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Recent development of direct asymmetric functionalization of inert C–H bonds

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The area of direct asymmetric functionalization of inert C–H bonds has attracted considerable attention in recent years. To realize this type of challenging but promising transformations, a lot of strategies have emerged including asymmetric C–H bond insertion by metal carbenoids or analogs, cross dehydrogenative coupling, [1,5]-hydride transfer, C–H bond functionalization involving a transient metal–carbon species and other miscellaneous methods. This review is intended to summarize and discuss the most recent developments (contributions mainly after 2009) within this area.

1. Introduction

The direct functionalization of inert C–H bonds is of great importance in modern synthetic organic chemistry.[1] To employ the simple hydrocarbon compounds, which are abundant and cheap chemical feedstocks as the starting materials for the versatile chemical synthesis without "pre-activation", makes the direct functionalization of inert C–H bonds meet the criteria of both atom economy[2] and step economy.[3] Therefore, this research area has received continuous attention and witnessed significant development in the last several decades. A large amount of catalytic systems including well-defined organometallic complexes, small molecular organocatalysts as well as enzymes have been proved effective for enabling the direct transformations of various inert C(sp^2)–H and C(sp^3)–H bonds. In addition, the emergence of these methodologies provides unprecedented disconnections in the retro-synthetic analyses of complex target molecules. Many elegant applications of the direct functionalization of inert C–H bonds in the total syntheses of natural products, molecules of pharmaceutical interests as well as diverse functional molecules have been reported in the literature.[4] However, a principle challenge still accompanied with the high-speed development of this area is the issue of selectivity.[5] Firstly, since the C–H bonds are the most fundamental and frequently encountered chemical bonds in organic molecules, to distinguish the reactivity among the numerous C–H bonds in one single molecule to achieve high level of regio- and enantioselectivity is certainly more difficult than traditional asymmetric catalysis which is in general the manipulation of functional groups. Secondly, due to the fact that the C–H bonds are among the strongest chemical bonds

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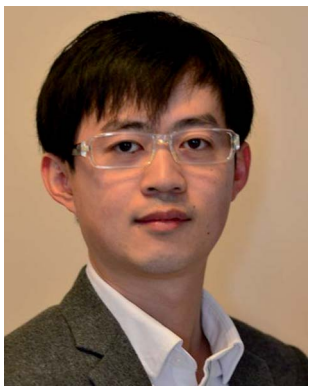

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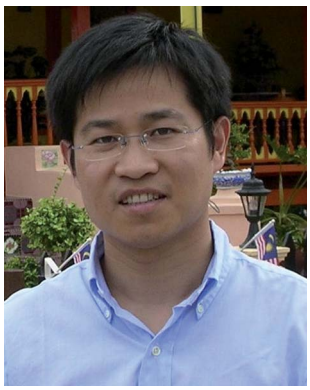


Dr Shu-Li You received his BSc in chemistry from Nankai University in 1996. He obtained his PhD from the Shanghai Institute of Organic Chemistry (SIOC) in 2001 under the supervision of Prof. Li-Xin Dai before doing postdoctoral studies with Prof. Jeffery W. Kelly at The Scripps Research Institute. From 2004, he worked at the Genomics Institute of the Novartis Research Foundation as a Principal Investigator before returning to SIOC in 2006. His research interests include asymmetric catalysis, synthetic methodology, natural product synthesis, as well as medicinal chemistry.

(BDE of C–H bonds are typically 90–110 kcal mol^{-1}), harsh reaction conditions (high temperature, stoichiometric amount of oxidants, *etc.*) are usually required for the cleavage and direct functionalization of these inert bonds, which poses a problem in discriminating the diastereomeric transition states during the asymmetric catalysis. Thirdly, chiral ligands and catalysts compatible with the complex reaction conditions are limited and novel catalytic systems and strategies for the direct asymmetric functionalization of inert C–H bonds are still in great demand.

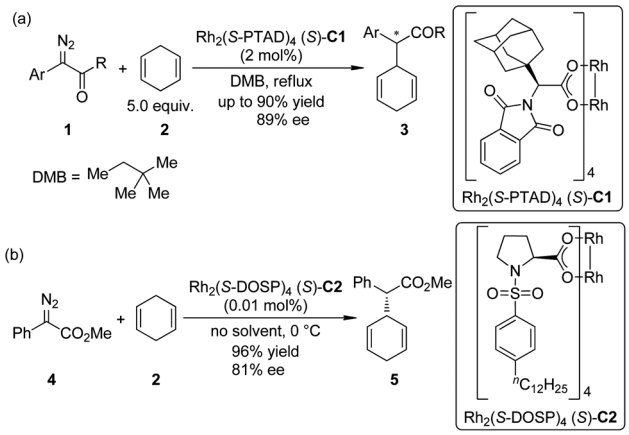
Despite the aforementioned obstacles, the journey to pursuit the direct asymmetric functionalization of inert C–H bonds has already led to fruitful results in recent years. In 2009, Yu and co-workers[5a] published a comprehensive review discussing the diastereoselective and enantioselective transition metal-catalyzed C–H bond activation reactions. In the past five years, dozens of excellent works on the direct asymmetric functionalization of inert C–H bonds with high efficiency and largely broadened substrate scope have appeared, which definitely refreshed on our impression on this subject. Hence, a timely review collecting and discussing the most recent development in this exciting and fast developing field is highly desired. In this review, we are trying to give the readers an overview of the state-of-the-art of the methodologies (contributions mainly after 2009) for the direct *catalytic asymmetric* functionalization of inert C–H bonds. The reactions are classified according to the strategies and the catalytic systems employed. The suggested mechanistic scenarios for the novel transformations are also briefly described. To be noted, this review does not cover the asymmetric functionalization of the aldehyde C–H bond *via* hydroacylation reactions[6] and *N*-heterocyclic carbene (NHC)-catalyzed umpolung reactions,[7] as well as the asymmetric functionalization of the allylic and benzylic C–H bonds *via* dienamine or trienamine catalysis.[8]

2. C–H bond insertion by metal carbenoids or related species

2.1. C–H bond insertion by metal carbenoids

The asymmetric insertion of metal carbenoids into C–H bonds are probably the relatively more traditional type of methods to realize the direct asymmetric functionalization of inert C–H bonds compared with other ones presented in this review.[9] Chiral complexes of several transition metals including Rh, Ir, Cu and Fe are typically employed in this type of transformations. α-Diazocarbonyl compounds are the most widely used carbene precursors.

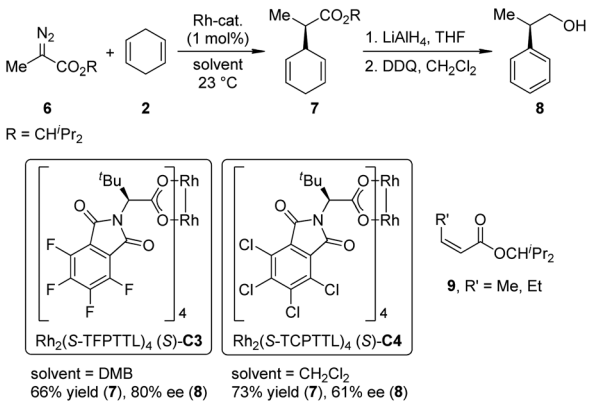
In 2009, Denton and Davies[10] reported that the donor/acceptor carbenoids[11] derived from α-aryl-α-diazoketones **1** and a chiral dirhodium complex Rh_2(*S*-PTAD)$_4$ (*S*)-**C1** could insert enantioselectively into the allylic C–H bonds of 1,4-cyclohexadiene **2** in refluxing 2,2-dimethylbutane (DMB) in up to 90% yield and 89% ee (Scheme 1(a)). (In this review, we use the numbers with a prefix "**C**" to denote the chiral catalysts or reagent, and "**L**" to denote the chiral ligand.) After realizing that the destroy of the chiral catalyst by the reactive carbenoids might be the major hindrance for achieving very high catalyst



Scheme 1 The asymmetric C–H bond insertion reactions of dirhodium carbenoids reported by Davies.

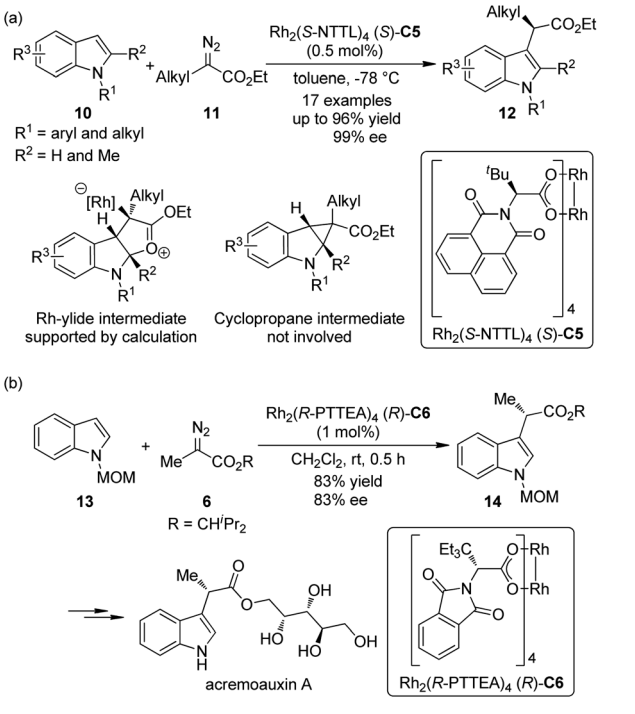
turnover numbers (TONs), Davies and co-workers[12] found that the highly efficient dirhodium-catalyzed asymmetric insertion reaction of methyl phenyldiazoacetate **4**, a proper precursor of donor/acceptor carbenoid that has a higher stability, went smoothly at 0 °C using **2** as the solvent (Scheme 1(b)). The high concentration of **2** could probably facilitate the trapping of Rh-carbenoid species by insertion into a C–H bond before the decomposition of the catalyst. The corresponding products **5** could be afforded in 96% yield with 81% ee, and the loading of catalyst Rh_2(*S*-DOSP)$_4$ (*S*)-**C2** could be reduced to 0.01 mol%.

Recently, Hashimoto and co-workers[13] reported the Rh-catalyzed intermolecular asymmetric insertion reaction of the carbenoid derived from α-methyl-α-diazoester **6** (Scheme 2). The dirhodium complexes derived from *N*-tetrahalophthaloyl-(*S*)-*tert*-leucine (Rh_2(*S*-TFPTTL)$_4$, (*S*)-**C3** and Rh_2(*S*-TCPTTL)$_4$, (*S*)-**C4**) are viable catalysts for this transformation. The insertion product **7** could be obtained in moderate yields and ee's (66% yield and 80% ee for (*S*)-**C3**, 73% yield and 61% ee for (*S*)-**C4**). Notably, when the methyl group in **6** was replaced by longer alkyl chains (ethyl or *n*-propyl), the *Z*-α,β-unsaturated esters **9** became the major or even the sole product *via* an [1,2]-hydride shift of the Rh-carbenoid intermediates.



Scheme 2 The asymmetric C–H bond insertion reactions of dirhodium carbenoids reported by Hashimoto.

Indoles are the most widely distributed heterocyclic motifs in naturally occurring alkaloids. Thus, the enantioselective functionalization of indoles has been a hot research topic for a long time.[14] In their seminal work on Rh-catalyzed [3 + 2] annulation of indoles, Lian and Davies[15] disclosed that methyl α-phenyl-α-diazoacetate could react with 1,2-dimethylindole to afford the C3 functionalization product in 95% yield by the Rh-catalyst (*S*)-**C2**, albeit negligible asymmetric induction (<5% ee) was observed. In 2011, Fox and co-workers[16] found that by using a catalytic amount of the chiral dirhodium complex Rh_2(*S*-NTTL)$_4$ (*S*)-**C5**, the C–H bond functionalization of indoles **10** with α-alkyl-α-diazoesters **11** could occur under mild conditions (Scheme 3(a)). Low temperature was critical to the success of the reaction. Excellent yields and ee's could be obtained for the *N*-aryl and *N*-alkyl indole derivatives with a small substituent (H or Me) at the indole C2 position. Control experiments precluded the cyclopropanation/fragmentation pathway and further density functional theory (DFT) calculations supported the mechanism that involves a Rh-ylide intermediate. The authors also suggested that the Rh-catalyst adopts the "chiral crown" conformation[17] in which the four phthalimide groups are projected on the same face of the complex during the reaction. Shortly after Fox's report, the Hashimoto group[18] realized the asymmetric C–H bond functionalization of *N*-MOM protected 2,3-unsubstituted indoles **13** with diazoester **6** by a Rh-catalyst Rh_2(*R*-PTTEA)$_4$ (*R*)-**C6** (Scheme 3(b)). The corresponding product **14** could be used in the asymmetric synthesis of acremoauxin A, a potent plant-growth inhibitor.[19] Markedly different from Fox's results, the 2-methylindole derivative is not a good substrate here.

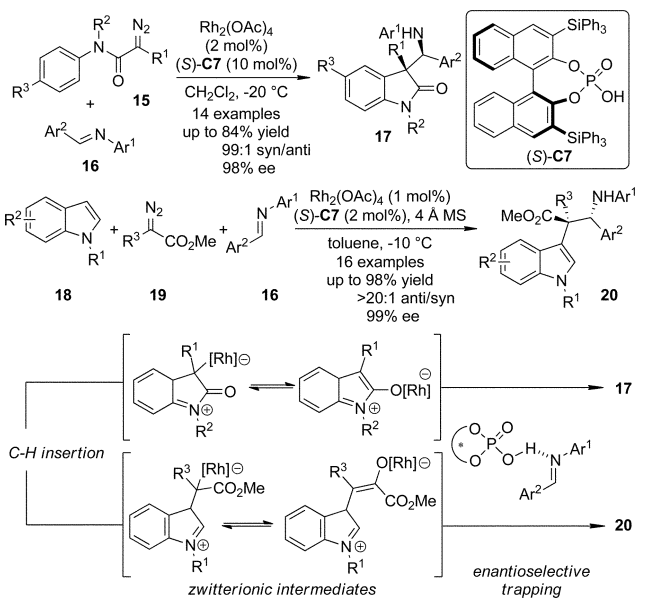


Scheme 3 The Rh-catalyzed asymmetric C–H bond functionalization reactions of indoles reported by (a) Fox and (b) Hashimoto, respectively.

