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Asymmetric Catalysis Powered by Chiral Cyclopentadienyl Ligands

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ABSTRACT: Application of chiral derivatives of the versatile and ubiquitous cyclopentadienyl ligand has long remained an underdeveloped area in asymmetric catalysis. In this Perspective we highlight recent exciting results that demonstrate their enormous potential. In particular, we provide a comparative analysis of the available ligand families, an overview of their complexation chemistry, and an examination of their application in catalytic enantioselective reactions. We also discuss current limitations and speculate on the developments that are necessary to advance the field further.

INTRODUCTION AND REVIEW SCOPE

The ability to access a single enantiomer of a molecule is a necessity in many industries. The field of asymmetric catalysis offers many elegant solutions, and central to this area of research is the development of new chiral ligands that can facilitate asymmetric reactions with high levels of enantiocontrol and efficiency. The most valuable ligand families effect a wide variety of transformations and allow for reaction optimization via the systematic modification of their architectures. Representative scaffolds that meet these demands include BINOL **1**,[1] BINAP **2**,[2] chiral SALEN derivatives **3**,[3] and the tartaric acid derived TADDOL family **4**[4] (Figure 1).

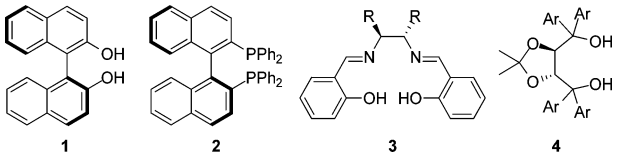

Figure 1. Representative privileged ligand scaffolds.

The cyclopentadienyl (Cp) ligand and its pentamethyl-substituted derivatives (Cp*) are of fundamental importance in organometallic chemistry. Cp complexes are known for all transition metals, most *f*-block metals, and enjoy application in a staggering number of catalytic processes.[5] In principle, there are three approaches to evoke enantiocontrol in reactions catalyzed by Cp complexes (Figure 2): combination of an achiral Cp with an additional external chiral ligand (**5**), construction of a Cp tether (**6**), or employment of a chiral Cp ligand with noncoordinating substituents (Cp^x) such as complex **7**.[6] Each of these strategies affords an increasing number of free coordination sites on the metal, and consequently each caters for different and complementary reaction classes. A number of complexes of type **5** have been successfully employed in asymmetric catalysis, and representative chiral ligands include diphosphines,[7] diamines,[8] and diols.[9] Complexes of type **6** incorporating tethered sulfoxides[10] or phosphines[11] have also been implemented in powerful asymmetric transformations, and the conceptually related *ansa*-metallocenes are important for the asymmetric ZACA reaction.[12] However, many Cp-catalyzed reactions require the maximum number of coordination sites available on the metal,[13] thus excluding complexes of type **5** and **6** in the development of asymmetric variants. Despite the great potential of Cp^x ligands, exploratory studies from the 1980s resulted in poor enantioselectivities.[14] Consequently, there has been little synthetic interest in their development, and applications have remained scarce.

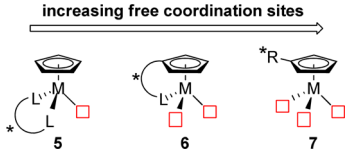

Figure 2. Chiral Cp complexes.

In this Perspective we highlight the strongly revived interest and recent progress regarding the development of Cp^x ligands. We begin by discussing the strategic principles behind ligand design, their transition-metal complexation chemistry, followed by an overview of their different applications in asymmetric synthesis. We have elected to limit discussion to the state-of-the-art, specifically, those complexes that have found success in highly enantioselective transformations. We conclude with a critique of current methodology and recommend directions for where we believe future research efforts should be focused.

THE COMPLEXES

Whereas many complexes of type **5** and **6** have been successfully employed in asymmetric catalysis, only five classes of Cp^x ligands have provided notable enantiocontrol. The first two reports are conceptually related, and both employ ligands derived from readily available, chiral pool starting materials (Scheme 1). The inaugural example from Erker and co-workers[15] describes the application of (+)-camphor derived $ZrCp^x$-complex **9**. Unlike related catalysts that can often be generated *in situ* from a chiral ligand with an appropriate metal source, Cp complexes require preassembly,[16] necessitating robust complexation and purification methodology for each ligand class and metal. In addition, methods for the conversion of metal−Cp complexes to the appropriate precatalyst also need to be developed (e.g., altering the metal oxidation state or

