The obtained heterocycle **21** bears stereogenic centers and is a potentially useful scaffold of interest. An asymmetric version of this transformation could only be enabled by a suitable chiral Cp^x ligand. We have therefore selected this reaction as proof of

**Scheme 3. Catalytic Cycle of the Rh(III)-Catalyzed Dihydroisoquinolone Synthesis**
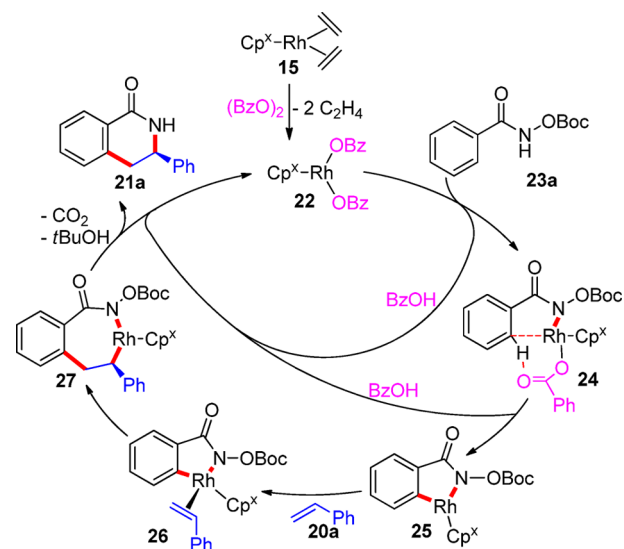
concept for our designed ligands. Mechanistically,[27] it is assumed that the reaction involves a Rh(III) catalyst bearing two carboxylate ligands (Scheme 3). The reaction proceeds after an induction period directly with the Rh(I) complexes **15** due to a presumed oxidation to Rh(III) by the substrate. However, in situ oxidation of **15** with dibenzoylperoxide rapidly generates the competent catalyst, resulting in a faster and cleaner reaction. Moreover, this method allows for an exact amount of carboxylate during the concerted-metalated-deprotonation

(CMD) step.[28] Coordination of catalyst **22** to the directing hydroxamate group would give **24**. The CMD step involving the carboxylate would remove the aromatic hydrogen atom and lead to the formation rhodacyclic intermediate **25**. This 16-electron fluxional key intermediate is now adopting a minimized conformation with respect to the chiral Cp^x ligand. Subsequent diastereoselective coordination of the olefin would form chiral-at-metal species **26**. This association is considered as the enantiodetermining step of the process. Subsequent migratory insertion delivers seven-membered rhodacycle **27**. In turn, reductive C–N bond formation closes the ring and reoxidation of the catalyst to Rh(III) by cleavage of the N–O bond of the internal oxidant occurs. The nature of leaving group of this built-in oxidant is important for the selectivity of the reaction and as well to some extent for the reactivity. The Boc-protected hydroxamate proved to be superior to other acyl derivatives in terms of the enantioselectivity. Moreover, the decomposition of the released *tert*-butyl carbonic acid into *tert*-butanol and carbon dioxide avoids increasing acidity of the reaction media and reduced reaction rates observed in the case of pivaloyl substituted substrates.

The impact of the different design parameters of the chiral CpRh(I) complexes **15** on enantioselectivity in the reaction of hydroxamate **23a** and styrene is depicted Scheme 4. Complex

Scheme 4. Selectivities of Different First Generation Cp^x Rhodium Complexes in the Enantioselective Dihydroisoquinolone Synthesis
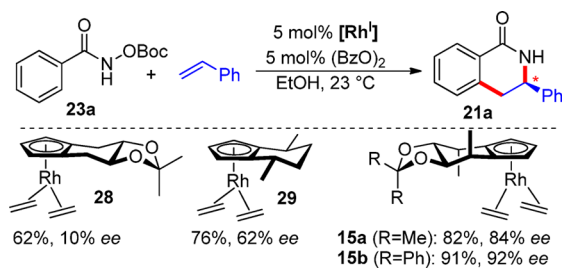
28 having as sole source of chirality the remote dimetyl ketal provided only a poor enantioselectivity of 10% ee. Bringing the chirality closer to the reactive metal center in the form of two methyl groups on the cyclohexane ring (**29**) improved the enantioselectivity already to 62% ee. Without conformational restriction, the methyl groups orient in a pseudoequatorial fashion. A pseudoaxial position brings them closer to the metal center and hence strengthens their influence on the ligand alignment around the metal. Indeed, combination of the acetal group fixing the methyl group in the axial position significantly enhanced the enantioselectivity to 84% ee with a dimethyl acetal **15a** and to 92% ee using a diphenyl ketal group (**15b**). Moreover, 1 mol % **15b** at ambient temperature in ethanol without any precaution of moisture and oxygen exclusion provides similar yields and selectivities. Importantly, complex **15b** efficiently operates in a range of solvents (alcohols, acetone, toluene dichloromethane) allowing an adaption to the substrate solubility.

The substrate scope of the transformation concerning aryl hydroxamates **23** is broad, tolerating a range of common functional groups. Besides several styrenes which provide consistently high enantioselectivities, other olefin classes are as well suitable. For instance, TIPS-buten-yne reacts exclusively with its olefin portion. Concerning higher substituted olefins, cyclic derivatives such as dihydrofuran, cyclopentene, or 1,3-cyclo-

Scheme 5. Selected Scope for the Dihydroisoquinolones
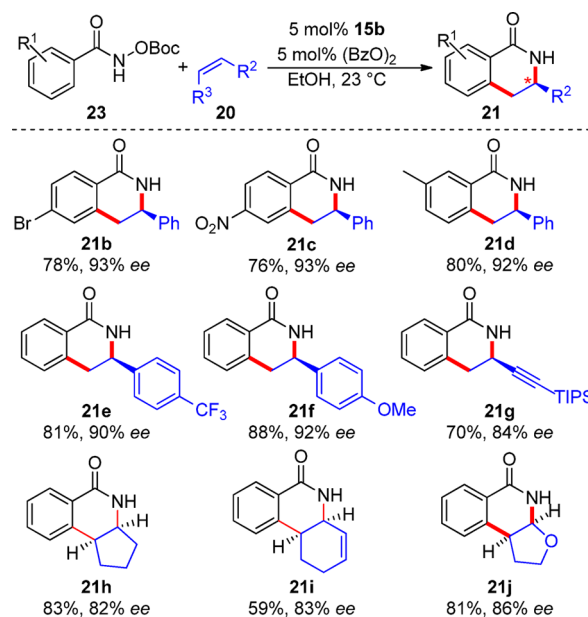
hexadiene provide the dihydroisoquinolone products in good enantioselectivities (Scheme 5). However, acrylates react only sluggishly, due to a suspected too strong binding to the rhodium center. Terminal aliphatic alkenes give regioisomeric mixtures and more substituted olefins do not react with the present catalyst system.