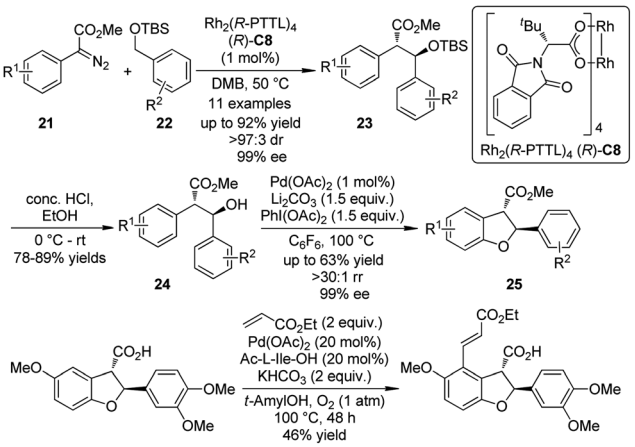
The zwitterionic intermediates are proposed to exist during the C–H bond insertion reactions in which the diazo compounds participate. These intermediates usually undergo rapid proton transfer to afford the C–H bond functionalization products.[20] Recently, Hu and co-workers[21] utilized chiral phosphoric acid (*S*)-**C7** activated *N*-aryl imines as the electrophiles to trap the zwitterionic intermediates generated from the Rh-catalyzed intra- or intermolecular carbenoid C–H bond insertion reactions (Scheme 4).[22] The polyfunctionalized oxindole and indole derivatives **17** and **20** bearing two consecutive chiral centers were obtained in one single step with exceptional diastereoselectivity and enantioselectivity (up to 99 : 1 dr and 99% ee) taking advantage of a dual catalytic system combining a transition metal salt and an organocatalyst.[23]

Based on the independent studies from the Davis group[24] on the Rh-catalyzed asymmetric intermolecular benzylic C–H bond insertion and the Yu group[25] on the Pd-catalyzed C–H activation/C–O cyclization, a collaboration of these two laboratories[26] led to the enantioselective synthesis of 2,3-dihydrobenzofurans by sequential C–H bond functionalization reactions (Scheme 5). The asymmetric insertion of the carbenoid species generated from α-aryl-α-diazoesters **21** and the dirhodium complex Rh_2(*R*-PTTL)$_4$ (*R*)-**C8** into the secondary benzylic ethers **22** afforded the corresponding products **23** in good yields and excellent enantioselective control (up to 92% yield, >97 : 3 dr and 99% ee). After removal of the TBS group, the 2,3-dihydrobenzofurans **25** were obtained by the Pd-catalyzed C–H activation/C–O cyclization sequence employing a Pd(II)/Pd(IV) catalytic cycle. No racemization could be observed. Further diversification of the benzofuran derivative was accomplished by a third C–H bond functionalization *via* the oxidative Heck coupling reaction.[27]

The α-diazo carbonyl compounds are not the only carbene precursors to realize the asymmetric C–H bond insertion



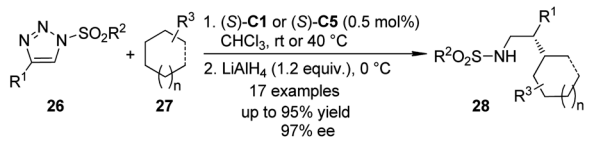
Scheme 4 The asymmetric trapping of the zwitterionic intermediates formed *via* C–H bond insertion reactions of dirhodium carbenoids reported by Hu.



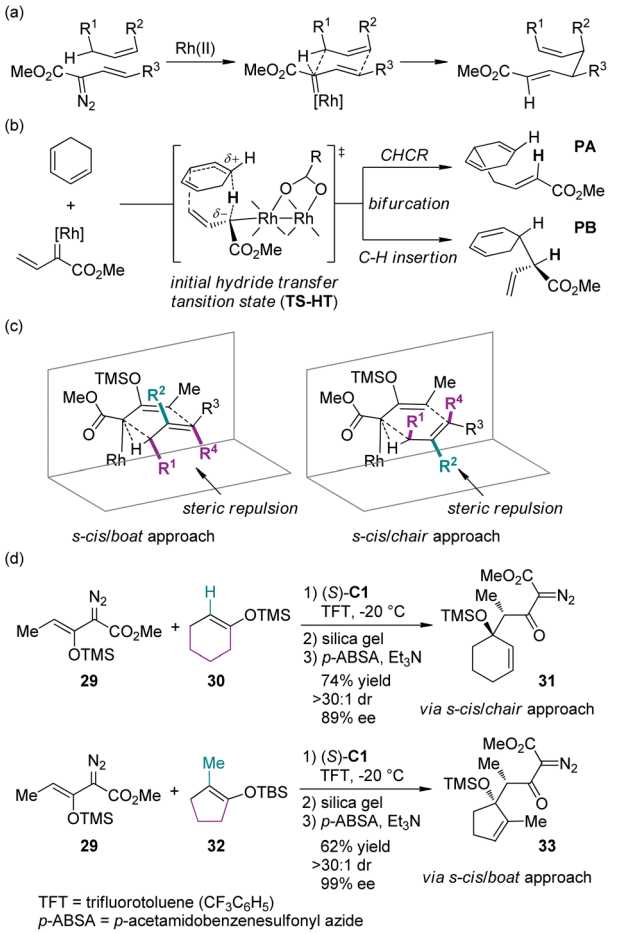
Scheme 5 The asymmetric sequential C–H bond functionalization reactions to synthesize benzofuran derivatives reported by Yu and Davies.

reactions. It was found that the 1-sulfonyl-1,2,3-triazoles which could be easily prepared by the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction[28] could serve as alternative carbene precursors for various transformations.[29] In 2011, the Fokin group[30] demonstrated that the azavinyl carbenoids derived from triazoles **26** and Rh-catalysts (*S*)-**C1** or (*S*)-**C5** underwent asymmetric C–H bond insertion reactions with a series of alkanes **27** under mild conditions (Scheme 6). The corresponding β-chiral amines **28** could be afforded after subsequent $LiAlH_4$ reduction in up to 97% ee. The high regioselectivity (5 : 1) of the insertion reaction favoring tertiary C–H bonds over secondary C–H bonds was observed. Notably, the hydrolysis of the direct insertion products only gave the aldehydes in a racemic form.

In recent years, the Davies group[31] has systematically studied the combined C–H functionalization/Cope rearrangement (CHCR), a reaction occurring between Rh-bound vinylcarbenoids and substrates containing allylic C–H bonds (Scheme 7(a)). This type of transformations offers accesses to products bearing two new stereocenters and has found broad applications in organic synthesis.[32] Detailed DFT calculations have been conducted to probe the mechanism of the CHCR reactions.[33] This study demonstrated that the initial C–H bond functionalization appeared to be a hydride transfer event. The charged transition state **TS-HT** could then bifurcate, leading to the CHCR product **PA** or the direct C–H bond insertion product **PB** (Scheme 7(b)). These results are in accord with the fact that in several cases, both products were formed and the



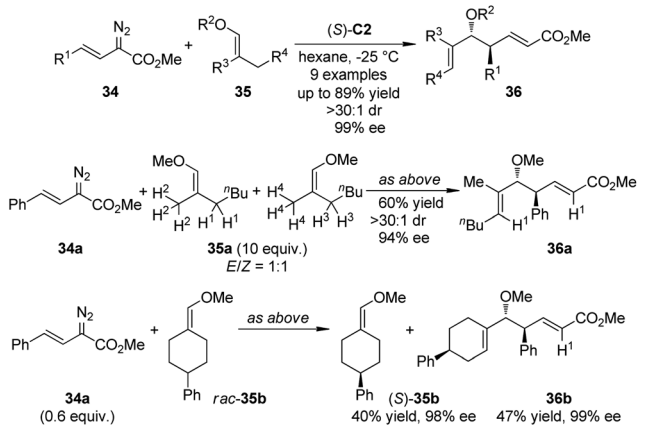
Scheme 6 The Rh-catalyzed asymmetric C–H bond insertion reactions of azavinyl carbenoids reported by Fokin.



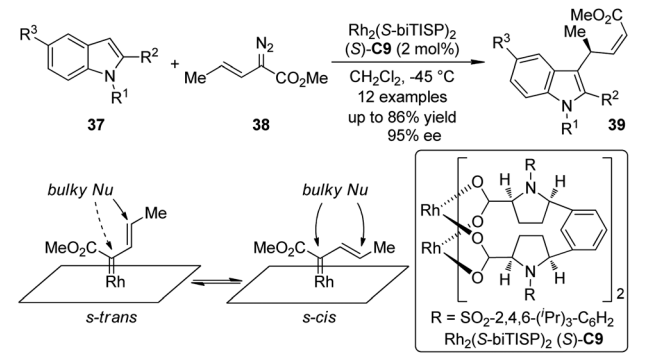
Scheme 7 The mechanistic studies of the Rh-catalyzed CHCR reactions reported by Davies.

enantioselectivity of the two products were often very similar or even identical.[34] The more intriguing information gained from the computational investigation is that, in principle, the transition states with different conformation and orientation of the substrates, which will lead to different stereochemical outcomes, are all energetically accessible. Thus, the diastereoselectivity could be possibly switched by using appropriate substrates: the substrates bearing large substituents at the R^2 position would prefer the s-*cis*/*boat* approach, and conversely, the substrates bearing large substituents at the R^1/R^4 positions would prefer the s-*cis*/*chair* approach (Scheme 7(c)). Davies and co-workers[35] verified this hypothesis by employing cyclohexene **30** and cyclopentene **32** as the reaction components, respectively (Scheme 7(d)). The corresponding β-keto-α-diazoacetates **31** and **33** were generated through CHCR reaction and subsequent transformations with high stereoselectivity but in the opposite diastereomeric series, which is consistent with the working models depicted in Scheme 7(c).

Lian and Davies[36] reported the application of the CHCR reaction of vinyl ethers as a surrogate for the vinylogous Mukaiyama aldol reactions.[37] By using (*S*)-**C2** as the catalyst, an array of Mukaiyama aldol-type products **36** were afforded in high yields with exceptional stereoselectivity (up to >30 : 1 dr



Scheme 8 The Rh-catalyzed CHCR reactions of vinyl ethers reported by Davies.

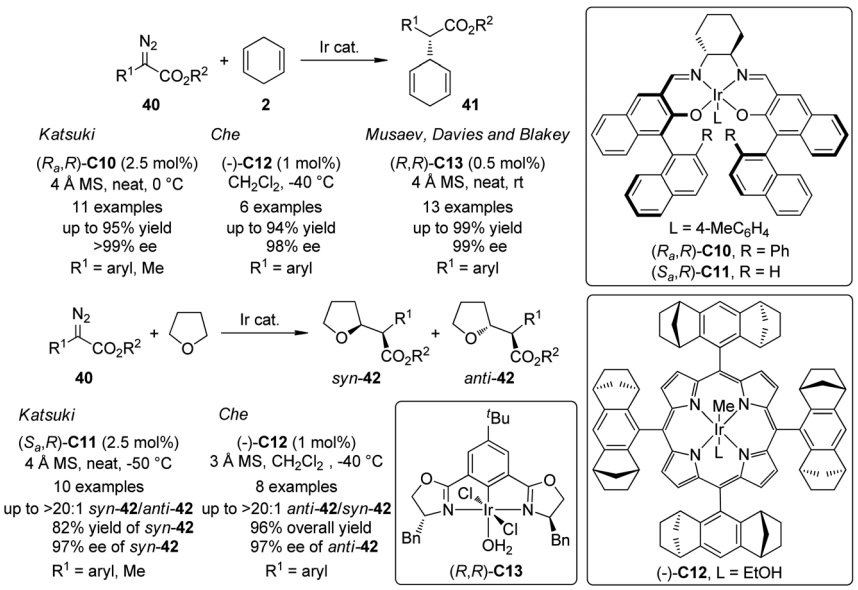


Scheme 9 The Rh-catalyzed asymmetric C–H bond functionalization reactions of indoles reported by Davies.

and 99% ee) under mild conditions (Scheme 8). The absolute configuration of **36** was found to be consistent with the s-*cis*/*boat* approach. The C–H bond functionalization was highly regioselective as only the secondary C–H bond *trans* to the methoxyl group in *E*-**35a** was cleavaged when an 1 : 1 mixture of *E*/*Z*-**35a** was used. The kinetic resolution of the racemic vinyl ether **35b** was also achieved efficiently.

The Davies group[38] also realized the asymmetric functionalization of indoles with vinylcarbenoids. It was known that the Rh-carbenoids generated from *E*-vinyldiazoacetates **38** could adopt s-*trans* or s-*cis* conformation. When a sterically demanding nucleophile was used, it would be possible to enhance the vinylogous reactivity of **38** by reinforcing the s-*trans* conformation of the carbenoid through the use of highly bulky catalysts. Indeed, when such a chiral catalyst Rh_2(*S*-biTISP)$_2$ (*S*)-**C9** was employed, the desired indole functionalization products **39** were obtained in up to 86% yield and 95% ee (Scheme 9). The newly formed double bonds were in *Z*-configuration. The corresponding pyrrole functionalization could be also achieved at a slightly elevated temperature (−20 °C) due to the decreased reactivity of pyrroles.

In addition to the extensively documented dirhodium catalysts, several chiral Ir-complexes have been used in the asymmetric C–H bond insertion reactions of metal carbenoids recently (Scheme 10). In 2009, Suematsu and Katsuki[39] reported that the Ir-carbenoids derived from α-diazoesters **40** and the Ir–salen complex (R_a,*R*)-**C10** could react with 1,4-cyclohexadiene **2** to afford the C–H bond insertion products **41** with up to 95% yield and >99% ee. Highly diastereo- and enantioselective C–H bond insertion into THF of the similar carbenoid species was also realized by using a sterically less hindered Ir–salen complex (S_a,*R*)-**C11**. The *syn*-**42** was obtained as the major diastereo isomer with satisfactory yields and ee's. Noticeably, the α-diazopropionate (**40**, R^1 = Me) was identified as a viable substrate for these two reactions since the product of the competing β-hydride elimination was not observed. Che and co-workers[40] found that an Ir-complex (−)-**C12** derived from a D_4-symmetric porphyrin ligand could catalyze similar transformations.

