Recent Advances in Enantioselective Direct C–H Addition to Carbonyls and Michael Acceptors#

Qing Gu,#1 Zhi-Jie Wu,1,2 and Shu-Li You,#1,2

1State 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, 345 Lingling Lu, Shanghai 200032, P. R. China
2School of Physical Science and Technology, ShanghaiTech University, 100 Haike Road, Shanghai 201210, P. R. China
E-mail: qinggu@sioc.ac.cn (Q. Gu), slyou@sioc.ac.cn (S.-L. You)

Received: November 5, 2020; Accepted: November 29, 2020; Web Released: December 5, 2020

Qing Gu
Qing Gu obtained his master’s and PhD degree 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) 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 interests include asymmetric catalysis and C–H bond functionalization.

Zhi-Jie Wu
Zhi-Jie Wu received his bachelor degree in chemistry from Hebei University under the supervision of Prof. Sheng-Hui Li (2016). He is currently a PhD candidate in the group of Prof. Shu-Li You. His research interests focus on asymmetric C–H functionalization.

Shu-Li You
Shu-Li You received his BSc in chemistry from Nankai Univ. (1996). He then obtained his PhD from Shanghai Institute of Organic Chemistry (SIOC) 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 interests mainly focus on asymmetric C–H functionalization and catalytic asymmetric dearomatization (CADA) reactions.

Abstract
Enantioselective C–H addition is one of the most straightforward and efficient approaches towards the synthesis of optically active molecules from readily available arenes. The most significant feature of these reactions is that the nucleophilic aryl metal species is generated catalytically in situ via C–H bond activation. These reactions typically proceed without requirement of either strongly basic or acidic conditions, thus with good functional group compatibility. In this review, recent progress on transition-metal-catalyzed enantioselective direct C–H addition to polar unsaturated bonds is summarized. The intramolecular C–H additions to carbonyls enabled by Ir(I) or Rh(III) catalyst provided an access to chiral alcohol scaffolds with high efficiency. Planar chiral 1,2-substituted ferrocenes were afforded by C–H addition of ferrocenes to acrylates by an Ir/chiral diene catalyst. In addition, the asymmetric hydroarylation reactions of Michael acceptors including acrylates, α, β-unsaturated esters and nitroolefins were also described.
Moreover, the enantioselective conjugate additions of aromatic and benzylic C-H bonds to α, β-unsaturated ketones catalyzed by Cp*M(III)/chiral acid hybrid catalyst (M = Rh, Co) were presented. These enantioselective C-H additions provided a straightforward access to structurally diverse and valuable chiral fragments. Meanwhile, the reaction mechanisms are also introduced.

**Keywords**: Asymmetric catalysis | C–H addition | Polar unsaturated bond

### 1. Introduction

In the past few years, transition-metal-catalyzed direct C-H addition to polar unsaturated bonds C= X (X = O, N, C) such as aldehydes, ketones, imines and electron-deficient alkenes has emerged as a powerful tool for the formation of carbon–carbon bonds. Compared with classical nucleophilic addition reaction by employing organometallic reagents (Scheme 1a), transition-metal-catalyzed direct C-H addition greatly reduces tedious manipulations and unwanted chemical wastes (Scheme 1b). Notably, this approach is atom-economic (100% atom efficiency) and particularly valuable when the organometallic reagent is difficult to prepare or air- and moisture-sensitive. Moreover, the C–H addition reaction usually proceeds with good functional group compatibility mainly because of its relatively mild reaction conditions. Therefore, all these advantages and features make the direct C-H addition reactions highly attractive. The proposed catalytic cycle exemplified by the addition of arene C-H to α, β-unsaturated carbonyl compound is shown in Figure 1. The nucleophilic species (I) is generated catalytically *in situ* via C–H bond activation, releasing one equivalent of proton simultaneously. Subsequent migratory insertion of the M–C bond into C= C bond generates intermediate II. Protonolysis of II releases the conjugate addition product and regenerates the metal catalyst.