The selectivity of the dihydroisoquinolone synthesis can be rationalized with a cartoon model of the cyclometalated intermediate **25** (Scheme 6). The large OBoc substituent of
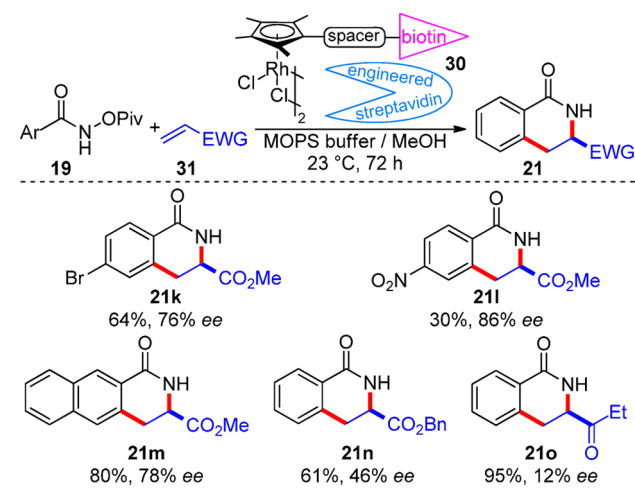
Scheme 6. Selectivity Model for the Enantioselective Dihydroisoquinolone Synthesis
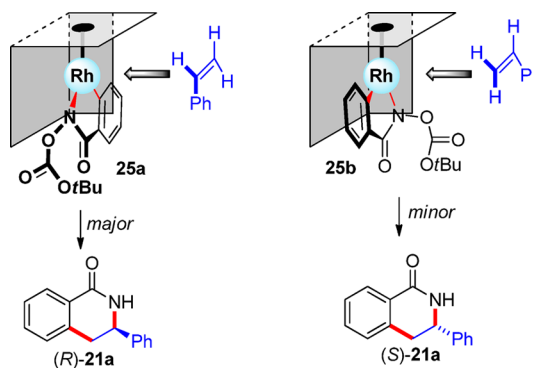
the hydroxamate unit favorably orients away from the steering methyl group of the side wall. The large acetal group acting as the back wall enforces an approach of the styrene from the accessible face. Its phenyl group is avoiding interaction with the Cp ring. Conformation **25a** is preferred over **25b** and thus the transformation is selectively leading to (*R*)-**21a**.

Complementary to our strategy using a rhodium-catalyst equipped with a small molecule ligand,[21] Rovis et al. reported a supramolecular catalyst system for the same transformation.[29] An achiral Cp*Rh(III) complex tethered by a linker to a biotin unit was used in conjunction with engineered streptavidin variants. The required chiral environment is created by the outstanding binding of streptavidin to the biotin entity. In this

Scheme 7. Asymmetric Dihydroisoquinolone Synthesis by Rovis−Ward Supramolecular Approach

Scheme 8. Pathways of Aryl Hydroxamate C(sp²)−H Functionalizations with Tethered Alkenes

supramolecular assembly, an artificial metalloenzyme is created, providing an efficient chiral pocket (Scheme 7). A specific engineered glutamic acid residue of the streptavidin is the carboxylate cofactor for the CMD step of the cyclometalation. Noteworthy, the substrate spectrum is complementary to the one of our catalyst. While 15b works most efficiently with styrenes, electron-deficient acrylates display low reactivities. For catalyst system 30, the acrylates are the most reactive and selective substrate class (Scheme 7). This complementary behavior can be attributed to the different steric and electronic properties of the disubstituted Cpˣ compared to the sterically more demanding and electron-rich pentasubstituted Cp* unit of 30.