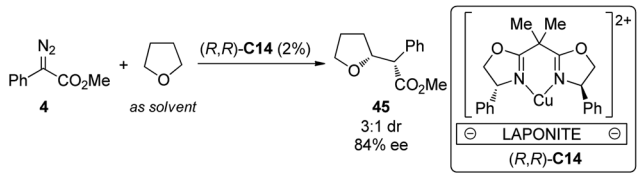


Scheme 10 The Ir-catalyzed asymmetric intermolecular C–H bond insertion reactions reported by several groups.

Comparable results were obtained for asymmetric C–H bond insertion between α-aryl-α-diazoesters **40** and 1,4-cyclohexadiene **2** (up to 94% yield and 98% ee). A catalyst TON of 9600 was observed in a scaled up reaction. Complementary to Katsuki's results, the asymmetric C–H bond insertion into THF catalyzed by (−)-**C12** exhibited high *anti*-selectivity. The enantioenriched *anti*-**42** (up to 97% ee) were the major products for a series of α-aryl-α-diazoester substrates. Very recently, Musaev, Davies, Blakey and co-workers[41] developed a phebox-ligated Ir-complex (*R*,*R*)-**C13** that is also capable to catalyze the asymmetric C–H bond insertion reactions between **40** and **2**. The reactions could proceed at ambient conditions. Slow addition of the diazoester and low temperature were not required. Substituted 1,4-cyclohexadienes were also subjected to the C–H bond insertion reactions and the subsequent oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) led to the corresponding α,α-biarylacetates in good yields (64–98%) with excellent enantioselectivity (90–99% ee). Further DFT calculations revealed that in the active catalytic species, the carbene fragment preferred to coordinate to the Ir center in the position perpendicular to the plane of the phebox ligand. A predictive model that could explain the experimentally observed enantioselectivity was also provided.

Che and co-workers[42] expanded the scope of Ir–porphyrin complex catalyzed asymmetric C–H bond insertion reaction to intramolecular variants. By utilizing a catalytic amount of (+)-**C12** (L = H_2O or solvent) as the catalyst, an array of benzyl α-aryl-α-diazoesters **43** underwent intramolecular asymmetric C–H bond insertion reaction to afford *cis*-β-lactones in good yields (up to 87%) and enantioselectivity (up to 78% ee) (Scheme 11). Common dirhodium carboxylate catalysts such as (*S*)-**C1** or Rh_2(*S*-MEPY)$_4$ (tetrakis[methyl 2-pyrrolidone-5(*S*)-carboxylate] dirhodium(II)) could not catalyze this reaction effectively.

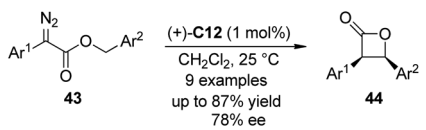
Cu is another widely employed transition metal to catalyze the carbene transformations. However, the applications of chiral Cu catalysts to asymmetric C–H bond insertion reaction are still very limited. Fraile and co-workers[43] disclosed that the homogeneous Cu complexes with bis(oxazoline) (BOX) and azabis(oxazoline) (azaBOX) ligands were able to catalyze the asymmetric insertion of α-diazo compounds **4** into the C–H bonds of cyclic ethers including THF, THP, 1,4-dioxane and 1,3-dioxolane. When the chiral complexes were immobilized by electrostatic interactions with laponite clay or supported on silica or silica-alumina, the catalytic performance was improved considerably in terms of conversion and stereoselectivity (Scheme 12). In addition, the heterogeneous catalyst could be recovered and reused for several times with similar results to those obtained in the first run. Very recently, Jiménez-Osés, Fraile and co-workers[44] unambiguously determined the absolute configuration of the conformationally flexible products of the Cu-catalyzed C–H bond insertion reactions between **4** and cyclic ethers using vibrational circular dichroism (VCD) spectroscopy in combination with rigorous quantum mechanics calculations.



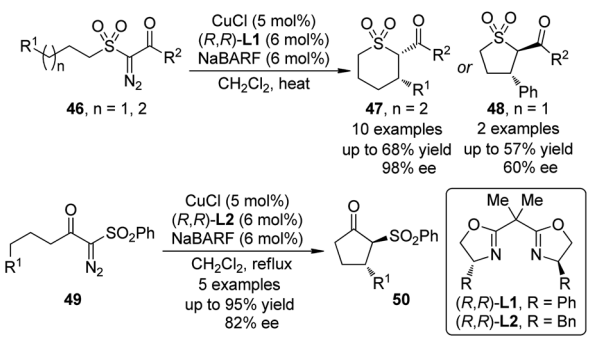
Scheme 12 The Cu-catalyzed heterogeneous asymmetric intramolecular C–H bond insertion reactions reported by Fraile.

In 2010, Maguire and co-workers[45] reported the first example of Cu-catalyzed enantioselective intramolecular C–H bond insertion reactions of α-diazosulfones **46** (Scheme 13). In the presence of catalytic amount of CuCl and chiral BOX ligand (*R*,*R*)-**L1**, the formation of *cis*-thiopyrans **47** was preferred in moderate yields (up to 68%) with excellent enantioselectivity (up to 98% ee). When this option was not possible, the insertion reaction was forced to proceed to give the *trans* five-membered ring products **48**. Notably, the dirhodium catalysts were not effective for this transformation. Shortly after these initial results, Slattery and Maguire[46] realized the asymmetric intramolecular C–H bond insertion reactions of α-diazo-β-keto sulfones **49** catalyzed by similar chiral Cu-BOX complexes. It was found that using NaBARF or KBARF (BARF = tetrakis[3,5-bis(trifluromethyl)phenyl]borate) as an additive is crucial for achieving high enantioselectivity for these two reactions. Further investigations[47] demonstrated that the naked alkali metal cations could alter the nature of the Cu catalyst through partial or complete chloride abstraction.

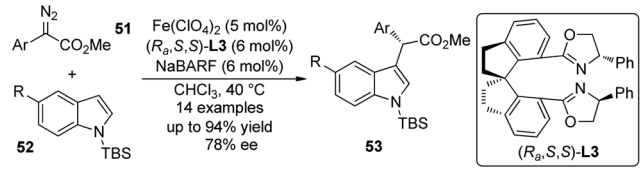
Fe-catalyzed asymmetric reactions[48] have been studied intensively in recent years in that iron is cheap, non-toxic and the most abundant metal in earth crust. Zhou and co-workers[49] demonstrated that the asymmetric C–H bond functionalization reactions of indoles could be accomplished by Fe-catalyzed insertion of carbenoid derived from α-aryl-α-diazoesters **51** (Scheme 14). The reaction of these substrates could not give



Scheme 11 The Ir-catalyzed asymmetric intramolecular C–H bond insertion reactions reported by Che.



Scheme 13 The Cu-catalyzed asymmetric intramolecular C–H bond insertion reactions of α-diazosulfones reported by Maguire.



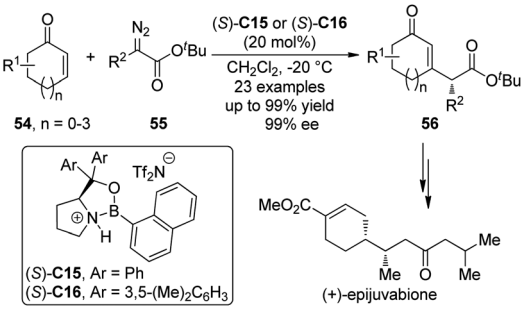
Scheme 14 The Fe-catalyzed asymmetric C–H bond functionalization reactions of indoles reported by Zhou.

satisfactory enantioselectivity when chiral dirhodium catalyst was utilized.[15] The detailed optimization of the reaction conditions revealed that the spiro bisoxazoline (R_a,*S*,*S*)-**L3** was the optimal ligand and $Fe(ClO_4)_2$ was the optimal Fe precursor. The corresponding α-aryl-α-indolylacetates **53** were constructed in up to 94% yield and 78% ee. Notably, most products are solid and can be easily purified by recrystallization. This study indicated a high potential for application of sustainable and environmentally benign catalysts in carbene transformations.

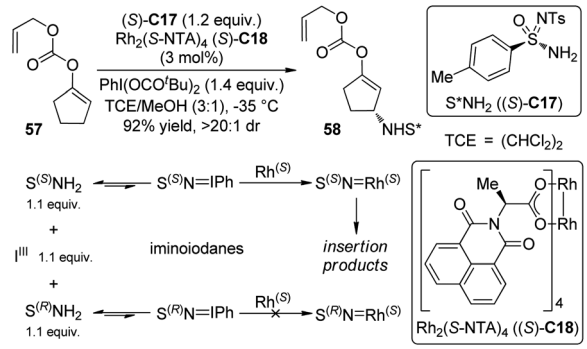
Interestingly, the group of Hwang and Ryu[50] reported the Lewis acid-catalyzed asymmetric insertion reactions into β-vinyl C–H bonds of cyclic enones.[51] It was found that by utilizing the chiral oxazaborolidinium salts (*S*)-**C15** or (*S*)-**C16** as the catalysts, the β-vinyl C–H bonds of various cyclic enones **54** could be functionalized by α-alkyl-α-diazoesters **55** leading to the β-substituted cyclic enones **56** in high yields with excellent enantioselectivity under mild conditions (Scheme 15).[52] In some cases, the catalyst loading could be lowered to 5 mol%. Efficient kinetic resolution was also achieved when racemic substrate **54** ($n = 1$, R^1 = 6-Me) was employed. The synthetic utility of this transformation was further demonstrated by the formal synthesis of a natural sesquiterpene (+)-epijuvabione.[53]

2.2. C–H bond insertion by metal nitrenoids

Nitrenes are the nitrogeneous isoelectronic analogs of the carbenes. The asymmetric insertion reaction of metal nitrenoids into the C–H bonds has emerged as a powerful tool for the construction of C–N bonds in recent years.[54,55] Dauban and co-workers[55a,b,56] systematically studied the diastereoselective nitrene C–H bond insertion reactions using a chiral sulfonimidamide (*S*)-**C17** in combination with the chiral dirhodium catalyst Rh_2(*S*-NTA)$_4$ (*S*)-**C18**. The benzylic methylene units of cyclic and linear compounds, the allylic methylene units of



Scheme 15 The Lewis acid-catalyzed asymmetric C–H bond functionalization reactions of enones reported by Hwang and Ryu.

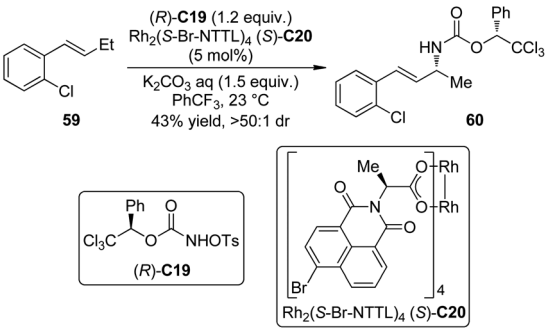


Scheme 16 The diastereoselective C–H bond amination reactions reported by Dauban.

terpenes and enol ethers as well as the tertiary C–H bonds of alkanes could be efficiently aminated with very high diastereomeric ratios under mild conditions (Scheme 16). The high regioselectivity was determined by the combination of steric, electronic and conformational factors. It is generally believed that, prior to the formation of the metal nitrenoids, an iminoiodane is generated from the reaction between the nitrogen source and the I(III) oxidant. Recent experiments[57] suggested that the equilibrium for this transformation is favored for the reactants because no iminoiodane could be detected by ^{1}H NMR. In addition, kinetic resolution could be observed when the racemic nitrene precursor (±)-**C17** was employed.[55b]

Lebel and co-workers[58] also realized Rh-catalyzed diastereoselective nitrene C–H bond insertion reactions of alkenes using a readily available chiral nitrene precursor *N*-tosyloxycarbamate (*R*)-**C19**. By utilizing the dirhodium complex Rh_2(*S*-Br-NTTL)$_4$ (*S*)-**C20** as the catalyst, *E*-β-ethylstyrenes and 2-phenylcyclohexene could be converted to the corresponding allylic amination products in moderate yields and good diastereoselectivity (Scheme 17). The Ph-Troc protecting group could be easily removed using Zn/HOAc to afford the allylic amine·HCl without racemization. On the other hand, *Z*-β-ethylstyrenes, *E*- or *Z*-β-methylstyrenes and terminal styrenes gave aziridination products with varied levels of diastereocontrol.

Hashimoto and co-workers[59] have documented the asymmetric synthesis of α-amino ketones by the Rh-catalyzed enantioselective amination reactions of silyl enol ethers derived from

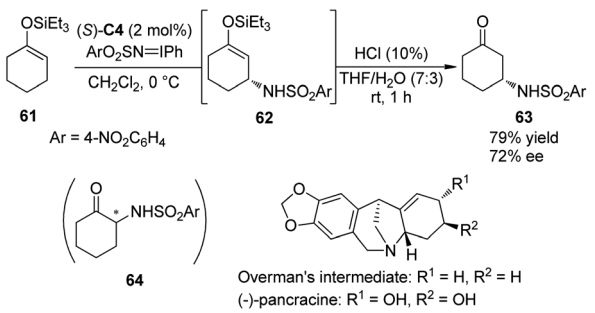


Scheme 17 The diastereoselective C–H bond amination reactions reported by Lebel.