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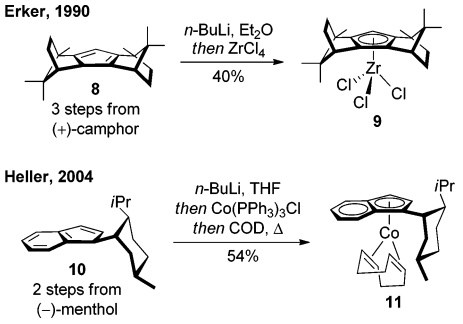
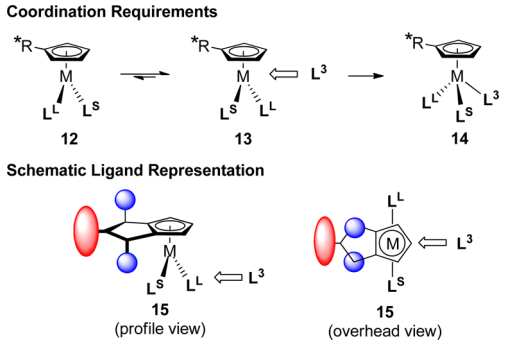
Scheme 1. Early Chiral Pool Approaches to Cp^x Ligands



exchanging the counterion). In the case of cyclopentadiene **8**, zirconium complexation was achieved by generation of the C_2 symmetric Li-Cp with *n*-BuLi (circumventing the need for a diastereoselective complexation), followed by a substitution reaction with $ZrCl_4$. Similarly, complexation of Heller's (−)-menthol derived Cp^x ligand **10** was accomplished by treatment with base, followed by a cobalt source. This mixture was then warmed in the presence of COD to yield the highly oxygen-sensitive Co(I) complex **11**.[17] Although complexes **9** and **11** can both be accessed in short order, any modification of the ligand framework is severely restricted by the chiral pool approach, impeding systematic catalyst structure optimization.

In 2012[18] and 2013[19] our group documented the development and application of two modifiable Cp^x scaffolds. The working model for ligand design was based on the assumption that two conditions were thought necessary to achieve enantiocontrol with chiral Cp^x ligands: a strong preference for one of the two possible tricoordinated species (**12** vs **13** in Scheme 2), and control of trajectory of the incoming third

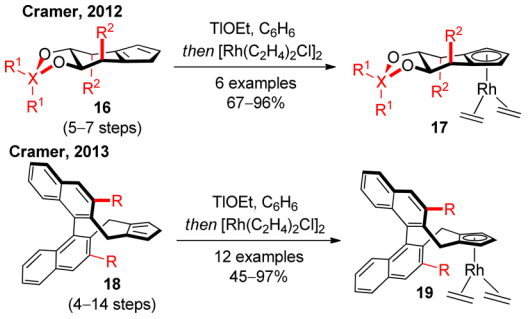
Scheme 2. Ligand Design Principles



ligand L^3. Provided both of these conditions could be met, one absolute configuration at the now stereogenic-at-metal complex **14** would be favored, eventually leading to the formation of a single product enantiomer. In order to provide an immutable chiral environment, a suitably substituted fused (and thus rigid) cyclic backbone was envisioned. Decoration with a sufficiently bulky group at the rear (highlighted in red in **15**) would ensure that approach of the L^3 ligand would occur from only one face. In turn, the orientations of L^S and L^L would be dictated by the adjustable substituents proximate to the metal (highlighted in blue), compelling the larger ligand to occupy the more remote site.

The first generation of ligands, disubstituted cyclopentadienes **16**, were synthesized in 5−7 steps (Scheme 3). Importantly, two sites of the scaffold were amenable to

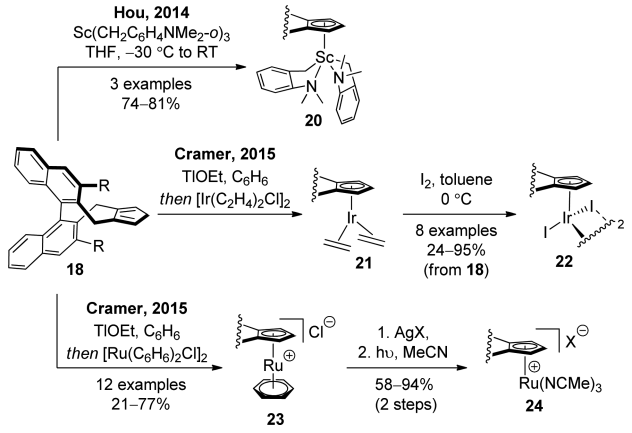
Scheme 3. Two Modifiable Cp^x Scaffolds and Conversion to their Rh(I) Complexes



modification (highlighted in red), enabling the synthesis of several derivatives. The ligands were designed as C_2 symmetric to simplify metal complexation, thus deprotonation of **16** with thallium ethoxide, accompanied by an *in situ* substitution with Rh(I) ethylene chloride, delivered the relatively stable and chromatographable Rh(I) complexes **17**.[18,20] One year later the same design principles were applied to a new ligand family, this time utilizing (*R*)-BINOL as the source of chirality. While the overall synthesis of **18** is lengthier, late stage functionalization assists with library preparation, and four separate reports now disclose the synthesis of derivatives.[19−22] Conversion to RhCp^x complexes **19** was achieved under identical conditions to their predecessor, and notably, complexes of this binaphthyl derived ligand family have demonstrated enhanced reactivity and selectivity.[20,23]

In addition to the aforementioned complexation with rhodium(I) salts, ligand family **18** has also been successfully applied in asymmetric catalysis as a complex with scandium(III),[24] iridium(III),[21] and ruthenium(II)[22] (Scheme 4). In

Scheme 4. Binaphthyl Derived Cp^x Metal Complexes of Sc(III), Ir(III), and Ru(II)