3.2. Benzofurans with Quaternary Stereocenters by Asymmetric Hydroarylations

The common limitation in scope for the dihydroisoquinolone synthesis is the low intrinsic reactivity toward higher substituted olefins with the exception of the aforementioned cyclic ones and strained methylenecyclopropanes.[30] 1,1-Di- or trisubstituted olefins failed to undergo a reaction with rhodacyclic intermediate pointing toward a weak binding to the metal or more difficult migratory insertion. In addition, regioselectivity becomes as well an issues. To overcome these limitations, we investigated tethering the olefin partner in the *meta*-position with respect to the hydroxamate ester group. Allyl ethers such as 32 might give access to valuable dihydrobenzofurans with quaternary stereogenic centers, being stable toward oxidative metabolism to aromatic benzofurans (Scheme 8).[31] For steric reasons, the CMD pathway should strongly favor the less congested *ortho*-position for the C−H activation step. However, this would lead to dead-end intermediate 34, but no polymerization would occur due to the low reactivity of the substituted olefin. The CMD step is reversible and added carboxylic acid should accelerate this behavior. Once the desired hindered *ortho*-position is addressed, species 33 can undergo a productive reaction pathway. Because of the tether, the regiochemistry for the 1,1-disubstituted olefin insertion is locked leading to intermediate 35 with a quaternary stereogenic center. In the absence of β-hydride elimination pathway and the lower propensity of the N-OMe directing group to engage in reductive C−N bond formation, proto-demetalation would become the favorable pathway. Again, additional carboxylic acid should enhance this protonation step. An exploratory achiral
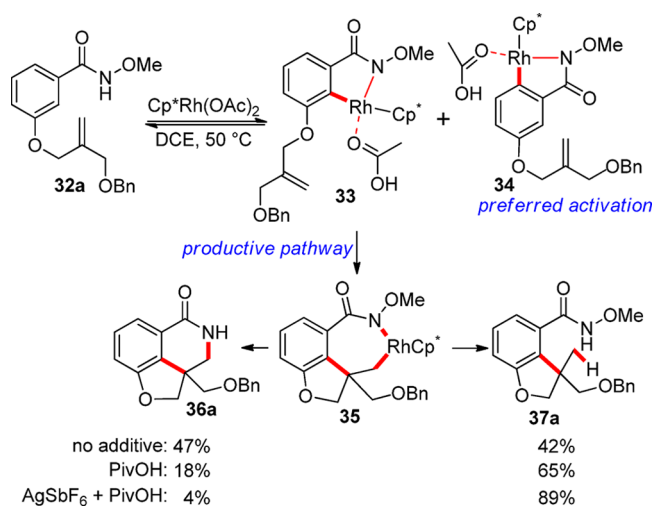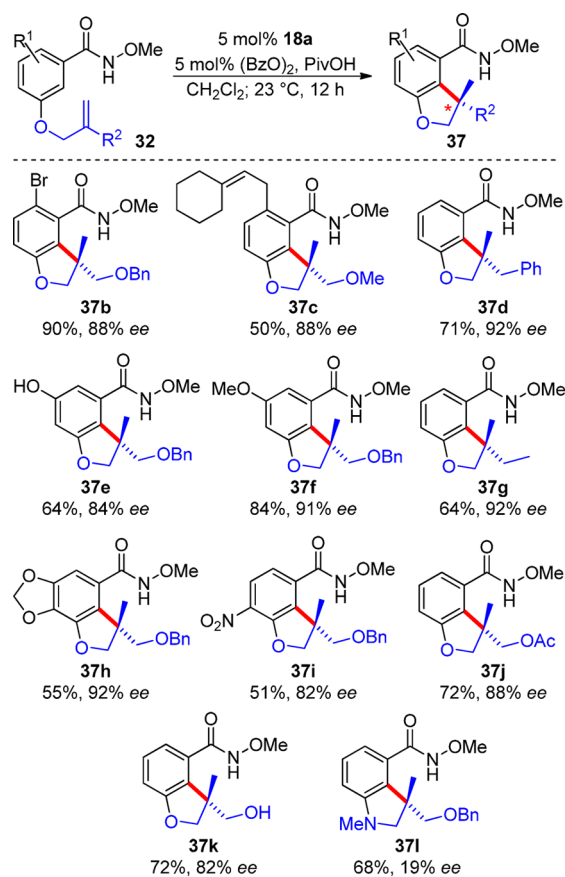
experiment revealed the influence of the additives, independently confirmed by findings from Rovis et al.[32] Without additives, products 36a and 37a were formed in roughly equal amounts. The addition of pivalic acid induced the selective formation of hydroarylated product 37a. Moreover, $AgSbF_6$ further enhanced the protonolysis.

Contrasting the behavior of Cp*, all chiral Cpˣ ligands provided irrespective of additives exclusively hydroarylation product 37a (Scheme 9). The previously best first generation

Scheme 9. Performance of Cpˣ Rhodium Complexes in Enantioselective Hydroarylations
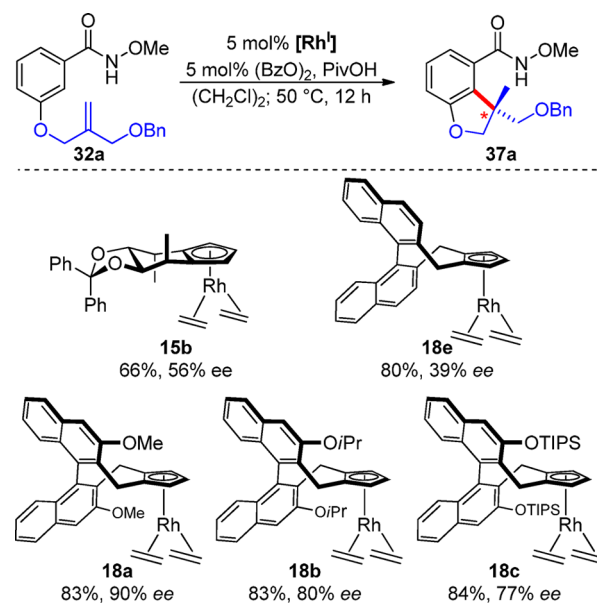
complex 15b afforded dihydrobenzofuran 37a with 56% ee, while the unsubstituted parent scaffold of the second generation complex 18e gave already rise to 39% ee. Complex 18a having two methoxy substituents in the *ortho*-positions dramatically improved the selectivity of 37a to 90% ee and 83% yield. The nature of the carboxylic acid had little influence on selectivity. However, for unclear reasons, the addition of silver salts almost completely abolished the enantioselectivity.

Scheme 10. Dihydrobenzofurans by Asymmetric Hydroarylation of Tethered Olefins

Scheme 11. Performance of Cp^x Rhodium Complexes in Enantioselective C−H Allylations

was observed with methoxy groups in both *ortho*-positions (**18a**). Increasing the bulk by a replacement of the OMe groups by larger OTIPS group (**18c**), gave an improved enantioselectivity of 80% ee which was further increased to 93% ee by conducting the transformation at −20 °C in dichloromethane. Remarkably, the C−H activation efficiently takes place at such low temperatures. In analogy to the previous transformations with the cyclometalated intermediates, steric and electronic variations of the hydroxamate substrate have little influence on the enantioselectivity of the allylation (Scheme 12). Furthermore, the transformation displays the typical good tolerance of functional groups. The nature of the allene acceptors does not interfere significantly with the selectivity of the reaction, and thus different esters, ethers and free hydroxyl groups are compatible. In addition, a highly sensitive allylic *bis*-benzylic stereogenic center (**40k**) is not racemized under the mild conditions.

Most likely, the selectivity criteria are based on steric considerations (Scheme 13). Rhodacyclic key intermediate **41** is preferentially arranged pointing its *O*-methyl hydroxamate moiety away from the bulky OTIPS tail of the ligand (**41a**). The allene acceptor approaches in a fashion orienting the substituent R away from the Cp part, minimizing its steric interactions giving selectively (*R*)-**40**.