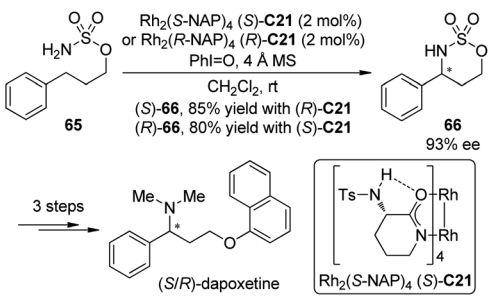
acyclic ketones or enones with (arenesulfonylimino)phenyliodanes. Interestingly, when 1-triethylsiloxy-1-cyclohexene **61** was subjected to this reaction, the expected α-amination product **64** could not be detected. Instead, β-amino ketone **63** derived from asymmetric allylic C–H bond insertion of Rh nitrenoid species was obtained. After further examination of the reaction parameters, the dirhodium complex Rh_2(*S*-TCPTTL)$_4$ (*S*)-**C4** was identified as the optimal chiral catalyst, affording **63** in 79% yield with 72% ee (Scheme 18).[60] By utilizing this method to construct the first chiral center, Hashimoto and co-workers accomplished the asymmetric synthesis of the key Overman's intermediate[61] for the amaryllidaceae alkaloid (−)-pancracine.[62]

(*S*)-(+)-Dapoxetine (Priligy) is a potent selective serotonin reuptake inhibitor (SSRI) with a short half-life and has been developed specifically for the treatment of premature ejaculation (PE).[63] In 2010, Kang and Lee[64] uncovered a highly efficient enantioselective synthesis of dapoxetine using the Du Bois asymmetric C–H bond amination reaction[55c] of the prochiral sulfamate **65** as the key transformation (Scheme 19). The (*S*)-(+)- and (*R*)-(−)-dapoxetine could be synthesized in 33% and 34% overall yields for five steps starting form 3-phenyl-1-propanol. During the course of this study, however, the absolute configuration of the major enantiomer of **66** prepared by the Du Bois asymmetric C–H bond amination reaction with Rh_2(*S*-NAP)$_4$ (*S*)-**C21** as the catalyst, was determined to be (*R*), not (*S*) as was originally reported.[55c]

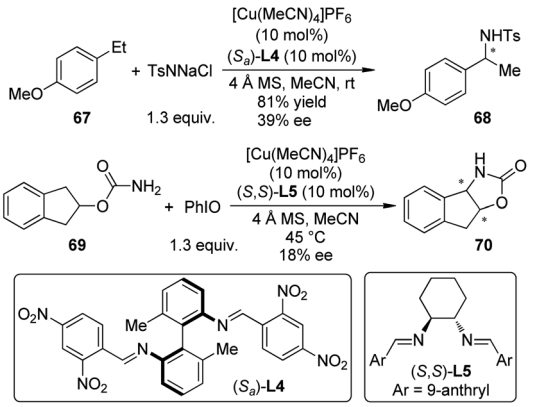
In 2010, Barman and Nicholas[65] reported the Cu-catalyzed intermolecular benzylic amination reactions employing



Scheme 18 The enantioselective formal synthesis of (−)-pancracine reported by Hashimoto.



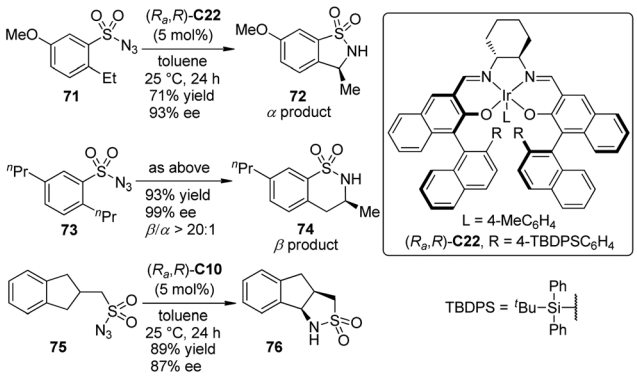
Scheme 19 The enantioselective synthesis of dapoxetine reported by Lee.



Scheme 20 The Cu-catalyzed asymmetric C–H bond amination reactions reported by Nicholas.

chloramine-T (TsNNaCl) as the aminating agent.[66] Several classes of ligands including α-amino acids, diphosphines, diamines, diimines, *etc*. could enable the amination effectively. Low to moderate ee's were obtained when homochiral diimine ligand (S_a)-**L4** was used for the benzylic amination of 4-ethylanisole **67** (Scheme 20). Further mechanistic probes by combining experimental and computational methods[67] suggested that a ground-state triplet Cu–imido complex [(diimine)Cu=NTs]$^+$ was the active aminating species, which transferred the NTs unit to the benzylic substrates *via* a stepwise, radical process. Shortly after this work, Barman and Nicholas[68] reported the synthesis of *N*,*O*-heterocycles by the intramolecular C–H bond amination reactions of carbamates and sulfamates with PhIO as the oxidant. Similar catalytic system ([Cu(MeCN)$_4$]PF$_6$ + (*S*,*S*)-**L5**), for example, was also tested, yet only 18% ee was obtained for the tricyclic product **70**, probably due to the radical nature of this amination process.

Based on their successes on Ir–salen complex catalyzed asymmetric carbenoid C–H and Si–H bond insertion reactions,[39,69] Katsuki and co-workers[70] demonstrated the enantioselective intramolecular benzylic C–H bond amination reaction using sulfonyl azide compounds as the atom-economical nitrene precursors. The sterically bulky Ir–salen complex (R_a,*R*)-**C22** exhibited the superior activity, permitting the benzylic (α

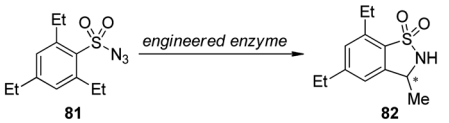


Scheme 21 The Ir-catalyzed asymmetric intramolecular C–H bond amination reactions reported by Katsuki.

position) C–H bond amination reaction of 2-ethyl substituted substrates **71** with high efficiency (Scheme 21). Surprisingly, the homobenzylic (β position) C–H bond amination reaction occurred preferentially when several 2-alkyl-substituted derivatives other than 2-ethyl substituted ones **73** were employed, delivering the six-membered sultam **74** with high enantioselectivity. It was inferred that the control of the regio- and stereoselectivity largely depends on whether the substrate can adopt a conformation suitable for the orbital interaction between the C–H and Ir–nitrenoid bonds for the reaction. A higher enantioselectivity was obtained for the substrates bearing a more flexible acyclic substituent. Notably, the scope of this reaction was not limited to arylsulfonyl azides. The desymmetrization of substrate **75** with Ir–salen complex (R_a,*R*)-**C10** as the catalyst led to tricyclic sultam **76** in 89% yield and 87% ee.

Very recently, the Katsuki group[71] achieved enantioselective intermolecular C–H bond amination at the benzylic and allylic positions with 2-(trimethylsilyl)ethanesulfonyl azide ($SESN_3$) as the nitrene precursor. A chiral Ru(CO)–salen complex (R_a,*R*)-**C23** proved to be the best catalyst for this transformation while the Ir–salen complex (R_a,*R*)-**C22** was not effective (Scheme 22). The amination of various alkylarenes and alkenes went smoothly in CH_2Cl_2, or alternatively, under solvent-free conditions. The reactions could be highly regioselective that an ethyl group was aminated selectively even in the presence of an ^{n}Pr group. Preliminary mechanistic investigation supported that the C–H bond amination through a putative metal nitrenoid intermediate proceeds in a concerted manner. However, the involvement of a short-lived radical species cannot be completely ruled out.[72]

It is well known that cytochrome P450 enzymes are powerful catalysts for the C–H bond oxidation reactions in biological systems.[73] However, the parallel C–H bond amination reactions *via* nitrenoid intermediates under natural enzyme catalysis have not been reported. In 2013, Arnold and co-workers[74] realized engineered cytochrome P450 enzyme-catalyzed asymmetric intramolecular C–H bond amination reactions using sulfonylazides as the nitrenoid precursors. As shown in Scheme 23, the modified enzyme $P411_{BM3}$-CIS-T438S exhibits enhanced catalytic activity and enantioselective control both *in vitro* and *in vivo*.



81 82

	enzyme	TTN[a]	ee (%)
in vitro	$P411_{BM3}$-CIS-T438S (0.1 mol%)	383	73
in vivo	$P411_{BM3}$-CIS-T438S (2.7 μM)	430	87

[a] TTN = total turnover number

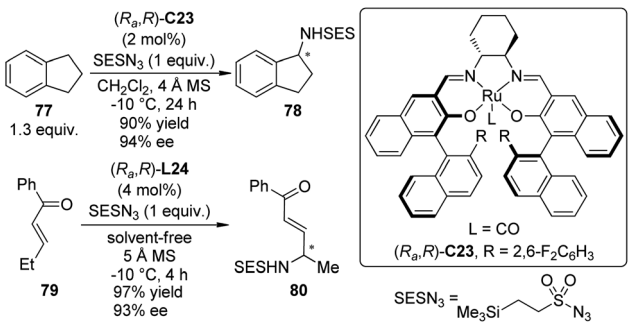
Scheme 23 The engineered cytochrome P450 enzymes catalyzed asymmetric intramolecular C–H bond amination reactions reported by Arnold.

2.3. C–H bond insertion by metal oxo species

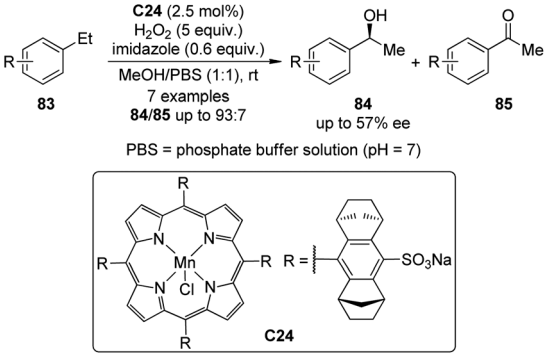
Compared with the catalytic asymmetric C–H bond insertion reactions by metal carbenoids and metal nitrenoids, the asymmetric C–H bond oxidation reactions by metal oxo species still remain challenging in organic synthesis.[75] One of the most difficult issues is how to avoid or reduce the over oxidation of the newly formed C(sp^3)–O bonds. In addition to the extensively studied biological catalytic systems such as cytochrome P450 enzymes,[73] a few artificial catalysts based on transition metals including Fe,[76] Mn[77] and Ru[78] have emerged as powerful tools for this transformation.

A recent contribution to this field reported by Simonneaux and co-workers[79] demonstrated the utility of the water-soluble Mn–porphyrin complex **C24** as the chiral catalyst to enable the asymmetric benzylic hydroxylation of arylalkane **83** using H_2O_2 as the oxidant (Scheme 24). The reactions were conducted in the mixed MeOH–water solution. The corresponding secondary alcohols **84** were delivered as the major products with up to 57% ee. Notably, imidazole was found to play an important role in this catalytic system, working as an axial ligand to the Mn center.[80]

A significant advance to be highlighted here is the predictably selective aliphatic C–H bond oxidation reactions developed by the White group.[81] By utilizing the highly electrophilic, sterically encumbered iron complex Fe(PDP) **C25** as the catalyst,



Scheme 22 The Ru-catalyzed asymmetric intermolecular C–H bond amination reactions reported by Katsuki.

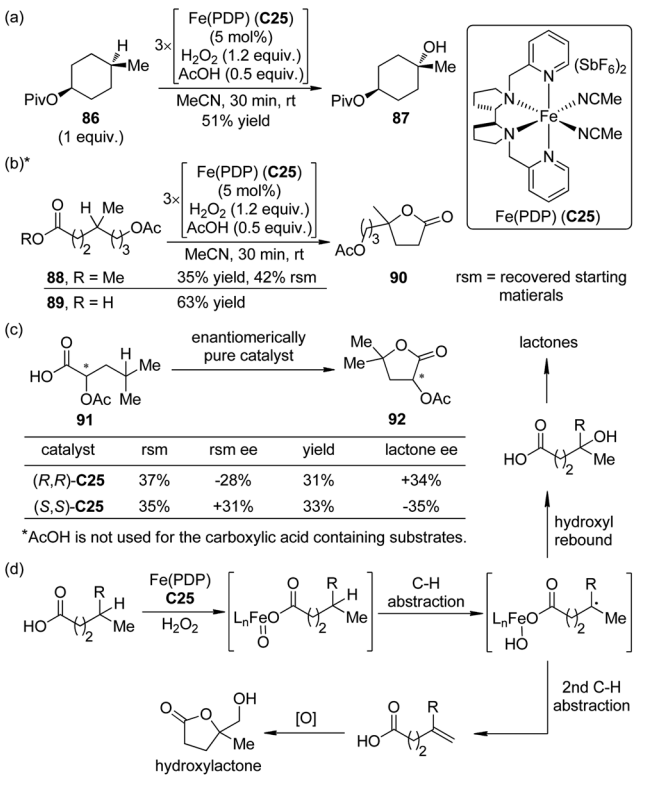


Scheme 24 The Mn-catalyzed asymmetric C–H bond hydroxylation reactions reported by Simonneaux.

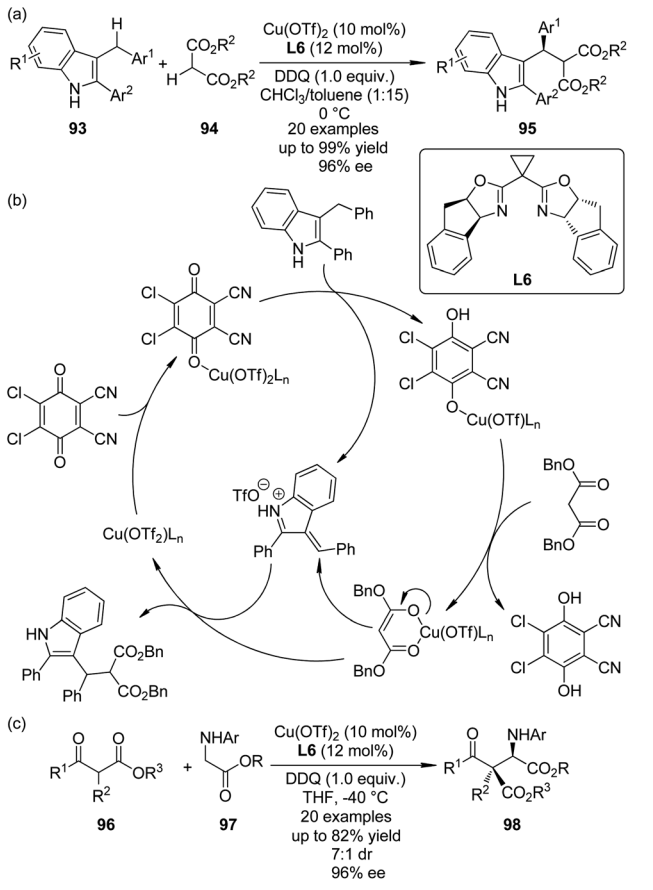
in combination with H_2O_2 as the oxidant, the inert tertiary C–H bonds in the complex molecules could be hydroxylated.[82] Predictable selectivity was achieved on the basis of the electronic and steric properties of the C–H bonds without the need for a directing group. The products of the hydroxylation at the most electron-rich and sterically accessible C–H bonds (such as **87**) could be obtained in synthetically useful yields (~50% yields with 1 equiv. of substrates) when acetic acid, which probably worked as a ligand to the iron center, was used (Scheme 25(a)). If no suitable tertiary C–H bonds existed in the substrates, selective oxidation of methylene moieties to ketones could be achieved by the same catalytic system.[83] Inspired by the importance of acetic acid, White and co-workers[84] later disclosed that the carboxylic acid containing substrate **89** were more reactive than the corresponding methyl ester **88** towards the oxidation reaction. The site selectivity was controlled by the carboxyl group, even overcoming the unfavorable electronic, steric and stereoelectronic effects within the substrates to deliver the γ-lactone products **90** (Scheme 25(b)). The proposed role of carboxylic acid as a ligand was further confirmed that chiral substrate **91** exhibited matched/mismatched behavior with chiral Fe(PDP) ligand. Furthermore, when racemic **91** was subjected to the standard reaction conditions, enantiomerically pure Fe(PDP) catalyst could promote kinetic resolution of the starting material, leading to moderate level of ee's of both recovered **91** and lactone product **92** (Scheme 25(c)). A plausible mechanism was also proposed for the aliphatic C–H bond oxidation reactions.[84,85] The Fe(PDP) catalyst reacts with H_2O_2 and carboxylic acid substrate to generate an iron oxo carboxylate as the active oxidant, which abstracts a hydrogen atom to afford a short-lived carbon-centered radical. The subsequent hydroxyl rebound step occurs very rapidly with complete stereoretention of the direct hydroxylated product as well as the lactone. Noticeably, the reaction profile of the alkyl radical diverts in a substrate-depended manner. For some carboxylic acid substrates, the second hydrogen abstraction furnishes the olefin intermediates. Further oxidation of these intermediates typically produces 10–20% yields of hydroxylactones as the "double oxidation" products (Scheme 25(d)).

