Science Bulletin 66 (2021) 210–213

Contents lists available at ScienceDirect

Science Bulletin

journal homepage: www.elsevier.com/locate/scib

Science Bulletin
www.scibull.com

Perspective

Chiral Cp^{x}Rh complexes for C–H functionalization reactions

Quannan Wang, Chen-Xu Liu, Qing Gu, Shu-Li You *

State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Shanghai 200032, China

Transition-metal-catalyzed C–H functionalization is becoming a general and straightforward strategy for the construction of carbon-carbon and carbon-heteroatom bonds in modern organic synthesis. In this regard, ligands often play a key role for the C–H functionalization processes. In addition to those neutral ligands such as phosphorus-type ligands, *N*-heterocyclic carbenes, etc., anionic type ligands derived from substituted cyclopentadienes have also received much attention. Their unique properties, including strong π-donation and stability, are responsible for forming robust Cp^{x}M (M = Co, Rh, Ir, Ru, etc.) catalysts. Moreover, these Cp ligands display superior performance such as enhanced reactivity, improved regioselectivity and diastereoselectivity through the modulation of the electronic and steric properties of the Cp rings.

Given the increasing importance and demand for optically active molecules, much attention has recently been paid to asymmetric Cp^{x}Rh-catalyzed C–H functionalization reactions [1]. To date, there are several strategies to achieve high levels of enantioselectivity in Rh catalysis. These include the utilization of chiral Cp ligands, artificial metalloenzyme modified CpRh, chiral sulfonates, carboxylic acids, and transient chiral directing groups. Among them, the employment of chiral Cp ligands has emerged to be an extremely powerful approach. Therefore, the design and synthesis of chiral Cp ligands now are one of the most intense directions in asymmetric C–H functionalization. In this perspective, we highlight the recent progress on the development of chiral Cp^x ligands and their applications in asymmetric Rh-catalyzed C–H functionalization reactions.

In 2012, Ward, Rovis and co-workers [2] ingeniously synthesized a biotinylated [Cp*Rh(III)] complex and combined it with engineered tetrameric streptavidin (tSav) to create an artificial metalloenzyme for C–H annulation of *N*-(pivaloyloxy)benzamides with alkenes (Scheme 1a). Simultaneously, Cramer group [3] for the first time reported that the rhodium(III) complexes bearing a class of simple C_2-symmetric Cp derivatives proved to be highly efficient for the same type reaction (Scheme 1b). These two reports introduced a new direction for asymmetric Rh-catalyzed C–H functionalization, and various chiral Cp^{x}Rh catalysts have been developed since then (Scheme 2).