3.4. Asymmetric Isoindolone Synthesis by Enantioselective Carbene Insertions

Expanding the trapping possibilities for the cyclometalated intermediate, Rovis reported the use of donor−acceptor-substituted diazo derivatives as one-carbon unit for the interception.[35] With Cp* as achiral ligand, racemic isoindolones possessing a stereogenic center are obtained as valuable products. A brief complex and condition screening of our chiral Cp^x ligand portfolio revealed that the large OTIPS version of the second generation ligand (**18c**) provided the best enantioselectivity, giving isoindolone **43a** in 93% ee and 83% yield (Scheme 14).[36] Moreover, the C−H activation and carbene insertion is operating at very mild ambient conditions. While the orientation of substrate with respect to the
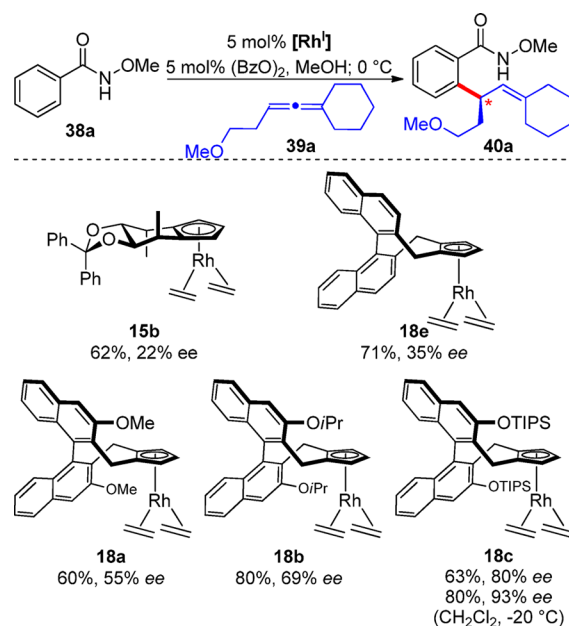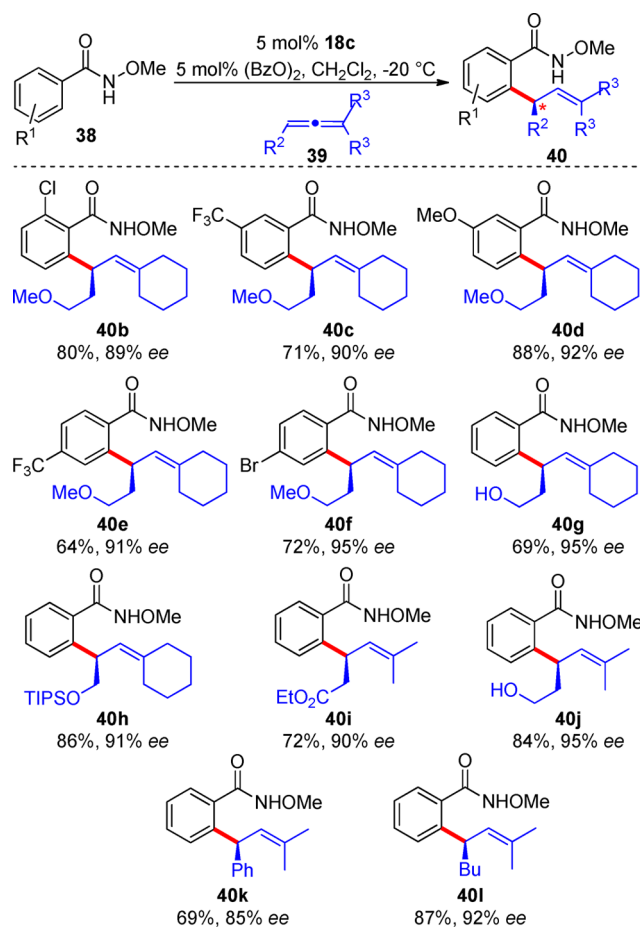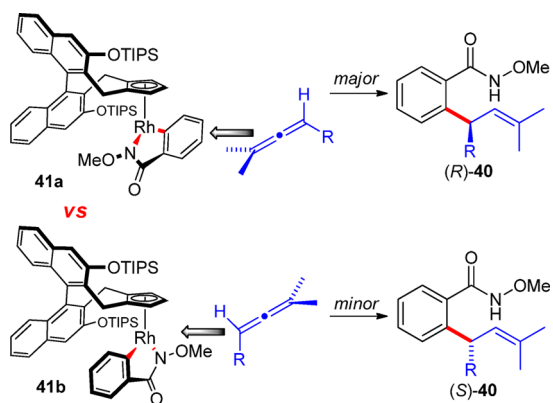
With the optimal conditions, the reaction is relatively robust in terms of yield and selectivity over a broad substrate range (Scheme 10). Besides common electron-rich and electron-poor groups, the mild nature of the transformation tolerates as well phenols and nitro groups on the hydroxamate portion. The olefin part is as well amenable to several variations, ranging from simple alkyl or aryl groups to functionalized ethers and free allylic alcohols. Noteworthy, an allylic acetate group reacts well without undergoing ionization to the π-allyl species usually observed with transition metals. In contrast, the nature of the heteroatom in the tether proved to be important for the selectivity. For instance, a basic nitrogen atom leads to comparable reactivity, but dramatically reduced enantioselectivity.

3.3. Directed Enantioselective C−H Allylations

To further expand the applicability of asymmetric C−H functionalization for intermolecular reactions, we identified allenes as reactive and valuable coupling partners. The principal reactivity of allenes toward cyclometalated Cp*Rh(III) intermediates has been demonstrated by Ma et al.[33] and Glorius and Wang[34] for nonasymmetric transformations. The use of an achiral trisubstituted allene such as **39a** would result in the formation of allylated product **40a** possessing a stereogenic center at the benzylic position.[22] In this respect, we evaluated the potential of the chiral Cp^{x}Rh complexes in the reaction *N*-OMe phenyl hydroxamate **38a** and trisubstituted allene **39a** (Scheme 11).

The second generation class of ligands proved again superior. The parent unsubstituted member **18e** gave allylated product **40a** in 35% ee (Scheme 12). An enhanced selectivity of 55% ee

**Scheme 12. Asymmetric Hydroarylation with Trisubstituted Allenes**

Scheme 13. Stereoselectivity Model for the C–H Allylation with the Second Class Chiral Cp^x Ligands

Cp^{x}Rh-fragment would be similar to the previous examples, the approach and coordination of the diazo component consists of the enantio-determining step. Large differences between the sizes of R^1 and R^2 of the carbene substituent should improve the enantioselectivity. Key for a high enantioselectivity was the use of the bulky 2,4-dimethyl-3-pentyl ester group of **42a**.