2014 Hou et al. demonstrated that Sc complex **20** could be prepared via a simple acid−base reaction between **18** and tris(*o*-dimethylaminobenzyl)Sc.[24] Cramer and co-workers disclosed routes to iridium(III)[21] and ruthenium(II)[22] complexes **22** and **24**. The former is prepared in analogous fashion to its Rh congeners by reaction with TlOEt, followed by addition of freshly prepared Ir(I) ethylene chloride. The Ir(III) complexes **22** are obtained by oxidation with molecular iodine. Ru(II) derivatives **24** were also synthesized from the appropriate thallium-Cp derivatives of **18**, in this case employing [Ru-

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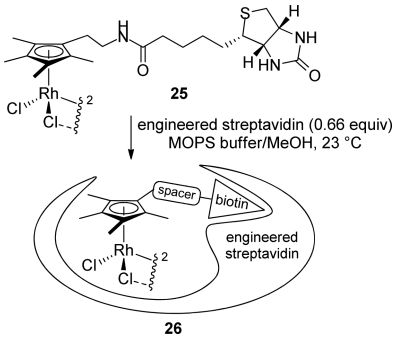
$(C_6H_6)Cl_2)]_2$ as the metal source. The highly robust arene complexes **23** allow for counterion metathesis, and photochemical ligand exchange provides tris-acetonitrile complex **24**.

A conceptually distinct supramolecular strategy toward chiral Cp facilitated asymmetric catalysis was disclosed by Ward and Rovis in 2012 (Scheme 5).[25] In this case, the chiral

Scheme 5. Synthesis of an Artificial Cp* Metalloenzyme by Ward and Rovis



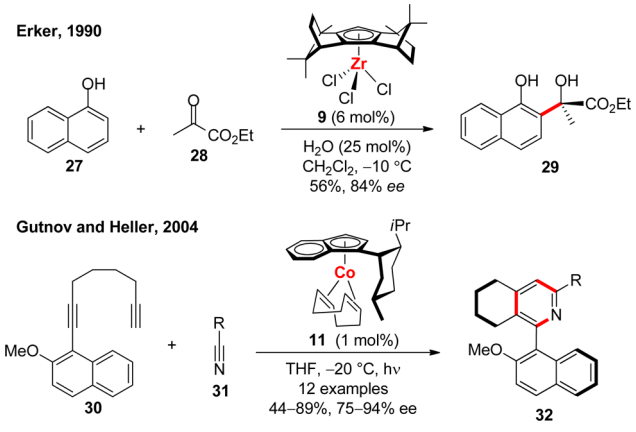
environment is generated *in situ* upon mixing of Cp* biotin-derivative **25**[26] with an engineered streptavidin protein. In comparison to the previously described ligand classes, this artificial metalloenzyme approach allows for effectively limitless optimization of the catalyst structure by means of protein evolution techniques. However, possible variations in reaction parameters like temperature, solvent, and water content of the media are restricted by the stability and solubility of the host protein.

APPLICATION IN ASYMMETRIC CATALYSIS

To date, only a single transformation has been realized for each zirconium,[15] cobalt,[27] scandium,[24] iridium,[21] and ruthenium[22] Cp^x complex. In comparison, $RhCp^x$ complexes have been used in a broader variety of transformations, most frequently with binaphthyl derived ligand family **18**.

The earliest enantioselective applications both employ ligands derived from chiral pool starting materials (Scheme 6). In 1990 Erker published the synthesis of naphthol **29** via the Friedel–Crafts hydroxyalkylation of **27**.[15] Zr-Cp^x complex **9** is believed to act simply as a Lewis acid, activating ethyl pyruvate (**28**) toward an enantioselective nucleophilic addition. Over a

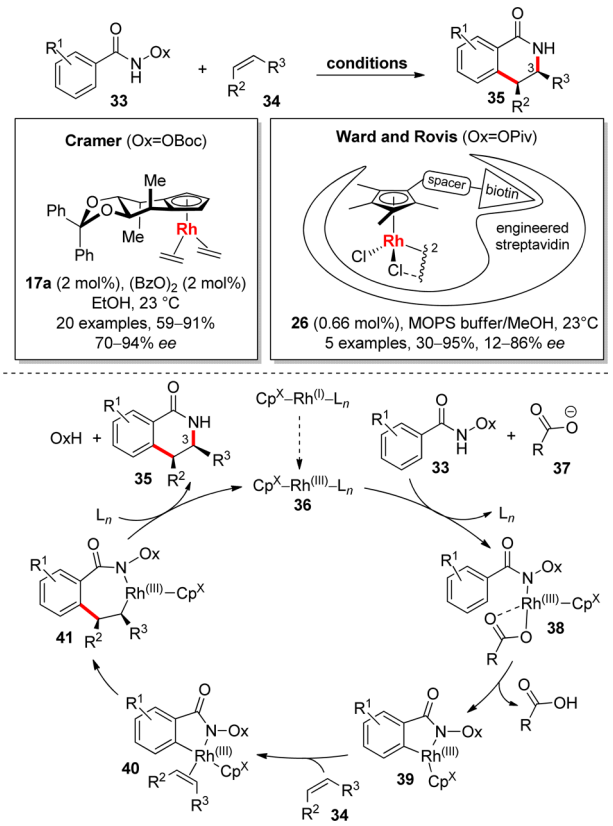
Scheme 6. Early Enantioselective Reactions of Chiral Pool Derived Cp^x Ligands