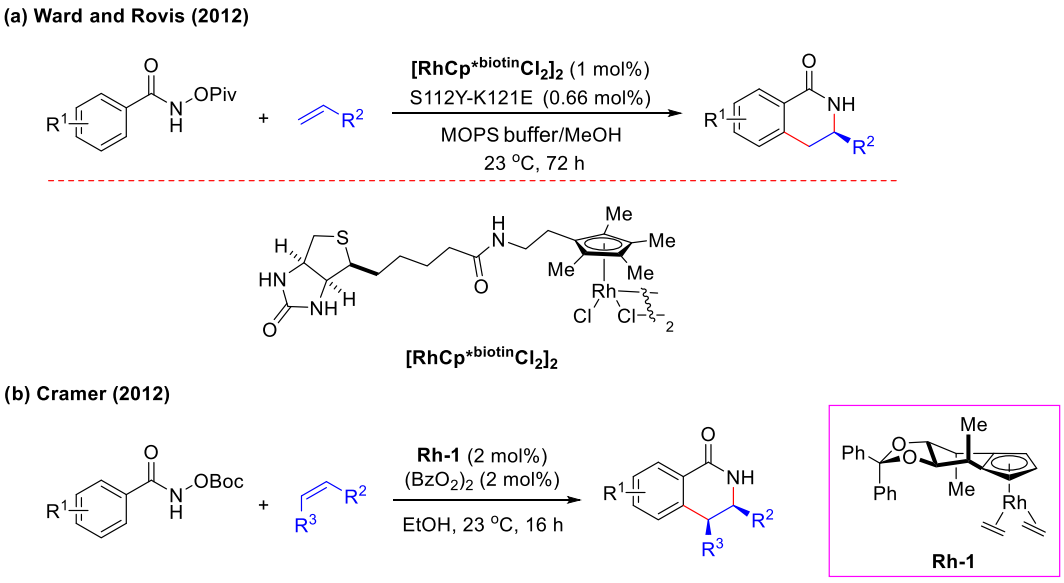
The binaphthyl-derived Cp^{x}Rh complexes. In 2013, the Cramer group [4] reported highly tunable chiral Cp ligands based on binaphthyl backbone (Scheme 2, **I**), which reacted with [Rh$(C_2H_4)_2$Cl]$_2$ leading to chiral Cp^{x}Rh^I complexes. The chiral environment at the metal center originates from both the rigid backwall and the 3,3′-substituents of BINOL-derived Cp ligands. The corresponding Rh complex was used for enantioselective C–H allylation of *N*-methoxybenzamides with allenes under mild conditions with excellent enantioselectivities and good functional group tolerance. The chiral binaphthyl-derived Cp^{x}Rh complexes were also applied for the highly enantioselective synthesis of axially chiral biaryls. In 2019, Li and co-workers [5] realized oxidative coupling of indoles with *o*-alkynylanilines/phenols employing binaphthyl-derived Cp^{x}Rh catalyst for the construction of 2,3′-biindolyls by merging C–H activation with nucleophilic cyclization (Scheme 2a). The reaction proceeded via initial C–H activation, followed by alkyne cyclization. Importantly, the chiral rhodacyclic intermediate was isolated and its crystal structure revealed that the bulky iodide group is disposed distal to the methoxy group of the Cp ligand. To date, the chiral binaphthyl-derived Cp^{x}Rh complexes (**I**) are the most widely used catalysts. However, an apparent drawback for the initial synthesis of these chiral binaphthyl-based Cp^{x}Rh catalysts is the requirement for highly toxic TlOEt reagent. To address this issue, Cramer and co-workers [6] disclosed a convenient and practical complexation method to access chiral Cp^{x}Rh complexes from the free Cp^{x}H with stable and commercially available [Rh(cod)OAc]$_2$ without the addition of base or any additive.

Of particular note, the multi-substituents on the Cp ring exhibited distinct reactivity, chemo- and regioselectivity in C–H functionalization reactions. However, there are only a few reports to investigate the effect of substituents (Me, ^{i}Pr, ^{t}Bu, etc) of the chiral Cp ligands on chemo, regio- and enantioselectivity. Therefore, the development of efficient approach to access tunable multi-substituted chiral cyclopentadienyl ligands is of great significance. Recently, You and co-workers [7] designed a series of chiral binaphthyl-based Cp^{x}Rh (Scheme 2, **II**) bearing multi-substituent groups on the Cp ring to tune the steric and electronic effects, by utilizing $Co_2(CO)_8$-mediated [2 + 2 + 1] cyclization as a key step. Employing such a chiral Cp^{x}Rh bearing trimethyl-substituents on the Cp ring, unprecedented enantioselective [4 + 1] annulation reaction of benzamides and alkenes was achieved, yielding a variety of isoindolinones with excellent regio- and enantioselectivity under mild reaction conditions (Scheme 2b).

The spiro Cp^{x}Rh complexes. 1,1′-Spirobiindane has become a privileged chiral scaffold, pioneered by the Zhou group [8]. In

* Corresponding author.
E-mail address: slyou@sioc.ac.cn (S.-L. You).

https://doi.org/10.1016/j.scib.2020.09.035



Scheme 1. (Color online) Enantioselective [4 + 2] annulation reactions.