Concerning the scope of this transformation, a broad range of the aryl hydroxamate substrates **19**, ranging from electron-poor, electron-rich, and halogenated substituents, are tolerated, a common feature of this kind of activations (Scheme 15).

Scheme 14. Performance of Cp^x Rhodium Complexes in Enantioselective Carbene Insertions
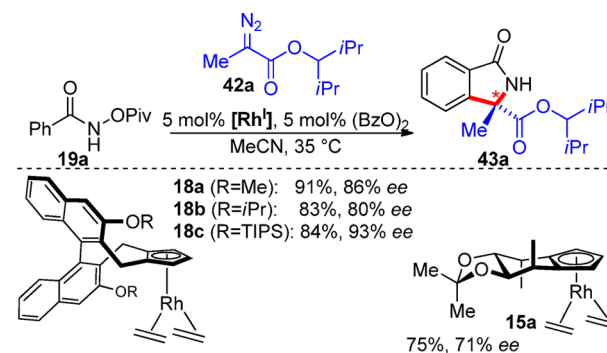

Scheme 15. Isoindolones by Enantioselective Carbene Insertions
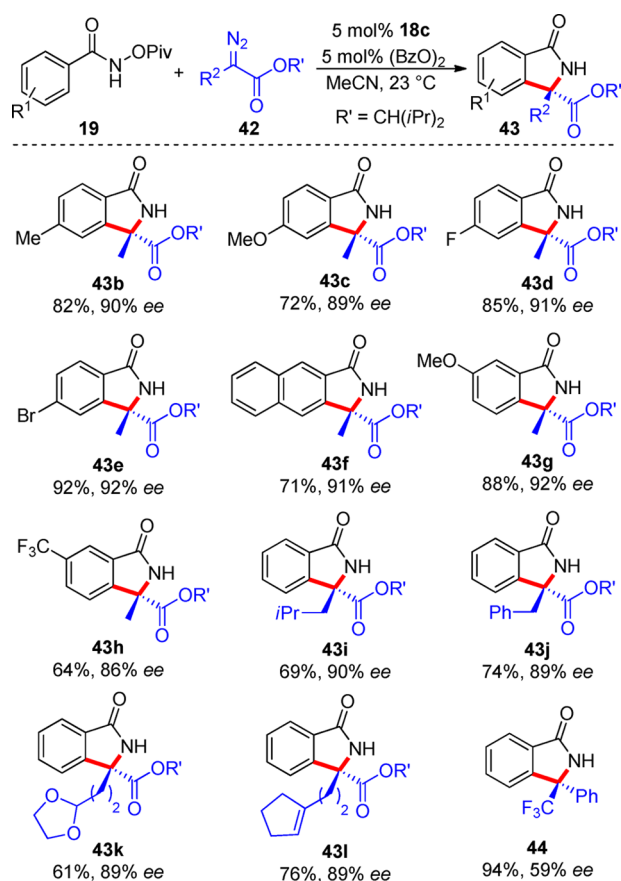
Carbene coupling partners basing on non-α-branched diazoesters **42** provide high enantioselectivities and can be peripherally modulated with functional groups.

The obtained selectivity in the isoindolone synthesis can be rationalized by the preferred substrate orientation with respect to the chiral Cp^x ligand (Scheme 16). In analogy to the afore-mentioned orientation of the cyclometalated intermediate, the O-Piv hydroxamate unit favors an orientation pointing away from bulky OTIPS tail of the ligand. The carbene bound to the rhodium atom has two options to minimize interaction with the Cp group. The one where the very bulky ester substituent of the carbene is pointing away from O-Piv hydroxamate unit is preferred (**45a**) over the opposite orientation (**45b**) suffering from a clash between the ester and the hydroxamate.

Scheme 16. Selectivity Model for the Enantioselective Isoindolone Synthesis
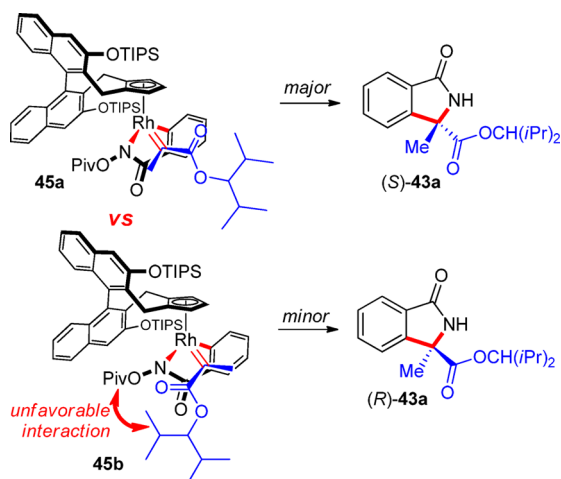
3.5. Synthesis of Axially Chiral Biaryl Compounds

In 2014, You and co-workers demonstrated the utility of our Cp^xRh(I) complexes in an enantioselective approach of axially chiral biaryls.[37] The chiral axis of the biaryl substrates **46a** having no substituent in the *ortho*-position interconverts at low temperature. Installation of a substituent at the *ortho*-position increases this rotational barrier generating stable axially chiral biaryls. The installation of this substituent has been realized by a directed C−H bond activation forming metallocycle **47** (Scheme 17). In turn, **47** is intercepted with an olefin in a

Scheme 17. Cp^x-Ligand Screen for the Enantioselective Dehydrogenative Heck Coupling
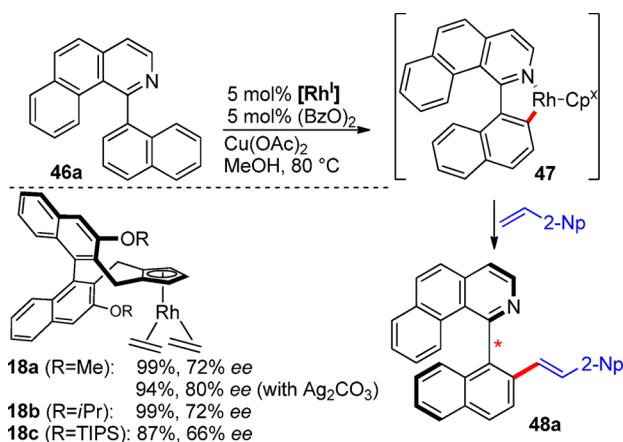

Heck-type coupling providing product **48a**. The Rh(III) catalyst is regenerated from the formed Rh(I) species by an external oxidant. A brief screening of chiral Cp^xRh(I) complexes equipped with the different members of the second generation ligand class revealed methoxy-substituted version **18a** as the most selective one. This ligand provides the properly balanced steric bulk inducing a good selectivity and while maintaining a high reactivity. Ligand with bulkier *ortho*-groups resulted in diminished yield and enantioselectivity. Besides the ligand choice, the composition of the reoxidation system contributed significantly to the reaction performance. The combination of stoichiometric amounts of Ag_2CO_3 with 20 mol % of $Cu(OAc)_2$ increased the enantioselectivity to

80% ee from 72% ee obtained from a reaction with $Cu(OAc)_2$ as sole oxidant.