3. Cross dehydrogenative coupling (CDC) reactions

The cross dehydrogenative coupling (CDC) reactions,[86] pioneered by the Murahashi group[87] and the Li group,[88] refers to the direct coupling reactions between one C(sp^3)–H bond α to a nitrogen, oxygen atom, or a carbonyl group and various C(sp)–H, C(sp^2)–H or C(sp^3)–H bonds under oxidative conditions without requiring preactivation. It has evolved to be an important method for the construction of C–C bonds in recent years. Asymmetric variants of this transformation have also been realized.[89]



Scheme 25 The selective aliphatic C–H oxidation reactions reported by White.



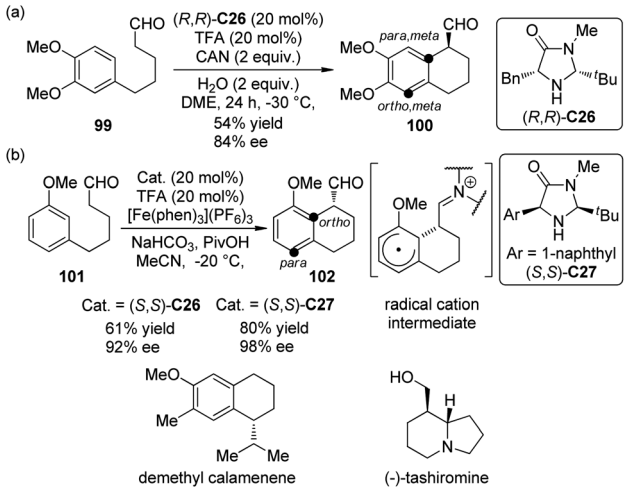
Scheme 26 The Cu-catalyzed asymmetric CDC reactions reported by (a), (b) Gong and (c) Wang, respectively.

In 2010, Gong and co-workers[90] reported the Lewis acid-catalyzed enantioselective CDC reactions between 3-indolylmethyl C–H bonds with 1,3-dicarbonyls. In the presence of a catalytic amount of $Cu(OTf)_2$ and amino-indanol derived BOX ligand **L6** as the chiral catalyst, in combination with DDQ as the stoichiometric oxidant, a variety of structurally diverse 3-arylmethylindole derivatives **93** could react with 1,3-diesters **94**, affording the corresponding products **95** in up to 99% yield and 96% ee (Scheme 26(a)). Based on further experimental and computational investigations, a plausible reaction mechanism was proposed. Since no ESR signal was observed for the reaction mixture, a cationic rather than radical species was believed as the key intermediate. Lewis acid could enhance the oxidizing ability by coordinating to one oxygen atom of DDQ, facilitating the dehydrogenation of 3-arylmethylindole. The resultant Cu phenoxide deprotonated the dibenzyl malonate to generate a chiral anion, which enantioselectively attacked the vinylogous iminium cation obtained from the first deprotonation to yield the final CDC product (Scheme 26(b)).

Shortly after Gong's work, the Wang group[91] reported an efficient enantioselective synthesis of α-alkyl α-amino acids **98** *via* the CDC reactions of glycine esters **97** with α-substituted β-ketoesters **96** enabled by the same chiral Cu catalyst and oxidant (Scheme 26(c)). Besides, this strategy could be extended to asymmetric synthesis of C1-alkylated tetrahydroisoquinolines by the similar reactions between Horner–Wadsworth–Emmons reagents and *N*-aryl tetrahydroisoquinolines. Different form Gong's results, preliminary mechanistic probe indicated that a radical cation intermediate might be involved in the catalytic cycle because a small amount of this species could be captured by 2,6-di-(^{t}Bu)$_2$-4-methylphenol (BHT).

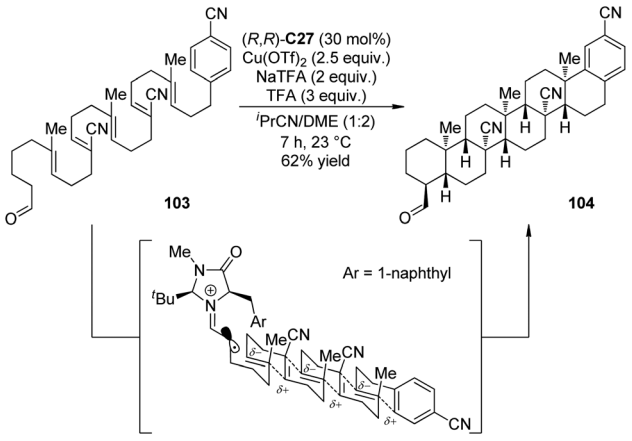
Enantioselective organo-SOMO activation[92] has witnessed considerable development in last several years and become an important complementary method to the strategies of LUMO (iminium) activation and HOMO (enamine) activation of secondary amine catalysis. In 2009, Nicolaou and co-workers[93] realized an asymmetric intramolecular α-arylation reactions of aldehydes by utilizing chiral secondary amine catalyst (*R*,*R*)-**C26** and $Ce(NH_3)_2(NO_3)_6$ (CAN) as the oxidant. When 1,3,4-trisubstituted arene substrate **99** was used, the *para*, *meta* selectivity was observed, giving the corresponding arylation product **100** in moderate yield and satisfactory ee (Scheme 27(a)). The application of this methodology was further demonstrated by the total synthesis of demethyl calamenene, a potent cytotoxic agent against human adenocarcinoma A549.[94]

Almost at the same time, MacMillan and co-workers[95] reported a very similar asymmetric intramolecular α-arylation reactions of aldehydes catalyzed by chiral secondary amine catalysts (*S*,*S*)-**C26** or (*S*,*S*)-**C27**. $[Fe(phen)_3](PF_6)_3$ was identified as the optimal oxidant. The reaction was highly regioselective for 1,3-disubstituted arene substrate **101** and only *ortho*-functionalization product **102** was formed (Scheme 27(b)). This SOMO α-arylation could be combined with Hantzsch ester hydride reduction[96] in a two-step organocatalytic sequence, and also be used in the total synthesis of (−)-tashiromine.[97] DFT calculations by Houk, MacMillan and co-workers[98] confirmed the radical cation nature of the cyclized intermediates (Scheme 27(b)). The *para*, *meta* selectivity for **99** and the *ortho* selectivity for **101** were also explained based on the computational results.



Scheme 27 The organocatalytic asymmetric intramolecular α-arylation reactions of aldehydes reported by (a) Nicolaou and (b) MacMillan, respectively.

Impressively, Rendler and MacMillan[99] accomplished the radical-mediated polyene cyclization reactions *via* organo-SOMO catalysis. Polyolefins that incorporate an alternating sequence of polarity-inverted C=C bonds (acrylonitrile and isobutene) were the suitable substrates. The electronic match between nucleophilic olefins with electron-deficient radical intermediates (and *vice versa*) allowed the cascade 6-*endo*-*trig* cyclization in the presence of chiral imidazolidinone (*R*,*R*)-**C27**. Notably, the reactions with strong oxidants like CAN and $[Fe(phen)_3](PF_6)_3$ could not afford the desired products. On the contrary, $Cu(OTf)_2$ was found as an effective oxidant. More importantly, slow addition of the oxidant *via* syringe pump, which kinetically preferred for the unimolecular cascade process over the interrupted pathway involving bimolecular radical oxidation, greatly improved the yields. By applying this strategy, the hexacyclization adduct **104** could be obtained as a

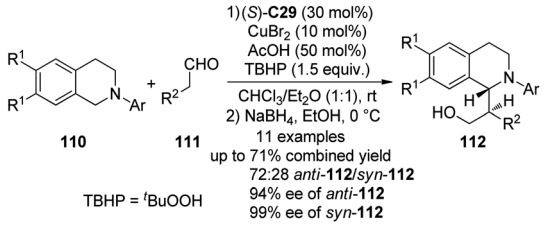


Scheme 28 The organocatalytic asymmetric radical-mediated polyene cyclization reactions reported by MacMillan.

single diastereomer in 62% yield and as many as 6 new C–C bonds and a total of 11 contiguous chiral centers were constructed from a simple acyclic starting material **103** (Scheme 28).

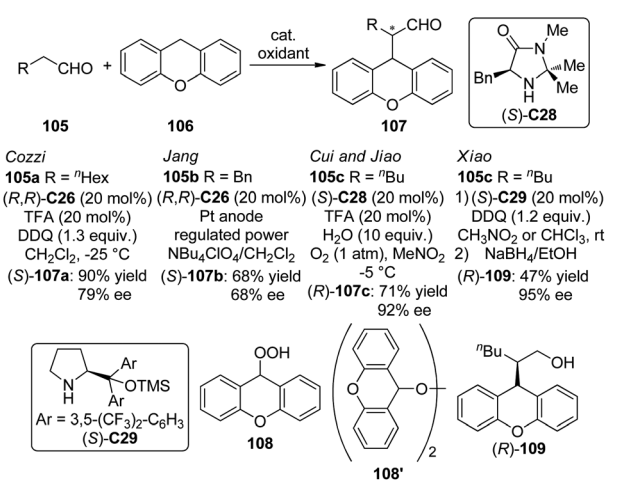
Organocatalytic asymmetric intermolecular dehydrogenative α-functionalization of aldehydes has also been reported. Cozzi and co-workers[100] disclosed that aliphatic aldehyde **105a** could react with xanthene **106** smoothly to deliver the corresponding product **107a** in 90% yield and 79% ee when (*R*,*R*)-**C26** was used as the catalyst (Scheme 29). The S_N1-type mechanism was believed to operate *via* the xanthene-derived benzylic carbocation generated from the oxidation by DDQ. Jang and co-workers[101] found that the asymmetric α-alkylation of aldehydes with xanthene could be achieved under electro-oxidation conditions to afford the corresponding products in up to 68% yield and 68% ee with (*R*,*R*)-**C26** as the catalyst. Cui, Jiao and co-workers[102] developed an enantioselective CDC protocol that involved molecular O_2 as the oxidant.[103] By using (*S*)-**C28** as the chiral catalyst, the α-functionalized product **107c** was obtained in 71% yield and 92% ee. Although the generated water during the formation of the enamine was considered possible to lead to side reaction with carbocation, yet in this system, 10 equiv. of water was employed as an additive to enhance the enantioselectivity. It was postulated that xanthene could be oxidized to peroxides **108** and/or **108′** by a radical pathway with O_2. Further investigation showed that **108′** might be the key intermediate of this transformation since independently synthesized **108′** could directly react with the aldehydes giving similar results. Xiao and co-workers[104] also realized organocatalytic asymmetric CDC reactions of aldelydes with benzylic C–H bonds utilizing the chiral diarylprolinol-based silyl ether (*S*)-**C29** as the catalyst and DDQ as the oxidant. The desired alcohol products **109** were delivered in up to 95% ee after the subsequent reduction by $NaBH_4$.

Recently, Chi and co-workers[105] reported the asymmetric CDC reactions between aldehydes and tertiary amines. An extensive survey revealed that (*S*)-**C29** in combination with $CuBr_2$ could be employed as an effective cooperative catalytic system when ^{t}BuOOH (TBHP) was used as the terminal oxidant. It was also found that using 50 mol% of AcOH could lead to improved yields. Under the optimized conditions, the reactions of various *N*-aryl tetrahydroisoquinolines **110** and aliphatic aldehydes **111** went smoothly. Because the direct Mannich adducts were rather unstable, the *in situ* $NaBH_4$ reduction was conducted to afford their corresponding alcohols **112** with reasonable diastereoselectivity (the ratio of *anti*-**112**/*syn*-**112** up to 72 : 28) and excellent enantioselectivity (up to 94% ee for *anti*-**112** and 99% ee for *syn*-**112**) in up to 71% combined yield (Scheme 30). In consistence with the observations by the Wang group,[91] the reaction pathway was suggested to involve a single-electron transfer (SET) radical mechanism. The yields of the coupling products decreased dramatically when the radical inhibitor BHT was added. Meanwhile, a racemic version of this CDC reaction was also realized *via* metal catalysis alone.