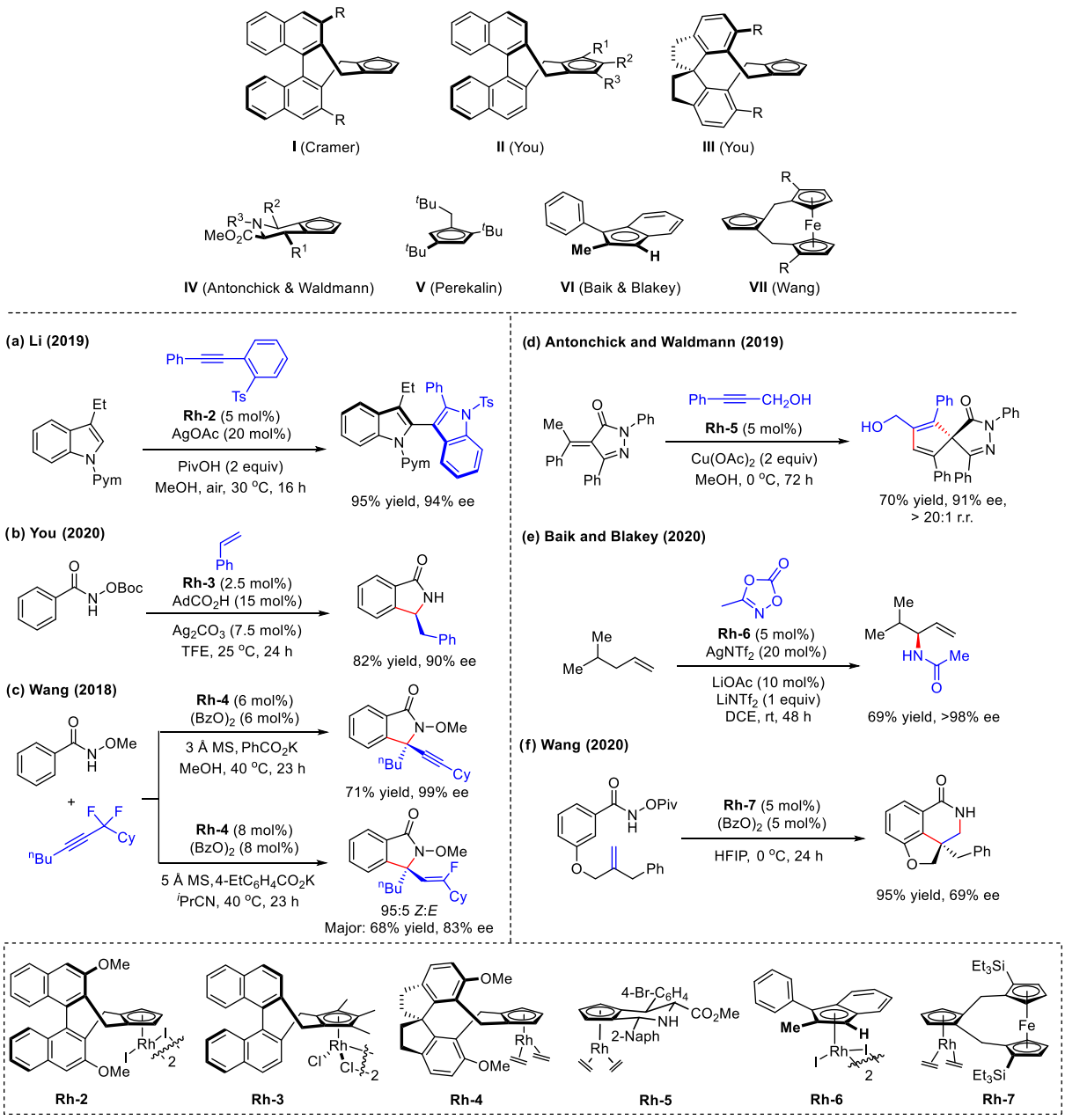
2016, You and co-workers [9] developed a series of novel cyclopentadienyl ligands (SCps) based on 1,1′-spirobiindane scaffold (Scheme 2, **III**). One of their corresponding Rh(I) complexes behaved as a superior catalyst in asymmetric oxidative C–H alkenylation of biaryl derivatives with olefins. Compared with binaphthyl-based Cp^{x}Rh (**I**), the X-ray crystal structure of 3,3′-dimethoxy substituted SCpRh complex revealed that the two methoxy groups as side walls are closer to the Rh center creating a better chiral environment. In 2018, the Wang group [10] reported a solvent-dependent enantioselective synthesis of alkynyl and monofluoroalkenyl isoindolinones from *N*-methoxybenzamides and α,α-difluoromethylene alkynes by C–H activation with the SCpRh catalyst (Scheme 2c). The alkynyl isoindolinones were generated in excellent enantioselectivities by using MeOH as solvent whereas the monofluoroalkenyl isoindolinones were formed in ^{i}PrCN.