In the past decade, numerous achievements have been made with transition-metal-catalyzed C-H additions to unsaturated C= X bonds in a racemic manner. These works have been extensively reviewed. Therefore, only brief discussion on this topic will be provided in this review. In recent years, rapid advances on enantioselective C-H addition have also been made with the development of efficient catalytic systems. Enantioselective C-H addition undoubtedly represents one of the most straightforward and efficient approaches towards the synthesis of optically active molecules from low cost hydrocarbons. Hence, a timely review for discussing these latest developments in this fast-growing field is highly desirable. In this article, advances in this important area are reviewed. To be noted, transition-metal-catalyzed asymmetric C–H alkylation with simple alkenes and enantioselective addition of terminal alkynes to polar unsaturated bonds are not included.

#### 2. Enantioselective C-H Bond Addition to Carbonyl

Direct nucleophilic addition of C-H bond to carbonyls via transition-metal-catalyzed C-H bond activation provides a concise and efficient pathway to synthesize alcohols. In 2009, Shibata and co-workers reported an asymmetric intramolecular addition of 2-oxo-N-phenylpropanamide C-H bond to ketone in the presence of a cationic Ir/(S)-H₆-BINAP catalyst. This cyclization reaction of the *meta*-substituted precursors predominantly occurred at the sterically more hindered *ortho* position, giving chiral oxindole product bearing a quaternary carbon center in 69% yield with 72% ee (Scheme 2). This reaction is a pioneering example of enantioselective direct C-H addition to ketone, and there is still room for improvement in terms of reaction efficiency and selectivity.

In 2014, Yamamoto and coworkers developed an Ir-catalyzed highly enantioselective intramolecular hydroarylation reaction of α-ketoamides. They found the reaction of α-ketoamide with a dimethyl amino carbonyl directing group could give a series of optically active 3-substituted 3-hydroxy-...
2-oxindoles in up to 99% yield with 98% ee by using [Ir(cod)_2]BF_4 and chiral O-linked bidentate phosphanimine ((R, R)-Me-BIPAM) as the catalyst (Scheme 3). To be noted, all reactions occurred at the sterically more hindered ortho position to the carbonyl group to achieve exclusive regioselectivity. A plausible catalytic cycle is proposed as depicted in Figure 2. Firstly, the C–H bond of a-ketoamide is cleaved in the presence of a cationic active species, which is generated from [Ir(cod)_2]BF_4 and (R, R)-Me-BIPAM in situ, giving aryliridium intermediate I. At this stage, there is an equilibrium between complexes I and II, and the latter is coordinated with the two carbonyl groups of the amide and ketone. Subsequently, asymmetric nucleophilic addition to the carbonyl group affords iridium alkoxide species III. Finally, reductive elimination occurs to give addition product and regenerate the active catalytic species. Kinetic experiments suggest that the turnover-limiting step of this reaction is more closely related to the insertion of a carbonyl group into the aryliridium intermediate.

Planar chiral ferrocenes represent one class of highly efficient and widely used ligands or catalysts in asymmetric catalysis. Thus, much attention has been paid to the efficient introduction of planar chirality to the ferrocene backbone. In 2014, Shibata and Shizuno developed an Ir/chiral diene-catalyzed asymmetric C–H addition of ferrocene to acrylate using an isoquinolin-2-yl directing group, giving 1,2-planar chiral adduct in 88% yield with 90% ee (Scheme 4). This reaction was also feasible with methyl vinyl ketone, albeit in 83% yield with 75% ee. A preliminary investigation suggested that both C–H bond cleavage process and insertion of alkene were likely reversible.

Chiral cyclopentadienyl (Cp)-based metal complexes have emerged as powerful and robust catalysts for asymmetric C–H functionalization in recent years since the pioneering works by Ward and Rovis, and Cramer independently. In this regard, the enantioselective addition of aryl C–H bond to carbonyl group is rarely studied due to the intrinsic low reactivity of aldehyde, except for several Ir(I)-catalyzed reactions with limited substrate scope. In 2015, Cramer and coworkers reported a Rh(III)-catalyzed intramolecular enantioselective C–H addition to aldehydes, and hydroxychromanes were obtained in 80% yield and 84% ee under mild conditions (Scheme 5).