decade later Gutnov, Heller, and co-workers described the first organometallic reaction of a Cp^x complex. Atropo-enantioselective cyclotrimerization of diyne **30** with nitriles **31** provided the axially chiral pyridines **32** in modest to good yields and enantioselectivities.[27a,c] This methodology could also be applied to the [2 + 2 + 2] cyclotrimerization of propargylic phosphine oxides with 2 equiv of acetylene.[27b] Both Erker and Gutnov's methodologies represent an early proof of concept in the field of Cp^x catalysis, and until recently they remained as intriguing singularities in an otherwise dormant field.[28]

In 2012 both Cramer[18] and Rovis[25] independently disclosed a Rh(III)-catalyzed enantioselective synthesis of dihydroisoquinolones **35** (Scheme 7).[29] The reaction proceeds via a directed

Scheme 7. $Cp^xRh(III)$-Catalyzed Enantioselective C–H Functionalization of Hydroxamic Acid Derivatives



C–H activation of hydroxamates **33**, followed by coupling with olefins **34**. A generalized version of the proposed mechanism is presented at the bottom of Scheme 7.[29a] Coordination of hydroxamate **33** and carboxylate **37** with the active Rh(III) catalyst **36** provides intermediate **38**, which can then participate in a carboxylate-assisted concerted-metalation-deprotonation event.[30] The preferred conformation of the resultant tricoordinate species **39** is controlled by the steric environment of the catalyst, resulting in diastereoselective coordination of olefin **34**. An enantiodetermining migratory insertion at the now stereogenic-at-metal complex **40** yields rhodacycle **41**, which following reductive elimination delivers dihydroisoquinolones **35**. The regioselectivity of the insertion is controlled by the steric bulk of both the Cp moiety and N-Ox substituent,[31] leading to exclusive formation of the C3-substitued regioisomer in both methodologies. Finally, reoxidation of the catalyst to Rh(III) by cleavage of the N–O bond of the internal oxidant

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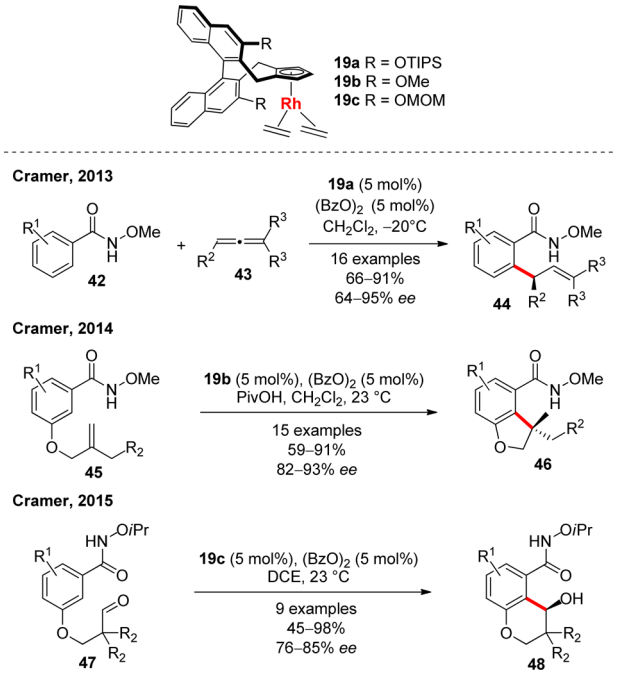
closes the catalytic cycle.[32] The two reported methodologies control the enantioselectivity of the reaction through conceptually complementary means. Specifically, Cramer et al. employ Rh complex **17a**, in which the steric environment of the chiral Cp ligand is in close proximity to the metal, thus dictating which enantiomer of **40** is preferred. This catalyst system allowed for the synthesis of 20 dihydroisoquinolone derivatives in yields up to 91% and in an enantiomeric excess up to 94%. In comparison, Rovis et al. employed their streptavidin-bound RhCp* complex **26**. The strong binding between these two partners creates an artificial Cp*-metalloenzyme equipped with a chiral pocket for enantioselective catalysis to occur. Although the catalyst is coordinated to the protein, the chiral environment is effectively external to the metal complex. In this case, yields varied from 30 to 95%, and enantioselectivities were as high as 86% ee. Notably, the olefin substrate scope is complementary between the two methods: While Cramer's catalyst works best for styrenes, the methodology of Ward and Rovis is best suited to electron-poor acrylates. This behavior can be attributed to the more sterically demanding and electron-rich nature of the Cp* unit in **26**, compared with the disubstituted Cp^x complex **17a**.