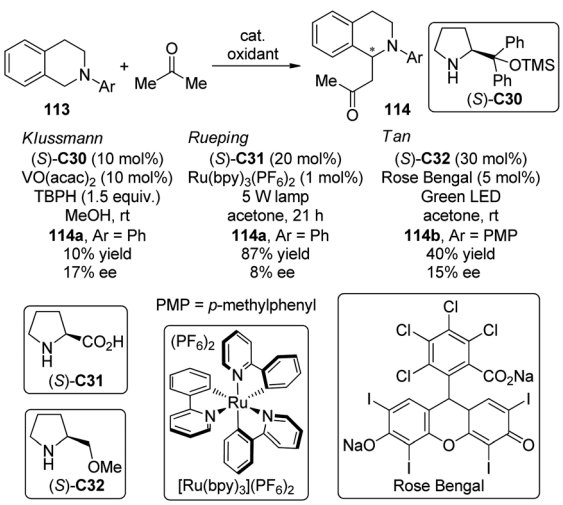


Scheme 30 The organocatalytic asymmetric CDC reactions of aldehydes reported by Chi.

The asymmetric CDC reactions between ketones and tertiary amines are much more challenging compared with their aldehyde counterparts. Several groups have been engaged in this subject. Klussmann and co-workers[106] found that such reactions between tetrahydroisoquinolines **113** and acetone could be achieved by combined vanadium(IV) salt $VO(acac)_2$ and chiral organocatalysts when TBHP was employed as the stoichiometric oxidant. However, the desired product **114a** was obtained with only 17% ee in the presence of (*S*)-**C30** (Scheme 31). Further



Scheme 29 The organocatalytic asymmetric intermolecular α-functionalization reactions of aldehydes reported by several groups.



Scheme 31 The asymmetric CDC reactions of ketones reported by several groups.

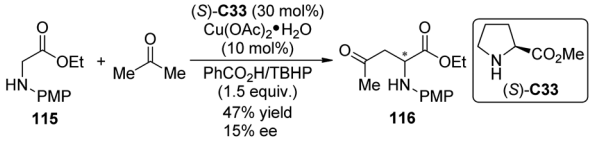
attempts to improve the enantioselectivity by using chiral vanadium complexes were failed because the enantiopure product slowly racemized under the reaction conditions. Rueping and co-workers,[107] on the other hand, realized similar transformations by utilizing the dual catalytic system containing photoredox catalyst $Ru(bpy)_3(PF_6)_2$[108] and L-proline (*S*)-**C31** under the irradiation of 5 W fluorescent bulb, albeit with low enantioselectivity (8% ee for **114a**). Instead of using the transition metal-based catalysts, Tan and co-workers[109] utilized the organic dye Rose Bengal as the environmentally benign photoredox catalyst to promote the CDC reactions of **113** with nitroalkanes or ketones. The green LED was identified as the light source matched with Rose Bengal. With L-prolinol methyl ether (*S*)-**C32** as the chiral secondary amine catalyst, however, the coupling product **146b** could only be obtained with 15% ee.

Shortly after Klussmann's work, Xie and Huang[110] reported the CDC reactions between *N*-substituted glycine esters with unmodified ketones by the cooperative catalytic system consisting of $Cu(OAc)_2 \cdot H_2O$ and pyrrolidine. TBHP and DDQ were found as the two effective oxidants suitable for acetone and cyclic ketone substrates, respectively. No enantioselectivity was achieved with all the chiral ligands employed. When methyl L-proline ester (*S*)-**C33** was used as the chiral organocatalyst for the reaction of glycine ester **115** and acetone, the product **116** was generated with 15% ee and decreased yield (47% *vs.* 73% with pyrrolidine) (Scheme 32).

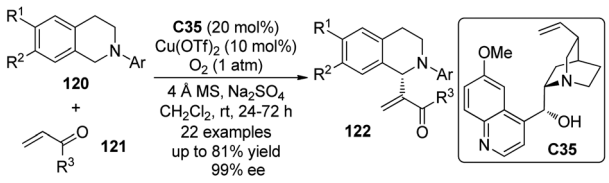
Highly enantioselective CDC reactions between tertiary amines and ketones have not been realized until very recently. By utilizing L-phenylalanine (*S*)-**C34** rather than secondary amine catalysts to activate the ketone substrates, Wang and co-workers[111a] accomplished the coupling reaction between *N*-aryl tetrahydroisoquinolines **117** and cyclic ketones **118**, delivering the corresponding products **119** in up to 81% yield with good stereocontrol (up to 13 : 1 dr and 94% ee) when anhydrous ^{i}PrOH was added to the reaction (Scheme 33). DDQ again was identified as the optimal stoichiometric oxidant, and the copper salts were not necessary. A chiral organic contact ion-pair interaction was proposed for the reaction. The enamine intermediate was generated from the ketone and the primary amine moiety of the L-phenylalanine. The interaction between this chiral anion and the iminium cation from oxidation probably contributed to the diastereomeric discrimination, which furnished this asymmetric metal-free CDC process. In addition, Wang and co-workers[111b] realized intramolecular metal-free CDC reactions between tertiary amine and ketone moieties. Modest enantioselectivity (14% ee) was reached when simple chiral phosphoric acid was utilized as the catalyst.

Wang and co-workers[112] also described an enantioselective CDC reaction of tertiary amines with the olefinic C–H bonds. In the presence of catalytic amount of quinine **C35** in combination with $Cu(OTf)_2$, *N*-aryl tetrahydroisoquinolines **120** reacted with the α,β-unsaturated aldehydes and ketones **121** smoothly to afford the α-functionalized products **122** (Scheme 34). Molecular O_2 was found to be the sole oxidant and the addition of anhydrous Na_2SO_4 was beneficial to achieve higher yield and enantioselectivity for an array of products (up to 81% yield and 99% ee).

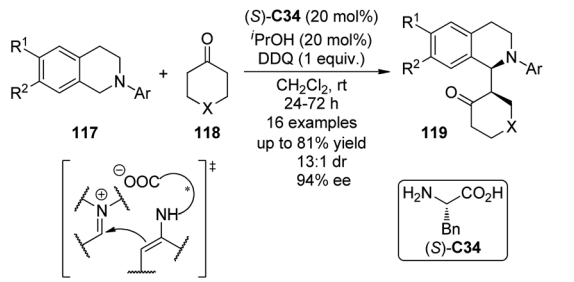
DiRocco and Rovis[113] realized asymmetric α-acylation reactions of tertiary amines **124** by taking advantage of a dual catalytic system of NHC and photoredox catalyst. Since the Breslow intermediate or the NHC itself can also be oxidized, a judicious choice of the oxidant and the photoredox catalyst is crucial. After careful evaluation of the reaction conditions, $Ru(bpy)_3Cl_2$ was selected as the optimal photoredox catalyst and *m*-dinitrobenzene (*m*-DNB) as the co-oxidant under irradiation with blue light. The aminoindanol-derived NHC (*R*,*S*)-**C36** (*in situ* generated from the corresponding triazolium salt using NaH) exhibited the best asymmetric induction. An array of the



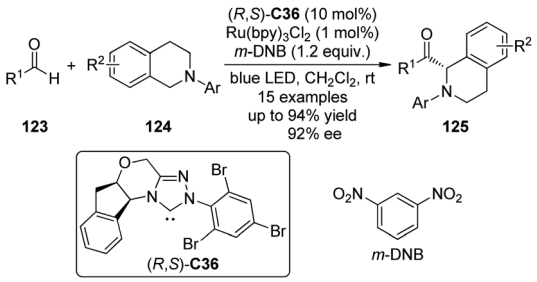
Scheme 32 The asymmetric CDC reactions of ketones reported by Huang.



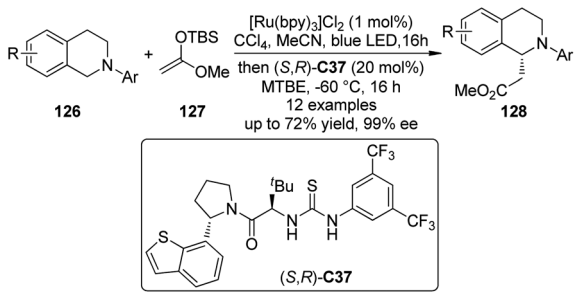
Scheme 34 The asymmetric CDC reactions of α,β-unsaturated aldehydes and ketones reported by Wang.



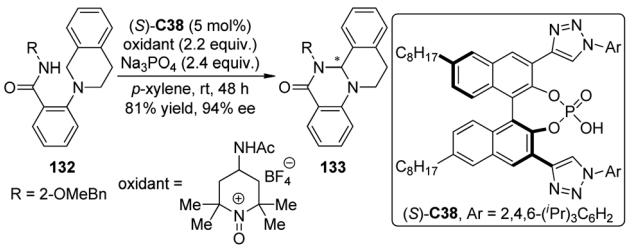
Scheme 33 The asymmetric CDC reactions of ketones reported by Wang.



Scheme 35 The asymmetric α-acylation reactions of tertiary amines reported by Rovis.



Scheme 36 The asymmetric synthesis of β-amino esters reported by Jacobsen and Stephenson.



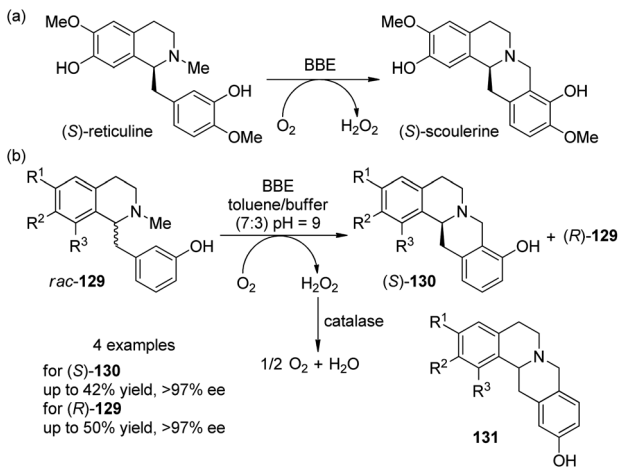
Scheme 38 The asymmetric intramolecular CDC reactions reported by Toste.

desired products **125** was afforded in up to 94% yield and 92% ee (Scheme 35).

Recently, Jacobsen, Stephenson and co-workers[114] developed an enantioselective synthesis of β-amino esters by the dual catalytic system combining photoredox activation and anion binding catalysis that is related to the CDC reactions.[115] In these transformations, the *N*-aryl tetrahydroisoquinolines **126** were firstly oxidized under photoredox conditions with CCl_4 as the stoichiometric oxidant. Subsequently, the corresponding iminium intermediates activated by the chiral thiourea catalyst (*S*,*R*)-**C37** *via* chloride binding interaction, were attacked enantioselectively by the silyl ketene acetal **127** to generate a variety of β-amino esters **128** in high yields and ee's (Scheme 36).[116]

Enzyme-catalyzed transformation has also been applied for the oxidative C–C coupling reactions. Berberine bridge enzyme (BBE) is a redox enzyme which converts (*S*)-reticuline as its natural substrate to the berbine derivative (*S*)-scoulerine at the expense of O_2 (Scheme 37(a)).[117] Kroutil and co-workers[118] disclosed that the BBE is efficient to act as a biocatalyst to promote the coupling reactions of four unnatual 1-benzylisoquinoline substrates **129**. After careful examination of the reaction parameters, it was found that the reactions worked well in a two-phase toluene–buffer mixture (7 : 3, pH = 9) and adding some catalase was necessary to disproportionate the formed H_2O_2 in order to avoid the inhibition or degradation of the enzyme. Excellent kinetic resolution behavior was observed for all the *rac*-**129** tested, with the reactions stopped at 50% conversion. The products (*S*)-**130** were obtained in up to 42% yield and >97% ee whereas the (*R*)-**129** was recovered in up to 50% yield and >97% ee (Scheme 37(b)). The reactions were also highly regioselective and only minor side products **131** were formed (4–10% yield). Notably, this enzyme-catalyzed reaction could also be performed on a 500 mg scale under mild conditions.

Asymmetric CDC reactions have been found effective to construct C–N bond recently. Toste and co-workers[119] envisioned that the enantioenriched cyclic aminals **133** could be delivered *via* intramolecular CDC reactions of substrates **132** catalyzed by a chiral counteranion with an appropriately chosen cationic oxidant. Since conventional chiral phosphate anions that only possess steric demanding groups on the skeleton of the catalyst failed to provide an effective chiral environment for the catalysis, the authors developed a series of triazole-containing chiral phosphoric acids like (*S*)-**C38** which exhibit high level asymmetric induction and catalytic activity for the designed reactions (Scheme 38). It was hypothesized that the triazole moieties might interact with the amide-containing substrates probably *via* attractive hydrogen-bonding interaction, leading to additional discrimination of the diastereomeric transition states.

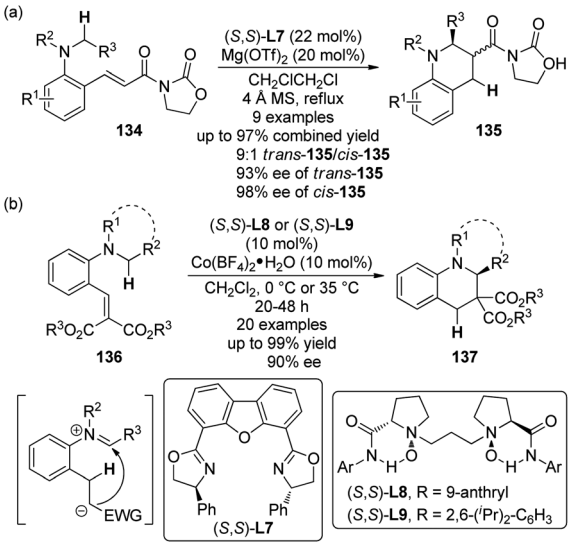


Scheme 37 The enzyme-catalyzed oxidative C–C coupling reactions reported by Kroutil.