### 3. Enantioselective C–H Bond Addition to Michael Acceptors

Hydroarylation of alkene involving addition of aromatic C–H bond to unsaturated compounds has the feature of atom- and step-economy. Styrenes and alkenyl ethers are mostly employed as the alkene components, however, asymmetric hydroarylation reactions of α, β-unsaturated carbonyl compounds, considered as a Michael addition reaction, are less studied. In 2015, Rovis and coworkers reported the first example of Rh(I)-catalyzed asymmetric C–H addition of benzoxazoles to acrylate derivatives. In the presence of [Rh(cod)OAc]_2 and bulky bisphosphine ligand (CTH-(R)-xylil-P-Phos), the reaction delivered diverse alkylated benzoxazole products in 31–98% yields with 68–96% ee (Scheme 6). The catalytic cycle was...
also proposed as depicted in Figure 3. Firstly, reversible C–H activation of heteroarene provides Rh–heteroaryl complex I. Migratory insertion to the acrylate affords Rh–enolate II, which isomerizes via β-H elimination and subsequent insertion to yield heterobenzyl-Rh IV. Finally, it is protonated by acetic acid to liberate the adduct. It should be noted that protonation appears to occur predominantly from heterobenzyl-Rh IV in this process, which is different from those of Rh(I) catalyzed hydroarylation with boronic acids. Therefore, isomerization of Rh–enolate II to Rh–heterobenzyl species IV ensures that α-stereocenter does not undergo epimerization. Mechanistic studies suggest that either migratory insertion or β-hydride elimination is the enantio-determining step.10

Apart from Rh(I) catalysis, Shibata and coworkers in 2017 reported an Ir-catalyzed enantioselective reaction of acetonilides with α, β-unsaturated esters by using cationic Ir-chiralphos or Ir-difluorphos catalyst. This approach provided direct access to chiral β-aryl substituted propanoates in high yields with good to excellent enantioselectivity (up to 99% ee). The utility of this method was demonstrated by diverse transformations of the products. For example, hydrolysis of the adduct readily afforded the known chiral δ-lactam in 98% yield and subsequent reduction by BH3-THF gave chiral tetrahydroquinoline in 62% yield (Scheme 7).11

This strategy could be further extended to intramolecular enantioselective C–H conjugate addition to β-substituted α, β-unsaturated esters. The chiral γ-lactones bearing a quaternary all-carbon stereogenic center were obtained in up to 98% yield and 97% ee in the presence of [Ir(cod)2]OTf and (S)-BINAP (Scheme 8).12

Nitroolefin is one of the most frequently used Michael acceptors due to its high electrophilicity and the diverse transformations of the nitro group. In 2017, the Ellman group pioneered a Rh(III)-catalyzed aryl C–H addition to nitroalkenes displaying a broad substrate scope. By utilizing the Cramer chiral cyclopentadienyl ligand based Rh-diodo dimer as the catalyst,10,13 the enantioselective variant was achieved in moderate yields and enantioselectivity (60–73% yields, 68–82% ee) (Scheme 9). This work provides a new general strategy for catalytic asymmetric addition to nitroalkenes.14

Inspired by Xu’s work on Rh(III)-catalyzed C–H bond annulation of N-methoxybenzamides with quinones,15 Wang and coworkers achieved an enantioselective variant of this C–H reaction by employing chiral spiro-CpRh (ScPPh) as the catalyst.16 This reaction proceeded via Rh-catalyzed C–H conjugate addition to α, β-unsaturated ketone and subsequent intramolecular nucleophilic addition to the carbonyl group, affording chiral tricyclic hydrophenanthridinones in up to 88% yield and 94% ee (Scheme 10).17 In this reaction, benzoquinone acted as

![Scheme 6. Rh(I)-catalyzed asymmetric C-H addition of benoxazoles to acrylate derivatives.](image)

![Figure 3. Proposed catalytic cycle.](image)

![Scheme 7. Ir-catalyzed enantioselective reaction of acetonilides with α, β-unsaturated esters.](image)
not only the Michael acceptor but also the oxidant to convert SCpRh(I) to the corresponding active species SCpRh(III).