The Cramer group have since expanded the scope of two-atom acceptor components (Scheme 8).[19,20,23b] Each of these

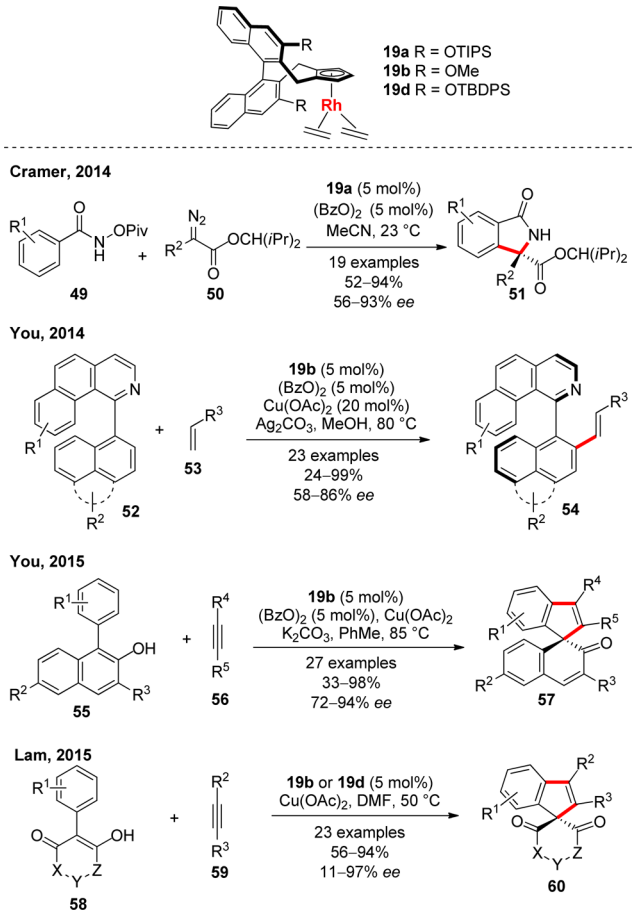
Scheme 8. Mechanistically Related Asymmetric Transformations of Arylhydroxamates Under Cp^{x}Rh(III) Catalysis



transformation is enabled by the binaphthyl derived Rh complex with alkoxy side-chains (**19a–c**) and is believed to proceed via an enantiodetermining migratory insertion of a π-bond moiety. Benzamides **44** were accessed via an intermolecular coupling of *N*-methoxybenzamides **42** with allenes **43**.[19] The reaction is completely selective for the less substituted π-bond, enabling the formation of the allylated products in good yields and with high enantiocontrol. In a subsequent study, dihydrofurans **46** were synthesized by means of an intramolecular cyclization of 1,1-disubstituted olefins **45**.[23a] In this case, C–C bond formation proceeds to form a quaternary stereocenter via a 5-*exo*-trig cyclization. In 2015 the range of suitable π-bond coupling partners was extended to include aldehydes,[20] demonstrating the nucleophilic character of the cyclometalated intermediates.[33] Thus, hydroxychromanes **48** were synthesized from aldehyde precursors **47** in 45–98% yield and up to 85% ee.

The scope of enantioselective C–H functionalization reactions catalyzed RhCp^x complexes **19** has since been extended to allow for carbenoid coupling partners,[23b] the synthesis of axially chiral benzo[*h*]isoquinolines,[34] as well as the synthesis of spirocyclic indene derivatives[35] (Scheme 9).

Scheme 9. Scope of C–H Functionalizations Catalyzed by Binaphthyl-Derived Cp^{x}Rh(III) Complexes



Cramer et al. reported that hydroxamates **49** and diazo derivatives **50** could be coupled to provide isoindolones **51** in good yields. The reaction proceeds via an enantiodetermining carbenoid insertion, and despite the geometric and conformational requirements of this process differing from the examples of two-atom components described earlier, up to 93% ee was still observed with the same ligand scaffold. Later, the You group demonstrated that RhCp^x-complex **19b** could be used for the synthesis of axially chiral molecules.[34] Substituted benzo[*h*]isoquinolines **54** were synthesized via an atropo-enantioselective dehydrogenative Mizoroki–Heck coupling of biaryls **52** with terminal alkenes **53**. With a mixture of $Cu(OAc)_2$ and Ag_2CO_3 as oxidants, the atropisomeric products were accessed in good yields and enantioselectivities. In 2015, two research groups independently disclosed an enantioselective intermo-