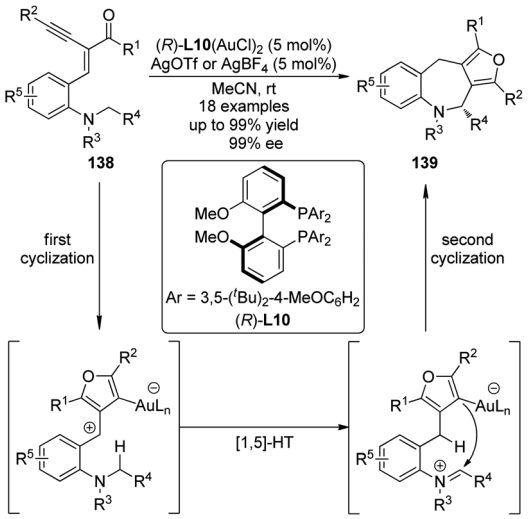
4. [1,5]-Hydride transfer reactions

Another important strategy to furnish the $C(sp^3)$–H bond functionalization at the α position to a tertiary amine group is the sequential intramolecular hydride transfer/ring closure reaction taking advantage of the "*tert*-amino effect".[120] This type of transformation features the redox-neutral process and therefore avoids the use of external oxidants. Traditionally, such reactions were typically thermal promoted.[121] Recent contributions revealed that Lewis acids are also feasible to catalyze these reactions,[122] thus making it possible to develop their asymmetric variants.[123]

The first catalytic highly enantioselective [1,5]-hydride transfer reactions was reported by the Seidel group.[124] The *ortho*-vinyl tertiary anilines **134** were selected as the substrates and the acyl oxazolidinone moiety was introduced to act as an acceptor for the chelation to a chiral metal complex. A screening



Scheme 39 The Lewis acid-catalyzed asymmetric [1,5]-hydride transfer reactions reported by (a) Seidel and (b) Feng, respectively.



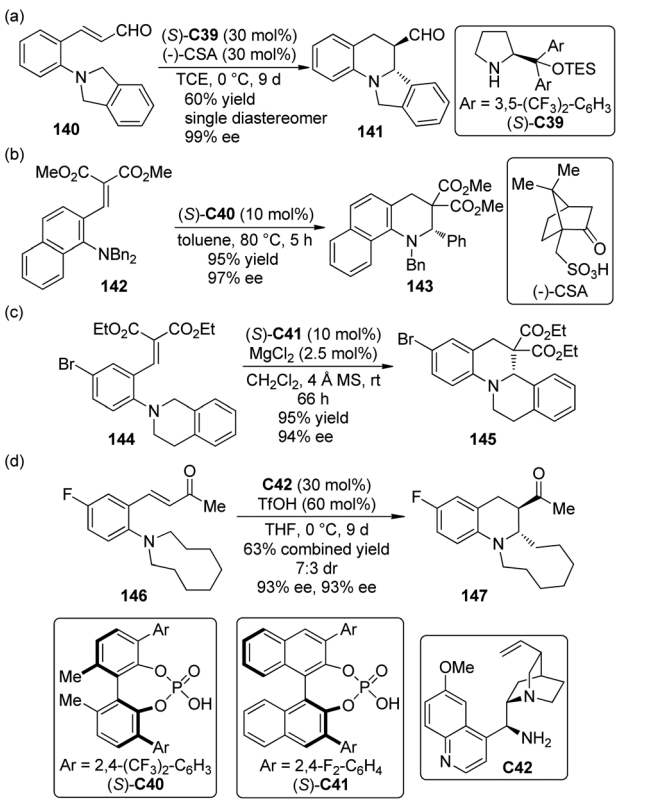
Scheme 40 The Au-catalyzed asymmetric domino reactions reported by Zhang.

of various Lewis acids and chiral ligands indicated that $Mg(OTf)_2$ in combination with DBFox ligand (*S*,*S*)-**L7** could give the best results, affording the desired tetrahydroquinoline products **135** *via* the [1,5]-hydride transfer and subsequent nucleophilic addition to the iminium ion generated *in situ* (Scheme 39(a)). Generally, good diastereoselectivity (up to 9 : 1 dr) and enantioselectivity (up to 93% ee for *trans*-**135** and 98% ee for *cis*-**135**) were observed for a series of products, despite at elevated temperature (84 °C). The reaction became very sluggish at lower temperature.

On the other hand, by utilizing their chiral *N*,*N*′-dioxide ligands ((*S*,*S*)-**L8** and (*S*,*S*)-**L9**),[125] Feng and co-workers[126] developed a [1,5]-hydride transfer induced asymmetric synthesis of tetrahydroquinoline derivatives **137** catalyzed by cobalt complexes (Scheme 39(b)). Notably, the reactions exhibited relatively broaden substrate scope and higher reactivity in that the reactions were typically conducted at 35 °C or 0 °C. In some cases, the catalyst loading could be lowered to 2 mol% without erosion of the ee values. Besides, a working model to explain the stereoinduction was also proposed.

The Zhang group[127] successfully integrated the [1,5]-hydride transfer reaction into the Au-catalyzed domino process[128] for the synthesis of furan-fused tetrahydroazepine derivatives **139.** The gold complex generated from the chiral ligand (*R*)-**L10** and $Au(SMe_2)Cl$ enabled the first cyclization of the starting materials **138** affording the furan intermediates which underwent the subsequent [1,5]-hydride transfer and the final ring closing reaction to furnish the desired products (Scheme 40).[129] The reactions could occur at room temperature with high enantioselectivity and thus offered a unique access to enantioenriched polycyclic compounds.

Organocatalytic strategies have also been applied to the asymmetric cascade [1,5]-hydride transfer/cyclization reactions. Kim and co-workers[130] first realized this type transformations of *ortho-tert*-amine-substituted cinnamaldehydes **140** by utilizing chiral secondary amine catalyst (*S*)-**C39** in combination with (−)-camphorsulfonic acid (CSA) (Scheme 41(a)). High to excellent diastereo- and enantioselectivity were obtained for a series of synthetically useful ring-fused tetrahydroquinoline derivatives **141** under mild conditions.



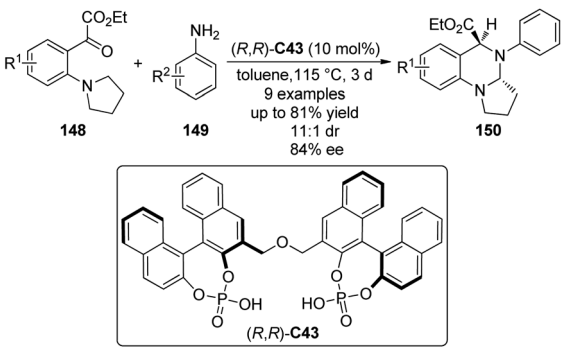
Scheme 41 The organocatalytic asymmetric [1,5]-hydride transfer reactions reported by (a) Kim, (b) Akiyama, (c) Luo and (d) Kim respectively.

Akiyama and co-workers,[131] on the other hand, developed similar asymmetric [1,5]-hydride transfer reactions catalyzed by the biphenyl-derived chiral phosphoric acid catalyst (*S*)-**C40** (Scheme 41(b)).[132] The reactions were highly enantioselective (up to 97% ee) even at higher temperature. It was found that a substituent *ortho* to the nitrogen atom could enhance the reactivity of the substrates.[133] More interestingly, control experiments showed that the enantioselectivity of this catalytic system probably arose from the discrimination of the two enantiotopic α-H atoms by the chiral catalyst in the hydride transfer step instead of the enantiofacial selection of the nucleophilic attack on the iminium ion as proposed by the Seidel group[124] and the Feng group.[126]

Luo and co-workers[134] also accomplished highly enantioselective [1,5]-hydride transfer/cyclization cascade reactions catalyzed by a binary-acid system[135] that comprised chiral phosphoric acid (*S*)-**C41** as well as the Lewis acid $MgCl_2$ or $Mg(BF_4)_2$ (Scheme 41(c)). The non-linear-effect study revealed that the active catalytic species was probably a 1 : 1 complex of the phosphoric acid and magnesium salt although excess amount of phosphoric acid was needed. Comprehensive theoretical calculations and experimental studies suggested that the stereospecific and suprafacial [1,5]-hydride transfer was both rate-limiting and stereocontrol step followed by a barrierless C–C bond formation.

Very recently, Kang and Kim[136] expanded the substrate scope of organocatalytic asymmetric [1,5]-hydride transfer/cyclization reaction to *ortho*-dialkylamine substituted benzylideneacetone derivatives **146**. By using chiral primary amine catalyst **C42** in conjunction with TfOH, the desired tetrahydroquinoline products **147** could be afforded in moderate to high yields with high enantioselectivity (Scheme 41(d)).

In addition to the synthesis of tetrahydroisoquinolines, Gong and co-workers[137] applied the chiral phosphoric acid catalyzed asymmetric [1,5]-hydride transfer/cyclization reactions for the synthesis of cyclic aminals. The bisphosphoric acid (*R*,*R*)-**C43** was identified as the optimal catalyst to enable the reactions of an array of *ortho-tert*-amine-substituted aromatic ketoesters **148** with aromatic amines **149** (Scheme 42). Typically, the desired products **150** could be afforded in moderate to high yields (up to 81%) and diastereo- and enantioselectivity (up to 11 : 1 dr and 84% ee).



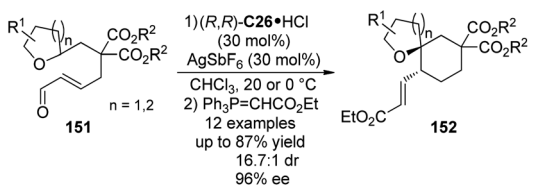
Scheme 42 The organocatalytic asymmetric [1,5]-hydride transfer reactions reported by Gong.

The catalytic functionalization of the C(sp^3)–H bonds α to an oxygen atom *via* [1,5]-hydride transfer reactions have been well studied by Sames[138] and others.[133b,139] The asymmetric version of this type of transformations, however, is scarce compared to their nitrogen-containing counterparts described above. Recently, Tu and co-workers[140] developed the enantioselective [1,5]-hydride transfer induced cyclization reactions of **151** by employing chiral secondary aminium salt (*R*,*R*)-**C26**·HCl (Scheme 43). The presence of $AgSbF_6$ was necessary to allow the reaction to proceed by enhancing the electrophilicity of the iminium intermediates with a more weakly coordinating anion. Finally the enantioenriched spiroethers **152** could be delivered in satisfactory yields and stereoselectivity after the subsequent Wittig reaction.

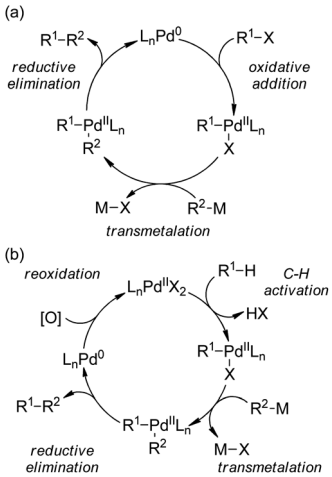
5. C–H bond functionalization involving a transient metal–carbon (M–C) species

5.1. Pd-Catalyzed reactions

5.1.1. Pd(II)/Pd(0) catalytic cycle. After extensive development for several decades, transition metal-catalyzed cross-coupling reactions have now become one of the most robust and reliable methods for the construction of C–C and C–heteroatom bonds, and routinely been applied in the modern synthesis of complex target molecules. The merits of these methodologies were exemplified by the fact that three pioneers in this area, Heck, Negishi, and Suzuki were awarded the Nobel Prize in Chemistry in 2010.[141] However, the traditional cross-coupling reactions catalyzed by Pd(0) complexes still suffer from the drawback of using organic halides (or equivalents) and organometallic reagents as the coupling partners, which will require additional steps for substrate synthesis and lead to stoichiometric amount of salt wastes (Scheme 44(a)). An attractive alternative strategy is to replace the Pd(0) catalysts and the organic halides (or equivalents) by the Pd(II) salts and the inert hydrocarbons as the reaction components. Instead of the oxidative addition of a C–X bond, the C–H bond is first cleaved with the Pd(II) catalyst generally under the assistance of a directing group. At the end of the catalytic cycle, the Pd(II) species is regenerated at the expense of an external oxidant (Scheme 44(b)). Although tremendous success has been made in recent years on the transition metal-catalyzed cross-coupling reactions initiated by both C(sp^2)–H bond and C(sp^3)–H bond activation,[142] challenges are still remained in developing their catalytic asymmetric variants. The major obstacles are rooted in



Scheme 43 The organocatalytic asymmetric [1,5]-hydride transfer reactions reported by Tu.



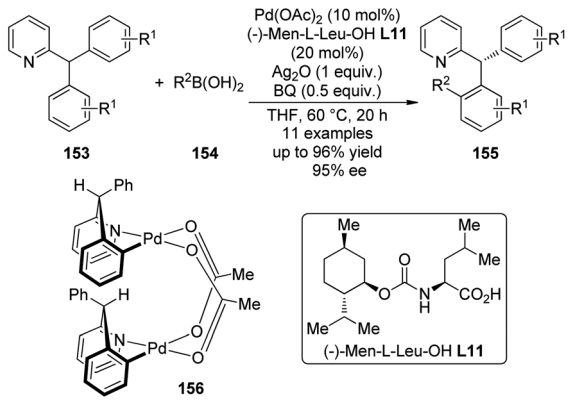
Scheme 44 Schematic mechanistic scenarios of (a) the traditional Pd(0)-catalyzed cross-coupling reaction and (b) the Pd(II)-catalyzed C–H activation/C–C coupling reaction.

the lack of suitable chiral ligands that both can promote the C–H bond cleavage event and are compatible with other steps in the catalytic cycle as well as the often complex reaction conditions.

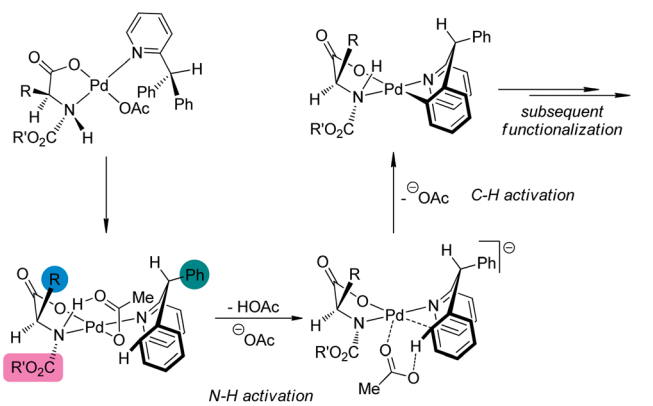
A major breakthrough was the application of the mono-*N*-protected chiral amino acids into the Pd(II) catalyzed C–H bond functionalization reactions first reported by the Yu group[143] in 2008. In order to develop a catalytic asymmetric C–H bond functionalization protocol, Yu and co-workers[144] set the C–H activation/C–C coupling of the prochiral substrates **153** (R^1 = 2-Me) with boronic acids **154** (R^2 = ^{n}Bu) as the model reaction. Inspired by the X-ray crystal structure of the dimeric Pd complex **156**, they hypothesized that the asymmetric induction might be achieved by using a chiral carboxylate as the ligand (Scheme 45). After screening a series of commercially available carboxylate, it was found that mono-*N*-protected chiral amino acids could lead to reasonable enantioselectivity of the reaction, probably owing to the *N*,*O*-bidentate coordination manner to the Pd center. It was also suggested that the larger steric difference at the α-carbon (α-hydrogen *vs.* bulky side chain) can induce improved stereocontrol, and to incorporate an electron-withdrawing group to the nitrogen atom to maintain the electrophilic nature of the Pd(II) center was necessary for the C–H bond cleavage. Finally by utilizing the (−)-Men-L-Leu-OH **L11** as the optimal ligand, an array of desymmetrized coupling products **155** were produced in up to 96% yield with 95% ee.