The piperidine-fused Cp^{x}Rh complexes. In 2017, Antonchick, Waldmann and co-workers [11] described a three-step gram-scale synthesis of chiral piperidine-fused Cp ligands (Scheme 2, **IV**). Their structure and configuration can be efficiently adjusted by means of flexible enantioselective [6 + 3] cycloaddition reactions. The corresponding Cp^{x}Rh^I complexes have proven to be efficient catalysts for asymmetric C–H functionalization. In 2019, they also described the first enantioselective C(sp^3)–H annulation of α-arylidene pyrazolones with alkynes by using the piperidine-fused Cp^x-Rh catalyst under mild conditions (Scheme 2d) [12]. This method gave access to a class of structurally diverse spiropyrazolones containing an all-carbon quaternary center with high yields and good to excellent enantioselectivity. The synthetic utility of this method was demonstrated by the late-stage functionalization of drugs and natural products as well as the preparation of enantioenriched [3]dendralenes.

The planar chiral Cp^{x}Rh complexes. In 2018, Perekalin and co-workers [13] reported the synthesis of planar chiral Cp^{x}Rh^{III} complex (Scheme 2, **V**). Firstly, the racemic Cp^{x}Rh^{III} complex was prepared from [Rh(cod)Cl]$_2$ in three steps. Subsequently, reaction with natural (*S*)-proline gave a mixture of diastereomeric adducts which were separated by recrystallization without chromatography to afford the single diastereomers. Finally, treatment with aqueous HI generated the chiral Cp^{x}Rh iodide complex as a pure enantiomer in almost quantitative yield. This planar chiral Cp^{x}Rh^{III} complex could effectively promote enantioselective C–H annulation of aryl hydroxamic acids with strained alkenes to give dihydroisoquinolones in high yields and excellent enantioselectivity. At the same time, Baik, Blakey and co-workers [14] reported a novel planar chiral CpRh^{III} complex for regio- and enantioselective amidation of allylic C–H bonds in good yields with excellent regio- and enantioselectivity (Scheme 2e, **VI**). The planar chiral CpRh^{III} can be quickly obtained. The complexation of 2-methyl-3-phenylindene with [Rh(cod)Cl]$_2$ provided a racemic mixture of the planar chiral CpRh^I complex. The subsequent optical resolution by chiral HPLC gave the pure enantiomers. The chiral CpRh^{III} complex was synthesized via oxidation of the corresponding CpRh^I complex.

In 2020, Wang group [15] developed a novel class of C_2-symmetric Cp ligands (FcCp) based on ferrocene backbone, which was synthesized in 5–7 steps from ferrocene (Scheme 2, **VII**). A series of corresponding chiral CpRh^I, CpIr^I, and CpRu^{II} complexes were reported, and the X-ray crystallographic analysis of the CpRh^I and CpRu^{II} complexes indicated that the chiral ferrocenyl moieties fold somewhat away from the metal centers. The corresponding rhodium(I) complexes were tested in the asymmetric intramolecular amidoarylation, providing excellent reactivity and moderate enantioselectivity (Scheme 2f).