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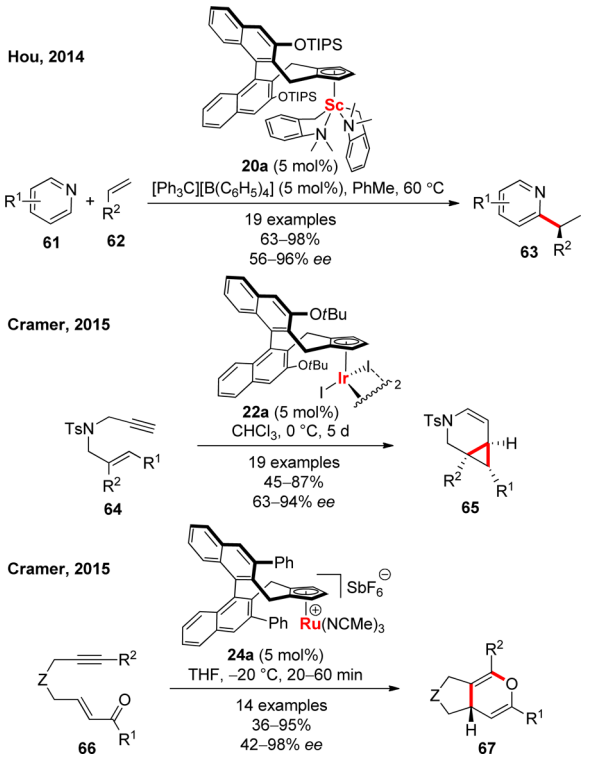
lecular [3 + 2] spiroannulation reaction.[35] You et al. developed a dearomatization strategy toward this structural motif from naphthols **55** and disubstituted alkynes **56**. In comparison, Lam and co-workers synthesized spiroindenes **60** from enols **58** and internal alkynes **59**. Both methodologies were enabled by binaphthyl-derived RhCp^x complex **19**, and both allow efficient access to the spirocyclic motif.

With several published reports of Cp^{x}Rh(III)-catalyzed reactions, recent efforts have been focused on exploiting the potential of the binaphthyl-derived ligands **18** with other transition metals (Scheme 10). In 2014 Hou and co-workers

Scheme 10. Catalytic Enantioselective Reactions of Cp^{x}Sc(III), Cp^{x}Ir(III), and Cp^{x}Ru(II) Complexes



disclosed an enantioselective C–H functionalization of substituted pyridines **61**, employing Sc complex **20a** as catalyst.[24] The strong affinity between **61** and the catalyst was controlled by increasing steric bulk proximate to nitrogen via the introduction of alkyl or halogen substituents. The desired pyridines **63** were isolated in moderate to excellent yields and enantioselectivities. The two most recently reported methodologies do not proceed via a C–H activation event, thus setting them apart from previous reactions catalyzed by complexes of ligand family **18**. In 2015 Cramer et al. described an enantioselective Cp^{x}Ir(III)-catalyzed intramolecular cycloisomerization of enynes **64**.[21,36] In this case, the Cp^x catalyst **22a** is believed to activate the alkyne toward intramolecular nucleophilic addition of the tethered alkene, ultimately leading to cyclopropanes **65**. The second report from the Cramer group[22] details an enantioselective formal hetero Diels–Alder reaction.[37] Yne-enones **66** were cyclized in only minutes at low temperature with the highly reactive phenyl-substituted Cp^{x}Ru(II) complex **24a**, providing pyranes **67** in excellent yields and enantioselectivities. In this methodology, not only could the effect of substitution on the binaphthyl backbone be explored but also the role of the counterion, thus introducing an additional element to catalyst refinement.

CONCLUSIONS AND FUTURE PROSPECTS

To date, three complementary philosophies to Cp^x complexes have been realized (Figure 3). In the earliest examples, the

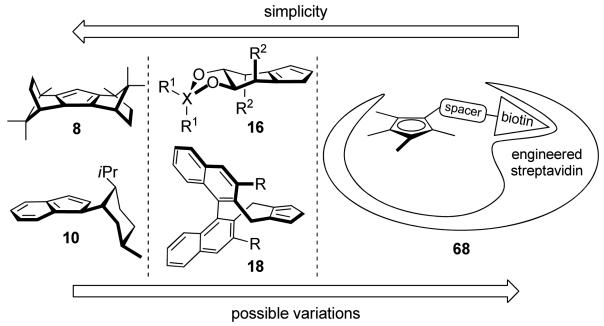


Figure 3. Approaches to chiral Cp^x complexes.

ligands were rapidly assembled from chiral pool starting materials, however, for this very reason they are severely limited in turns of possible structural modifications. At the other end of the spectrum lies the metalloenzyme type catalyst **68**. This significantly more complex scaffold can be adjusted and optimized almost without limit, but its generality has yet to be tested and is presumably less compatible with many standard solvents, or significant changes from ambient reaction temperatures. Somewhere between these two extremes of complexity and accessibility lie the modifiable and modular scaffolds **16** and **18**.

For any chiral ligand family to be branded as truly general, it must provide high levels of enantiocontrol in a variety of mechanistically disparate processes. Currently it is not clear what structural features make any given scaffold widely successful,[38] particularly when considering their applicability in the emerging field of Cp^x catalysis. However, in this context we believe the results presented in this Perspective demonstrate that binaphthyl-derived ligand family **18** shows much promise as a general scaffold. To date, it has been successfully employed as a complex with four different transition metals and has been applied in a variety of mechanistically distinct transformations. In these studies, minor changes at the modifiable positions enabled the optimization of catalyst structure, resulting in high levels of enantiocontrol in each application. The success of scaffold **18** can likely be attributed to a high level of facial discrimination between the two possible tricoordinated species, as exemplified by the schematic representation in Figure 4 (derived from the X-ray structure of complex **19b**).[18] In this example, preferential coordination of the smaller substituent proximate to the methoxy group of the scaffold should be preferred (**69** vs **70**), ultimately controlling the enantioselectivity of the reaction. Interestingly, related biaryl ligand scaffolds, such as BINOL,[1] BINAP,[2] or TRIP,[39] demonstrate just how prevalent this immensely useful motif is in the area of asymmetric catalysis.