For the scope of the reaction, few variations of the directing group bearing portion were investigated (Scheme 18). The

**Scheme 18. Construction of Axially Chiral Biaryl Compounds**
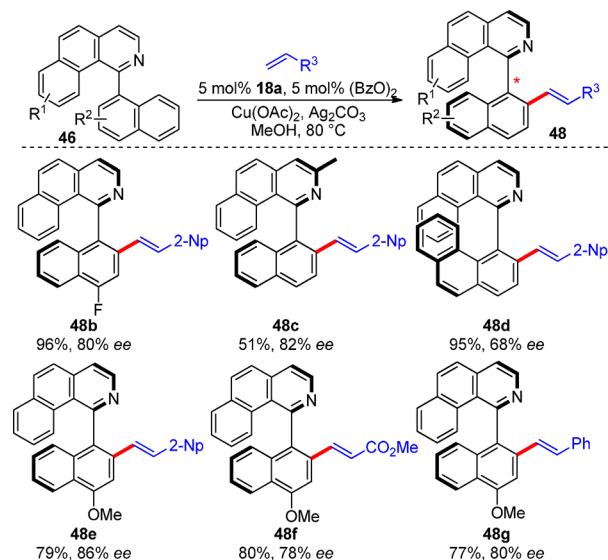
naphthalene portion can be varied, although a significant impact on the reactivity and selectivity has been observed. As long it is terminal, the nature of the olefin acceptor can be varied over a wide range (styrenes, acrylates, acrylamides, vinyl phosphate, ethylene) with minor influence on the enantioselectivity. This is an indication that the chiral axis might be set during the cyclometalation step forming intermediate **47**, and the C−C bond formation is locking and conserving the axis.

3.6. Applications with Other Metals

In 2014, Hou and co-workers showed the suitability of our second generation chiral Cp^x ligand system in asymmetric rare-earth metal catalysis.[38] The required scandium complexes **49** were prepared by mixing the cyclopentadiene ligand precursor with cyclometalated complex $Sc(CH_2C_6H_4NMe_2-o)_3$ at low temperature in THF. The obtained Cp^x scandium complexes **49** were subsequently used to catalyze asymmetric hydro-2-pyridylations of olefins (Scheme 19). Under the optimized conditions, the reaction of 2-picoline (**50a**) and norbornene

Scheme 19. Asymmetric Olefin Hydropyridylation with Chiral Scandium Cp^x Complexes
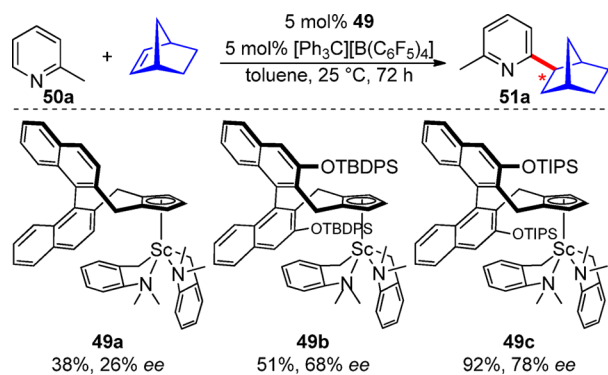
gave **51a** in 92% yield and 78% ee with the large OTIPS second generation ligand (complex **49c**).

The process was further utilized for the hydropyridylation of terminal olefins. The reaction operates at mild conditions and is selective for the branched products. The observed selectivity for 1-hexene is superior to the one for norbornene, giving products **51** in up to 96% ee (Scheme 20). Besides 1-picoline, a variety of

Scheme 20. Scope of the Asymmetric Olefin Hydropyridylation
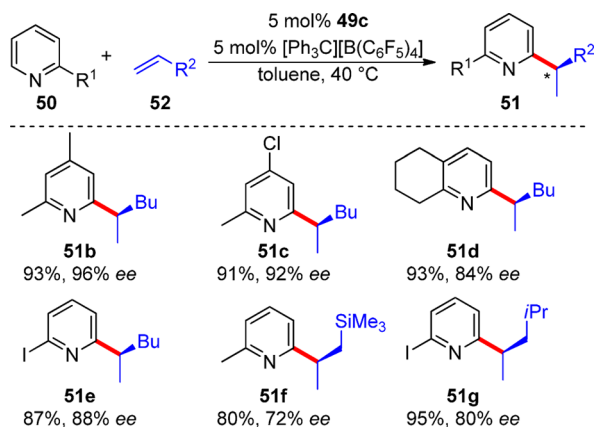
ortho-substituted pyridines including iodo, chloro, and bromo substituents are tolerated. Longer terminal olefins as well as β-branched hydrocarbons are efficiently transformed.