Over the past several years, the development of chiral Cp^{x}Rh-catalyzed asymmetric C–H functionalization reactions has progressed rapidly. A variety of chiral cyclopentadiene ligands such as cyclohexane-fused Cp, binaphthyl-based Cp, piperidine-fused Cp, and planar chiral Cp were developed. In addition, a number of chiral Cp^{x}M-catalysts such as Ru, Ir, and Co have been successfully applied for enantioselective C–H functionalization reactions. Despite of these notable progresses achieved, the development of chiral Cp^{x}Rh-catalyzed asymmetric C–H functionalization remains a challenge. The following aspects will be the future development direction. Firstly, the tedious synthetic routes and manipulations for chiral Cp ligands and their Rh complexes hamper further applications. For example, the synthesis of chiral binaphthyl-derived Cp^{x}Rh complexes (**I**) requires at least nine steps from BINOL. Therefore, optimization of synthetic routes of the known Cp ligands is highly desirable in order to improve the practical utility. In addition, the development of efficient and concise synthesis of new chiral Cp ligands will be an important research topic. Secondly, traditional method for the synthesis of the chiral Cp^{x}Rh complexes requires the use of toxic reagents such as the thallium salt.



Scheme 2. (Color online) Cyclopentadienes and their applications in Rh-catalyzed C–H functionalization reactions.

Although an improved complexation approach for the synthesis of specific chiral CpRh complexes has been developed, more practical and general methods, employing only environmentally benign reagents need to be developed with the discovery of new Cp ligands. Thirdly, the stereoselective model and reaction mechanism for Rh-catalyzed asymmetric C–H functionalization remain unclear in most cases. Particularly, the critical role of the substituents on the Cp ring in controlling the reactivity and selectivity requires more investigation on the basis of systematic experimental and theoretical studies, which could guide the rational design of catalysts and C–H functionalization reactions with high efficiency and selectivity. Fourthly, compared with Cp^xRh-catalyzed asymmetric C(sp^2)–H functionalization, the C(sp^3)–H functionalization reactions are less studied, and more challenging. The employment of appropriate directing groups and catalytic systems will likely provide a solution to address this issue. Finally, future studies on the functionality oriented asymmetric C–H functionalization reactions will be directed to construct valuable molecules with potential application in both materials and medicinal chemistry. Notably, the artificial metalloenzyme strategy, mixing of an achiral Cp^*Rh complex with an engineered protein, may offer an effective asymmetric C–H functionalization with practical reactivity and selectivity, but it remains infancy to date.

In this perspective, we have highlighted recent developments on the synthesis of Cp^x ligands and their applications in Rh-catalyzed asymmetric C–H functionalization reactions. We hope this perspective would give an introduction of this emerging field and inspire more future research efforts toward harnessing the full

potential of chiral Cp^x ligands. We have no doubt that many elegant syntheses and applications of chiral Cp^x are yet to come.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (21821002, 91856201), and the Science and Technology Commission of Shanghai Municipality (18JC1411302).