As the ligands have yet to be commercialized, their currently lengthy preparation constitutes a barrier to prospective users. However, as they become more widely adopted by the synthetic community, we expect that shorter and more efficient syntheses will be developed. In terms of their complexation chemistry, currently the best method for the synthesis of the

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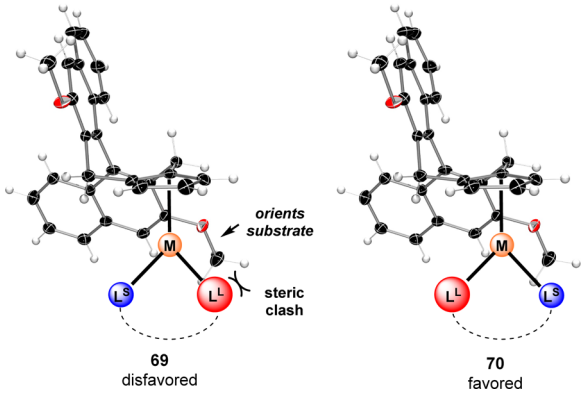

Figure 4. Scaffold control of ligand coordination.

Rh, Ir and Ru-complexes requires toxic thallium salts. Nevertheless, we view this as just a technical hurdle, and the implementation of either more environmentally benign bases or conceptually different complexation strategies should address this problem. A number of additional advancements can be envisioned to make this ligand family truly general. For example, systematic structural modifications at various positions on the ligand scaffold or the development of complexation procedures for additional transition metals will both assist with broadening reaction scope. Further to the discussion of ligand structure, the steric and electronic nature of the Cp^x unit has yet to be investigated in the context of enantioselective catalysis. Notably, several studies exploring the role of Cp substitution with respect to nonenantioselective transformations have demonstrated that reactions can be highly sensitive in terms of reactivity and selectivity to such modifications.[40] In some cases, complete reversal of reaction regioselectivity was observed, underscoring how even seemingly small modifications to an already established ligand scaffold may have much to offer. Practically speaking, the development of most catalytic enantioselective reactions begins with an initial screening of ligand families, followed by ligand fine-tuning and reaction condition optimization. Unquestionably, additional and complementary chiral Cp^x ligand families would be desirable, as no ligand family will be universally suitable. Predictions regarding the design of new ligand scaffolds are difficult to make, and serendipity invariably still plays a central role. Once a satisfactory library of ligands has been established, focus will shift away from ligand development and more toward reaction discovery and optimization. The need to expedite the ligand screening process will become increasingly relevant, and the ability to form the active catalyst *in situ* from the corresponding free Cp^x ligand precursor and an appropriate metal source, in analogy to many chiral phosphine ligands, would be a powerful advancement. The Ward and Rovis metalloenzyme strategy, generated by mixing of Cp complex **25** with an engineered protein, is the only example in this sense. However, Hou's operationally simple synthesis of scandium complex **20** provides tantalizing evidence that a one-pot complexation/reaction procedure may be possible for many Cp^x transition-metal complexes.

In this Perspective we have highlighted recent developments regarding the synthesis chiral Cp^x ligands and their increasing importance as tools for asymmetric catalysis. We hope this record serves not only to introduce readers to this emerging field but also to inspire future research efforts toward harnessing the full potential of chiral Cp^x ligands. We have no doubt that many elegant applications are yet to come.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) Brunel, J. M. *Chem. Rev.* **2005**, *105*, 857.
(2) Noyori, R.; Takaya, H. *Acc. Chem. Res.* **1990**, *23*, 345.
(3) Canali, L.; Sherrington, D. C. *Chem. Soc. Rev.* **1999**, *28*, 85.
(4) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92.
(5) Hartwig, J. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010.
(6) Ye, B.; Cramer, N. *Acc. Chem. Res.* **2015**, *48*, 1308.
(7) Kündig, E. P.; Saudan, C. M.; Viton, F. *Adv. Synth. Catal.* **2001**, *343*, 51.
(8) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186.
(9) Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321.
(10) Trost, B. M.; Rao, M.; Dieskau, A. P. *J. Am. Chem. Soc.* **2013**, *135*, 18697.
(11) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-a.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405.
(12) Negishi, E. I. *Arkivoc* **2011**, 34.
(13) (a) Kuhl, N.; Schröder, N.; Glorius, F. *Adv. Synth. Catal.* **2014**, *356*, 1443. (b) Song, G.; Wang, F.; Li, X. *Chem. Soc. Rev.* **2012**, *41*, 3651. (c) Zhou, M.; Schley, N. D.; Crabtree, R. H. *J. Am. Chem. Soc.* **2010**, *132*, 12550. (d) Satoh, T.; Miura, M. *Chem. - Eur. J.* **2010**, *16*, 11212. (e) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630. (f) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (g) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165.
(14) (a) Halterman, R. L. *Chem. Rev.* **1992**, *92*, 965. (b) Colletti, S. L.; Halterman, R. L. *Organometallics* **1991**, *10*, 3438. (c) Halterman, R. L.; Vollhardt, K. P. C. *Tetrahedron Lett.* **1986**, *27*, 1461.
(15) Erker, G.; van der Zeijden, A. A. H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 512.
(16) Bellus, D.; Ley, S. V.; Noyori, R.; Regitz, M.; Reider, P. J.; Schaumann, E.; Shinkai, I.; Thomas, E. J.; Trost, B. M. *Science of Synthesis—Methods of Molecular Transformations*; Lautens, M., Ed.; Wiley: New York, 2001; Vol. *1*.
(17) Gutnov, A.; Drexler, H.-J.; Spannenberg, A.; Oehme, G.; Heller, B. *Organometallics* **2004**, *23*, 1002.
(18) Ye, B.; Cramer, N. *Science* **2012**, *338*, 504.
(19) Ye, B.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 636.
(20) Ye, B.; Cramer, N. *Synlett* **2015**, *26*, 1490.
(21) Dieckmann, M.; Jang, Y.-S.; Cramer, N. *Angew. Chem.* **2015**, *127*, 12317.
(22) Kossler, D.; Cramer, N. *J. Am. Chem. Soc.* **2015**, *137*, 12478.
(23) (a) Ye, B.; Donets, P. A.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 507. (b) Ye, B.; Cramer, N. *Angew. Chem., Int. Ed.* **2014**, *53*, 7896.
(24) Song, G.; O, W. W. N.; Hou, Z. *J. Am. Chem. Soc.* **2014**, *136*, 12209.
(25) Hyster, T. K.; Knörr, L.; Ward, T. R.; Rovis, T. *Science* **2012**, *338*, 500.