4. SUMMARY AND CONCLUSION

The rapid growth in C−H functionalization technology and especially the broad reactivity profile of Rh(III) catalysts strongly revived the interest in chiral half-sandwich metal complexes. Over the past few years, our group has developed two complementary classes of chiral C_2-symmetric cyclopentadiene derivatives. Both are amenable to late stage modifications to adapt them to the specific reaction requirements. Their corresponding Cp^xRh^I complexes have proven to be efficient chiral catalysts for asymmetric C−H functionalizations. While the catalytic applications so far have concentrated on Rh(III)-catalyzed transformations, the ligands have as well a promising potential for other transition metals. The number of different reactions catalyzed by Cp* complexes of late transition metals ranging from Rh, Ir, Ru to Co, Fe, Ni, as well as early transition metals is large. Showcasing the potential of our ligands with these metals became a focus of our research. In the future, additional critical tasks comprise a refinement of the understanding of the selectivity-determining factors of the transformations. This knowledge would build an essential foundation to the design of additional modular and even more selective ligand platforms. Moreover, more efficient and shortened ligand syntheses and, along the same lines, better complexation strategies from stable precursors are required to further enhance the user-friendliness of these ligands in asymmetric catalysis.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nicolai.cramer@epfl.ch.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

Biographies

Baihua Ye received his Master in Chemistry from EPFL, Switzerland (2010). After an internship at Hoffmann-La Roche AG in Basel, he started his Ph.D. in the group of Nicolai Cramer. His thesis focuses on the development of chiral cyclopentadienyl ligands for enantioselective rhodium(III)-catalyzed C−H functionalizations.

Nicolai Cramer received his Ph.D. from the University of Stuttgart, Germany (2005). After a short research stage at Osaka University, Japan, he joined Stanford University as a Feodor-Lynen postdoctoral fellow working with Barry M. Trost. From 2007 on, he worked on his habilitation at the ETH Zurich, Switzerland, and received his *venia legendi*. In 2010, he joint EPFL, Switzerland, and was promoted to Associate Professor in 2013. His research interests encompass enantioselective metal-catalyzed transformations and their implementation for the synthesis of biologically active molecules.

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) Kealy, T. J.; Pauson, P. L. A New Type of Organo-Iron Compound. *Nature* **1951**, *168*, 1039−1040.

(2) Hartwig, J. *Organotransition Metal Chemistry*; University Science Books: Herndon, VA, 2010.

(3) Togni, A. Developing New Chiral Ferrocenyl Ligands for Asymmetric Catalysis: A Personal Account. *Chimia* **1996**, *50*, 86−93.

(4) (a) Ewen, J. A. Mechanisms of Stereochemical Control in Propylene Polymerizations with Soluble Group 4B Metallocene/Methylalumoxane Cata1ysts. *J. Am. Chem. Soc.* **1984**, *106*, 6355−6364. (b) Kaminsky, W.; Külper, K.; Brintzinger, H. H.; Wild, F. R. W. P. Polymerization of Propene and Butene with a Chiral Zirconocene and Methylalumoxane as Cocatalyst. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 507−508.

(5) (a) Hoveyda, A. H.; Morken, J. P. Enantioselective C-C and C-H Bond Formation Mediated or Catalyzed by Chiral ebthi Complexes of Titanium and Zirconium. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1262−1284. (b) Broene, R. D.; Buchwald, S. L. Asymmetric Hydrogenation of Unfunctionalized Trisubstituted Olefins with a Chiral Titanocene Catalyst. *J. Am. Chem. Soc.* **1993**, *115*, 12569−12570.

(6) (a) Murata, K.; Ikariya, T.; Noyori, R. New Chiral Rhodium and Iridium Complexes with Chiral Diamine Ligands for Asymmetric Transfer-Hydrogenation of Aromatic Ketones. *J. Org. Chem.* **1999**, *64*, 2186−2187.

(7) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. Enantioselective Allyltitanation of Aldehydes with Cyclopentadienyldialkoxyallyltitanium Complexes. *J. Am. Chem. Soc.* **1992**, *114*, 2321−2336.

(8) Kündig, E. P.; Saudan, C. M.; Viton, F. Chiral Cyclopentadienyl-Iron and -Ruthenium Lewis Acids Containing the Electron-Poor BIPHOP-F Ligand: A Comparison as Catalysts in an Asymmetric Diels-Alder Reaction. *Adv. Synth. Catal.* **2001**, *343*, 51−56.

(9) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. Asymmetric Catalysis of Planar-Chiral Cyclopentadienylruthenium Complexes in Allylic Amination and Alkylation. *J. Am. Chem. Soc.* **2001**, *123*, 10405−10406.

(10) Trost, B. M.; Rao, M.; Dieskau, A. P. A Chiral Sulfoxide-Ligated Ruthenium Complex for Asymmetric Catalysis: Enantio- and

Regioselective Allylic Substitution. *J. Am. Chem. Soc.* **2013**, *135*, 18697−18704.

(11) Lenges, C. P.; Brookhart, M. Co(I)-Catalyzed Inter- and Intramolecular Hydroacylation of Olefins with Aromatic Aldehydes. *J. Am. Chem. Soc.* **1997**, *119*, 3165−3166.

(12) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. Thermal, Catalytic, Regiospecific Functionalization of Alkanes. *Science* **2000**, *287*, 1995−1997.

(13) (a) Kuhl, N.; Schröder, N.; Glorius, F. Formal S$_N$-Type Reactions in Rhodium(III)-Catalyzed C-H Bond Activation. *Adv. Synth. Catal.* **2014**, *356*, 1443−1460. (b) Song, G.; Wang, F.; Li, X. C−C, C−O, C−N Bond Formation *via* Rhodium(III)-Catalyzed Oxidative C-H Activation. *Chem. Soc. Rev.* **2012**, *41*, 3651−3678. (c) Satoh, T.; Miura, M. Oxidative Coupling of Aromatic Substrates with Alkynes and Alkenes under Rhodium Catalysis. *Chem.—Eur. J.* **2010**, *16*, 11212−11222.

(14) Zhou, M.; Schley, N. D.; Crabtree, R. H. Cp* Iridium Complexes Give Catalytic Alkane Hydroxylation with Retention of Stereochemistry. *J. Am. Chem. Soc.* **2010**, *132*, 12550−12551.

(15) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. Ruthenium-Catalyzed Reactions - A Treasure Trove of Atom-Economic Transformations. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630−6666.

(16) (a) Halterman, R. L.; Vollhardt, K. P. C. Synthesis and Asymmetric Reactivity of Enantiomerically Pure Cyclopentadienylmetal Complexes Derived From the Chiral Pool. *Organometallics* **1988**, *7*, 883−892. (b) Halterman, R. L.; Vollhardt, K. P. C.; Welker, M. E. A Designed, Enantiomerically Pure, Fused Cyclopentadienyl Ligand with C$_2$ Symmetry: Synthesis and Use in Enantioselective Titanocene-Catalyzed Hydrogenations of Alkenes. *J. Am. Chem. Soc.* **1987**, *109*, 8105−8107. (c) Halterman, R. L.; Vollhardt, K. P. C. Practical Synthesis of Two Annulated Optically Active Cyclopentadienes from the Chiral Pool and Their Transition Metal Complexes. *Tetrahedron Lett.* **1986**, *27*, 1461−1464.