References

[1] Yoshino T, Satake S, Matsunaga S. Diverse approaches for enantioselective C-H functionalization reactions using group 9 Cp^xM^{III} catalysts. Chem Eur J 2020;26:7346–57.
[2] Hyster TK, Knorr L, Ward TR, et al. Biotinylated Rh(III) complexes in engineered streptavidin for accelerated asymmetric C–H activation. Science 2012;338:500–3.
[3] Ye B, Cramer N. Chiral cyclopentadienyl ligands as stereocontrolling element in asymmetric C–H functionalization. Science 2012;338:504–6.
[4] 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;135:636–9.
[5] Tian M, Bai D, Zheng G, et al. Rh(III)-catalyzed asymmetric synthesis of axially chiral biindolyls by merging C–H activation and nucleophilic cyclization. J Am Chem Soc 2019;141:9527–32.
[6] Audic B, Wodrich MD, Cramer N. Mild complexation protocol for chiral Cp^xRh and Ir complexes suitable for in situ catalysis. Chem Sci 2019;10:781–7.
[7] Cui W-J, Wu Z-J, Gu Q, et al. Divergent synthesis of tunable cyclopentadienyl ligands and their application in Rh-catalyzed enantioselective synthesis of isoindolinone. J Am Chem Soc 2020;142:7379–85.
[8] Xie J, Zhou Q. Magical chiral spiro ligands. Acta Chim Sin 2014;72:778–97.
[9] Zheng J, Cui W-J, Zheng C, et al. Synthesis and application of chiral spiro Cp ligands in rhodium-catalyzed asymmetric oxidative coupling of biaryl compounds with alkenes. J Am Chem Soc 2016;138:5242–5.
[10] Li T, Zhou C, Yan X, et al. Solvent-dependent asymmetric synthesis of alkynyl and monofluoroalkenyl isoindolinones by $CpRh^{III}$-catalyzed C–H activation. Angew Chem Int Ed 2018;57:4048–52.
[11] Jia Z-J, Merten C, Gontla R, et al. General enantioselective C–H activation with efficiently tunable cyclopentadienyl ligands. Angew Chem Int Ed 2017;56:2429–34.
[12] Li H, Gontla R, Flegel J, et al. Enantioselective formal $C(sp^3)$–H bond activation in the synthesis of bioactive spiropyrazolone derivatives. Angew Chem Int Ed 2019;58:307–11.
[13] Trifonova EA, Ankudinov NM, Mikhaylov AA, et al. 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;57:7714–8.
[14] Farr CMB, Kazerouni AM, Park B, et al. Designing a planar chiral rhodium indenyl catalyst for regio- and enantioselective allylic C–H amidation. J Am Chem Soc 2020;142:13996–4004.
[15] Liang H, Vasamsetty L, Li T, et al. A new class of C_2-symmetric chiral Cp ligand derived from ferrocene scaffold: design, synthesis and application. Chem Eur J 2020;26:14546–50.

Quannan Wang received his B.Sc. degree from Hefei University of Technology in 2014. He obtained his Ph.D. degree from Dalian Institute of Chemical Physics (DICP), Chinese Academy of Sciences in 2019 under the supervision of Prof. Zhengkun Yu. In 2020, he joined Prof. Shu-Li You's group for postdoctoral studies. His current research interest focuses on asymmetric C–H functionalization.

Chen-Xu Liu received his bachelor degree (2017) in Applied Chemistry from Donghua University under the supervision of Prof. Yong-Fen Xu. And now he is a Ph.D. candidate in the group of Prof. Shu-Li You. His research interest focuses on the construction of new chiral skeletons via asymmetric C–H activation.

Qing Gu obtained his master and Ph.D. degrees from East China University of Science and Technology (ECUST) in 2005 and 2008, respectively. He carried out his postdoctoral research at Shanghai Institute of Organic Chemistry (SIOC), Chinese Academy of Sciences, from 2009 to 2011 and at Georg-August-University of Göttingen from 2012 to 2013. In 2011, he joined SIOC as an associate professor. His current research interest includes asymmetric catalysis and C–H bond functionalization.

Shu-Li You received his B.Sc. degree in Chemistry from Nankai University (1996). He then obtained his Ph.D. degree from SIOC, Chinese Academy of Sciences in 2001 under the supervision of Prof. Lixin Dai before doing postdoctoral studies with Prof. Jeffery Kelly at the Scripps Research Institute. From 2004, he worked at the Genomics Institute of the Novartis Research Foundation as a PI before returning to SIOC as a professor in 2006. He is currently the deputy director of SIOC and director of the State Key Laboratory of Organometallic Chemistry. His research interest mainly focuses on asymmetric C–H functionalization and catalytic asymmetric dearomatization (CADA) reactions.