DOI: 10.1021/jacs.5b12964
J. Am. Chem. Soc. 2016, 138, 3935−3941

(26) Reiner, T.; Jantke, D.; Raba, A.; Marziale, A. N.; Eppinger, J. *J. Organomet. Chem.* **2009**, *694*, 1934.
(27) (a) Hapke, M.; Kral, K.; Fischer, C.; Spannenberg, A.; Gutnov, A.; Redkin, D.; Heller, B. *J. Org. Chem.* **2010**, *75*, 3993. (b) Heller, B.; Gutnov, A.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Redkin, D.; Sundermann, C.; Sundermann, B. *Chem. - Eur. J.* **2007**, *13*, 1117. (c) Gutnov, A.; Heller, B.; Fischer, C.; Drexler, H.-J.; Spannenberg, A.; Sundermann, B.; Sundermann, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 3795.
(28) Nugent, W. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 8936.
(29) (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (b) Rakshit, S.; Grohmann, C.; Besset, T.; Glorius, F. *J. Am. Chem. Soc.* **2011**, *133*, 2350.
(30) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.
(31) Wodrich, M. D.; Ye, B.; Gonthier, J. F.; Corminboeuf, C.; Cramer, N. *Chem. - Eur. J.* **2014**, *20*, 15409.
(32) Xu, L.; Zhu, Q.; Huang, G.; Cheng, B.; Xia, Y. *J. Org. Chem.* **2012**, *77*, 3017.
(33) Song, G.; Li, X. *Acc. Chem. Res.* **2015**, *48*, 1007.
(34) Zheng, J.; You, S.-L. *Angew. Chem., Int. Ed.* **2014**, *53*, 13244.
(35) (a) Zheng, J.; Wang, S.-B.; Zheng, C.; You, S.-L. *J. Am. Chem. Soc.* **2015**, *137*, 4880. (b) Reddy Chidipudi, S.; Burns, D. J.; Khan, I.; Lam, H. W. *Angew. Chem., Int. Ed.* **2015**, *54*, 13975.
(36) (a) Benedetti, E.; Simonneau, A.; Hours, A.; Amouri, H.; Penoni, A.; Palmisano, G.; Malacria, M.; Goddard, J.-P.; Fensterbank, L. *Adv. Synth. Catal.* **2011**, *353*, 1908. (b) Watson, I. D. G.; Toste, F. D. *Chem. Sci.* **2012**, *3*, 2899.
(37) Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877.
(38) Yoon, T. P.; Jacobsen, E. N. *Science* **2003**, *299*, 1691.
(39) Parmar, D.; Sugiono, E.; Raja, S.; Rueping, M. *Chem. Rev.* **2014**, *114*, 9047.
(40) (a) Hyster, T. K.; Dalton, D. M.; Rovis, T. *Chem. Sci.* **2015**, *6*, 254. (b) Fukui, M.; Hoshino, Y.; Satoh, T.; Miura, M.; Tanaka, K. *Adv. Synth. Catal.* **2014**, *356*, 1638. (c) Hoshino, Y.; Shibata, Y.; Tanaka, K. *Adv. Synth. Catal.* **2014**, *356*, 1577. (d) Hyster, T. K.; Rovis, T. *Chem. Commun.* **2011**, *47*, 11846.

DOI: 10.1021/jacs.5b12964
J. Am. Chem. Soc. 2016, 138, 3935−3941