Despite the rapid development of catalytic asymmetric C-H functionalization reactions using chiral cyclopentadiene-metal complexes, these chiral Cp ligands usually require tedious synthetic steps and manipulations, impeding the synthetic application of these methods.\(^\text{18}\) The combination of achiral Cp\(^*\)M(III) and chiral acid such as disulfonate or carboxylic acid has offered an alternative approach to enantioselective C-H functionalization reactions. In these cases, the enantioselectivity is induced by the chiral anion. In 2018, Yoshino, Matsunaga and coworkers ingeniously developed an enantioselective conjugate addition of aromatic C-H bond to \(\alpha, \beta\)-unsaturated ketones catalyzed by Cp\(^*\)Rh(III)/BINSate (BINSate = 1,1'-binaphthyl-2,2'-disulfonate), which was readily prepared by treatment of (S)-1,1'-binaphthyl-2,2'-disulfonic acid ((S)-BINSA) with Ag\(_2\)CO\(_3\), followed by [Cp\(^*\)RhCl\(_2\)]\(_2\) in CH\(_3\)CN. Various addition products were obtained with good enantioselectivity (up to 95:5 er) in the presence of a catalytic amount of 2-methylquinoline (Scheme 11). This hybrid catalytic system displayed good functional group compatibility. The proposed catalytic cycle is shown as depicted in Figure 4. The rhodacycle intermediate (III) is generated after C-H bond activation via a concerted metalation deprotonation (CMD) mechanism or aromatic electrophilic substitution. The bisulfonic acid serves as a chiral proton source and participates in the protonation. Subsequent reversible insertion of enone leads to two enantiomeric intermediates (IV and IV'), followed by selective protonation to provide the product in an enantioselective manner. However, it is also possible that the BINSate serves as a chiral counteranion to construct a chiral environment for enantioselective insertion of \(\alpha, \beta\)-unsaturated ketone to afford IV, subsequently leading to the desired product.\(^\text{19}\)

Subsequently, the same group further realized enantioselective 1,4-addition reactions of indoles to maleimides by employing a combination of achiral Cp\(^*\)Co(III)/chiral carboxylic acid. The corresponding products were obtained in up to 99% yield and 81:19 er (Scheme 12). A similar mechanism was
Figure 4. Proposed catalytic cycle.

Scheme 12. Enantioselective 1,4-addition reaction of indoles to maleimides.

Scheme 13. Enantioselective C-H addition of 8-ethylquinolines to enones.

been summarized. The enantioselective C-H bond addition to carbonyls and Michael acceptors could be catalyzed by Ir(I)/chiral P ligand, Rh(I)/chiral P ligand, chiral Cp-Rh(III) complex or achiral Cp*M(III)/chiral acid hybrid catalyst. These reactions provide a straightforward access to optically active molecules from readily available arenes. Notably, these reactions typically occur without the utilization of either strong acid or base additive, and therefore usually proceed with excellent functional group compatibility.

While the achievements made to date are notable, work in this field is still in its infancy. The stereoselective mechanism in some cases such as hybrid catalysis remains unclear. The efficiency and selectivity of the reported reactions need to be further improved by developing more efficient catalytic systems. Apart from carbonyls and Michael acceptors, the enantioselective C-H bond additions involving other type of electrophiles are highly desirable and remain underexplored. Undoubtedly, future studies on functionality-oriented asymmetric

4. Conclusion and Prospect

In this review, recent developments on transition-metal-catalyzed enantioselective direct C-H addition reactions have
C–H addition will be directed to construct valuable molecules in material and medicinal chemistry.

We thank the National Key R&D Program of China (2016YFA0202900), National Natural Science Foundation of China (21821002, 91856201, 22071260), the CAS (XDB20000000) and Science and Technology Commission of Shanghai Municipality (18JC1411302, 19590750400) for generous financial support.

References

# Dedicated to Professor Eiichi Nakamura on the occasion of his 70th birthday.