(17) (a) Colletti, S. L.; Halterman, R. L. Asymmetric Synthesis and Metalation of a Binaphthylcyclopentadiene, a C$_2$-Symmetric Chiral Cyclopentadiene. *Organometallics* **1991**, *10*, 3438−3448. (b) Chen, Z.; Halterman, R. L. Asymmetric Synthesis of C$_2$-Symmetric Annulated Bicyclooctylcyclopentadienes. *Synlett* **1990**, 103−104. (c) Colletti, S. L.; Halterman, R. L. Binaphthylcyclopentadiene: A C$_2$-Symmetric Annulated Cyclopentadienyl Ligand with Axial Chirality. *Tetrahedron Lett.* **1989**, *30*, 3513−3516.

(18) (a) Li, Z.; Vasella, A. Synthesis of Enantiomerically Pure Carbohydrate-Derived Annulated Cyclopentadienes and Ferrocenes. *Helv. Chim. Acta* **1996**, *79*, 2201−2218. (b) Erker, G.; Schamberger, J.; van der Zeijden, A. A. H.; Dehnicke, S.; Krüger, C.; Goddard, R.; Nolte, M. On the Structural Features of the Chiral Organometallic Lewis-Acid Catalyst "(Dibornacyclopentadienyl)zirconiumtrichloride. *J. Organomet. Chem.* **1993**, *459*, 107−115. (c) Paquette, L. A.; Moriarty, K. J.; MaKinney, J. A.; Rogers, R. D. Analysis of the π-Facial Preference for Complexation of a Camphor-Derived, Enantiomerically Pure Cyclopentadienyl Ligand to CpMCl$_2$ Fragments (M = Ti and Zr). *Organometallics* **1989**, *8*, 1707−1713.

(19) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. Cobalt(I)-Catalyzed Asymmetric [2 + 2+2] Cycloaddition of Alkynes and Nitriles: Synthesis of Enantiomerically Enriched Atropoisomers of 2-Arylpyridines. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795−3797.

(20) Halterman, R. L. Synthesis and Applications of Chiral Cyclopentadienylmetal Complexes. *Chem. Rev.* **1992**, *92*, 965−994.

(21) Ye, B.; Cramer, N. Chiral Cyclopentadienyl Ligands as Stereocontrolling Element in Asymmetric C-H Functionalization. *Science* **2012**, *338*, 504−506.

(22) 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*, 636−639.

(23) Ooi, T.; Kameda, M.; Maruoka, K. Design of *N*-Spiro C$_2$-Symmetric Chiral Quaternary Ammonium Bromides as Novel Chiral Phase-Transfer Catalysts: Synthesis and Application to Practical Asymmetric Synthesis of α-Amino Acids. *J. Am. Chem. Soc.* **2003**, *125*, 5139−5151.

(24) (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. Transition Metal-Catalyzed C−H Activation Reactions: Diastereoselectivity and Enantioselectivity. *Chem. Soc. Rev.* **2009**, *38*, 3242−3272. (b) Zheng, C.; You, S.-L. Recent Development of Direct Asymmetric Functionalization of Inert C−H Bonds. *RSC Adv.* **2014**, *4*, 6173−6214.

(25) 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*, 6449−6457.

(26) 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*, 2350−2353.

(27) (a) 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*, 15409−15418. (b) Xu, L.; Zhu, Q.; Huang, G.; Cheng, B.; Xia, Y. Computational Elucidation of the Internal Oxidant-Controlled Reaction Pathways in Rh(III)-Catalyzed Aromatic C-H Functionalization. *J. Org. Chem.* **2012**, *77*, 3017−3024.

(28) Ackermann, L. Carboxylate-Assisted Transition-Metal-Catalyzed C−H Bond Functionalizations: Mechanism and Scope. *Chem. Rev.* **2011**, *111*, 1315−1345.

(29) Hyster, T.; Knörr, L.; Ward, T. R.; Rovis, T. Biotinylated Rh(III) Complexes in Engineered Streptavidin for Accelerated Asymmetric C−H Activation. *Science* **2012**, *338*, 500−503.

(30) Cui, S.; Zhang, Y.; Wu, Q. Rh(III)-Catalyzed C−H Activation/Cycloaddition of Benzamides and Methylenecyclopropanes: Divergence in Ring Formation. *Chem. Sci.* **2013**, *4*, 3421−3426.

(31) 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*, 507−511.

(32) 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*, 14181−14185.

(33) Zeng, R.; Fu, C.; Ma, S. Highly Selective Mild Stepwise Allylation of *N*-Methoxybenzamides with Allenes. *J. Am. Chem. Soc.* **2012**, *134*, 9597−9600.

(34) Wang, H.; Glorius, F. Mild Rhodium(III)-Catalyzed C−H Activation and Intermolecular Annulation with Allenes. *Angew. Chem., Int. Ed.* **2012**, *51*, 7318−7322.

(35) Hyster, T. K.; Ruhl, K. E.; Rovis, T. A Coupling of Benzamides and Donor/Acceptor Diazo Compounds to Form γ-Lactams *via* Rh(III)-Catalyzed C−H Activation. *J. Am. Chem. Soc.* **2013**, *135*, 5364−5367.

(36) Ye, B.; Cramer, N. Asymmetric Synthesis of Isoindolones by Chiral Cyclopentadienyl-Rhodium(III)-Catalyzed C−H Functionalizations. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896−7899.

(37) Zheng, J.; You, S.-L. Construction of Axial Chirality by Rhodium-Catalyzed Asymmetric Dehydrogenative Heck Coupling of Biaryl Compounds with Alkenes. *Angew. Chem., Int. Ed.* **2014**, *53*, 13244−13247.

(38) Song, G.; W. N. O, W.; Hou, Z. Enantioselective C−H Bond Addition of Pyridines to Alkenes Catalyzed by Chiral Half-Sandwich Rare-Earth Complexes. *J. Am. Chem. Soc.* **2014**, *136*, 12209−12212.