A detailed DFT calculation by Musaev, Yu and co-workers[145] offered in depth understanding of the mechanism of this novel asymmetric C–H bond functionalization protocol. It was confirmed that the ligand was bound in a bidentate fashion to the Pd center. The first step of the reaction was the cleavage of the N–H moiety of the ligand by the coordinated acetate group, leaving an vacant coordination site of the Pd(II) center. At the next stage, one *ortho* C–H bond of the substrate was cleaved with the assistance of another acetate anion, furnishing the palladacycle with concomitant formation of a new stereocenter at the benzylic position (Scheme 46). (It is worth noting that several concepts have arisen to describe the transition metal-catalyzed C–H bond cleavage with the assistance of an external or coordinated base such as "concerted metallation deprotonation (CMD)",[146] and "ambiphilic metal–ligand activation (AMLA)".[147] The nomenclature and classification of the transition metal-catalyzed C–H bond cleavage are still topics in the literature and beyond the scope of this review. To simplify the discussion, we prefer not to use these terms here.) The chiral information at the α-carbon of the ligand could be geared to the nitrogen atom (the bulky *N*-protecting group is forced *trans* to the side chain of the amino acid ligand), which further arranges the substrate in a proper conformation for the asymmetric C–H bond functionalization. The experimentally observed preference for the formation of (*R*) products could also be well reproduced in the computational investigations.

Shortly after the above success, Yu and co-workers[148] were able to replace the 2-pyridyl moiety of the prochiral substrates **153** with a carboxylate group in the Pd(II)-catalyzed asymmetric C–H bond functionalization reactions. The use of a directing group that features relatively weak coordinating ability and at the same time is a useful functional group that can be readily



Scheme 45 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by Yu.

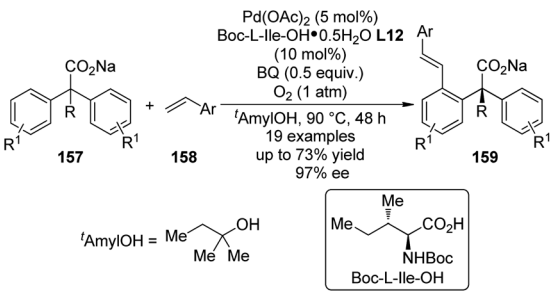


Scheme 46 The schematic description of the mechanism of the Pd-catalyzed asymmetric C–H bond functionalization reactions reported by Musaev and Yu.

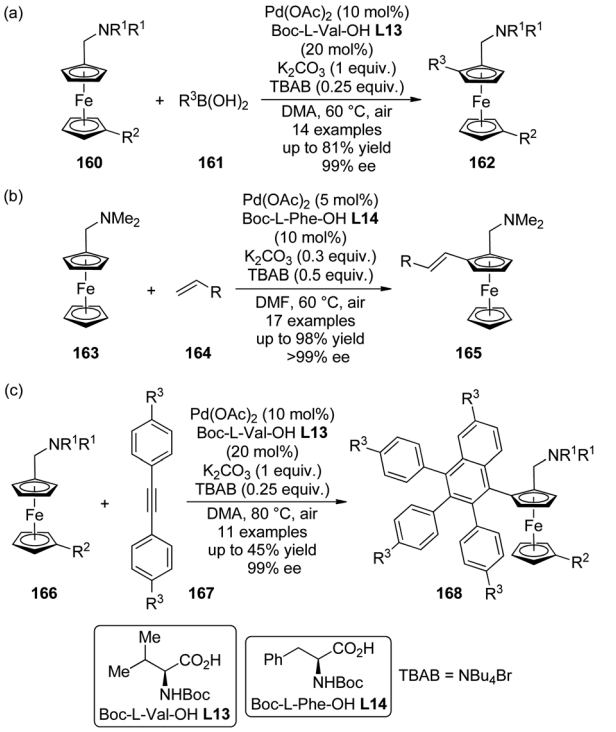
involved in further transformation is of particular importance in developing more efficient and practical C–H functionalization methodologies.[149] An extensive screening of the reaction parameters showed that Boc-L-Ile-OH·0.5H_2O **L12** was the best ligand for the asymmetric C–H bond olefination of the sodium diphenylcarboxylates **157** with styrene derivatives (or acrylates) **158** (Scheme 47). The loading of $Pd(OAc)_2$ and chiral ligand could be lowered to 5 mol% and 10 mol%, respectively, and O_2 (1 atm) could be used as the terminal oxidant. The desired products **159** were typically afforded in moderate yields (up to 73%) and good ee's (up to 97% ee).

Notably, despite enabling asymmetric C–H bond functionalization reactions, the mono-*N*-protected chiral amino acid ligands could also induce the Pd(II)-catalyzed C–H bond functionalization reactions in highly position-selective fashion.[150] In addition, the valuable "ligand-acceleration effect" was observed for several Pd(II)-catalyzed direct C–H bond olefination[150a,151] and arylation[152] reactions when mono-*N*-protected chiral amino acid ligands were employed, possibly due to the mechanistic switch for the C–H bond breaking step.[153] Fueled with these protocols, the Yu group achieved versatile direct C–H bond functionalization reactions effectively,[154] even in the late stage of complex molecule synthesis.[155]

The catalytic system comprised of $Pd(OAc)_2$ and mono-*N*-protected chiral amino acid ligands have recently been employed for the construction of planar-chiral ferrocene derivatives[156] *via* Pd(II)-catalyzed direct asymmetric C–H bond functionalization reactions.[157] Gu, You and co-workers[158] reported such cross-coupling reactions of *N*,*N*-dialkylaminomethylferrocenes **160** with arylboronic acids **161** (Scheme 48(a)). Boc-L-Val-OH **L13** was identified as the optimal ligand and adding catalytic amount of tetrabutylammonium bromide (TBAB) was critical to result in reasonable yields. A series of desired products **162** could be generated in DMA at elevated temperature (60 °C) under air in up to 81% yields with excellent enantiocontrol (up to 99% ee). Notably, a moderate kinetic resolution was observed for the formation of the bisarylation product. As the reaction time was prolonged, both the ratio of the bisarylation product and the ee of **162** increased slightly. A bromo-substituent on the other cyclopentadienyl ring was well tolerant (**160**, R^2 = Br), which allowed further transformation of the corresponding product to a planar-chiral *P*,*N*-ligand that could enable the Pd-catalyzed asymmetric allylic alkylation reactions.



Scheme 47 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by Yu.

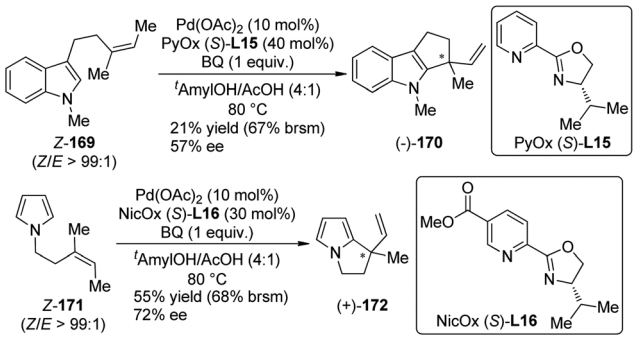


Scheme 48 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by (a) Gu and You, (b) Cui and Wu and (c) You, respectively.

Soon after, Cui, Wu and co-workers[159] communicated Pd(II)-catalyzed oxidative Heck reactions of ferrocene derivative **163** with various terminal olefins **164** including styrenes, α,β-unsaturated esters and phosphates (Scheme 48(b)). The *N*,*N*-dimethylaminomethyl moiety once again was the feasible directing group and Boc-L-Phe-OH **L14** exhibited the optimal catalytic activity. The results of the controlled experiments suggested that the redox process of ferrocene scaffolds by air facilitated the regeneration of active Pd(II) catalyst from the Pd(0) species.

By applying the same strategy, You and co-workers[160] realized the asymmetric synthesis of planar-chiral ferrocene derivatives **168** *via* Pd(II)-catalyzed direct coupling of ferrocene substrates **166** with diarylethynes **167**.[161] Under rather similar conditions to the previously reported asymmetric C–H bond arylation reactions,[158] such transformations were achieved with excellent enantioselectivity (up to 99% ee) albeit the yields are typically moderate (Scheme 48(c)). Notably, a sterically more demanding planar-chiral *P*,*N*-ligand derived from the coupling product shows enhanced chiral induction in Pd-catalyzed asymmetric allylic substitution reactions compared to that reported previously.[158]

Inspired by Stoltz's work on Pd(II)-catalyzed racemic oxidation indole annulation,[162] Oestreich and co-workers[163] developed the enantioselective version of this intramolecular Fujiwara–Moritani reactions[164] of indole and pyrrole derivatives **169** and **171**. With a PyOX ligand (*S*)-**L15** or a newly synthesized nicotine-based oxazoline ligand NicOX (*S*)-**L16**, 5-*exo-trig* cyclization occurred in moderate yields (up to 68% yield based on



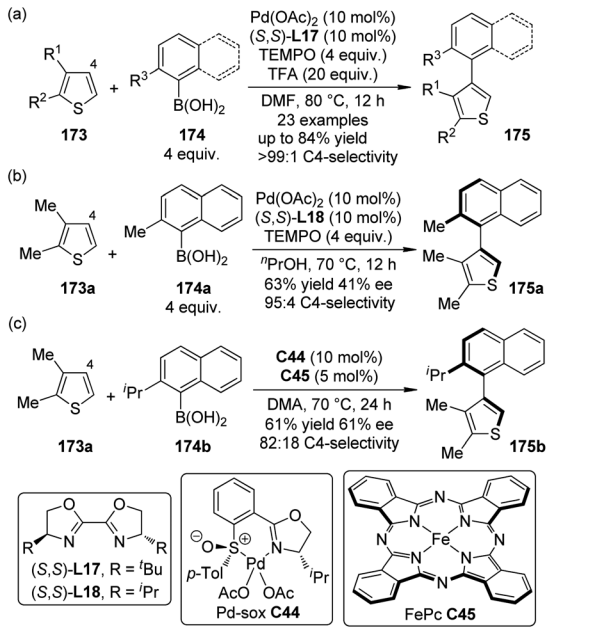
Scheme 49 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by Oestreich.

recovered starting material) and ee's (up to 72% ee), affording the desired products with a chiral quaternary carbon center (Scheme 49). Notably, the *Z*/*E* ratio of the double bond in the substrates has a strong influence of the stereochemical outcomes.

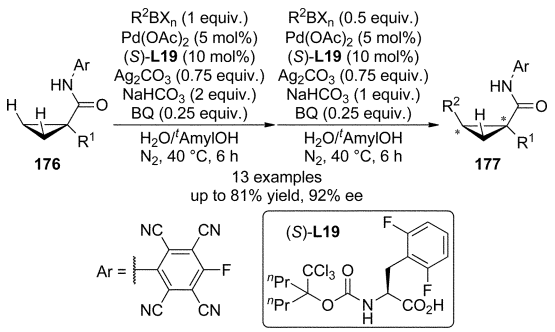
Biaryls and heterobiaryls are often important compounds of biological activity.[165] The synthesis of sterically hindered (hetero)biaryls with multiple *ortho*-substituents can be challenging owing to the low reactivity of the hindered coupling components. Based on their previous work on the C4-selective C–H bond arylation reactions of thiophenes with arylboronic acids,[166] Yamaguchi, Itami and co-workers[167] disclosed that the highly C4-selective coupling reactions of the 2,3-disubstituted thiophenes **173** with the *ortho*-substituted arylboronic acids **174** were promoted by a catalytic amount of $Pd(OAc)_2$ in combination with BOX ligand (*S*,*S*)-**L17** and TEMPO as the oxidant (Scheme 50(a)). The yields of the desired products **175** could be significantly improved (up to 84%) by adding TFA to the reaction mixture. The heteroaromatic substrates were not limited to thiophenes in that benzofurans and indoles could also participate in such reactions. By employing a slightly modified reaction conditions, asymmetric induction was achieved with the $Pd(OAc)_2$/(*S*,*S*)-**L18** catalyst, although the yield and ee of product **175a** were only moderate (Scheme 50(b)). Recently, the same group[168] disclosed a dual catalytic system comprising Pd(II)-sulfoxide-oxazoline complex (Pd-sox, **C44**) and Fe-phthalocyanine (FePc, **C45**) that can enable similar asymmetric coupling under air without stoichiometric co-oxidants (Scheme 50(c)).

Transition metal-catalyzed direct functionalization of $C(sp^3)$–H bonds that involves a transient M–C species are much more difficult compared with that of $C(sp^2)$–H bonds due to their weak coordinating ability to the metal centers.[169] In their seminal report on the use of mono-*N*-protected amino acids as the ligands for the Pd(II)-catalyzed asymmetric aromatic C–H bond functionalization in 2008,[144] Yu and co-workers described promising initial results (37% ee) for asymmetric functionalization of terminal methyl group. In 2011, the Yu group[170] developed the Pd(II)-catalyzed enantioselective C–H bond functionalization reactions of cyclopropanes. The 1,1-disubstituted cyclopropanes **176** bearing an acidic *N*-arylamides as weakly coordinating directing groups[171] were utilized as the substrates. The systematic evaluation of structurally diverse *N*-protecting groups as well as the amino acid backbones of the chiral ligands revealed that (*S*)-**L19** containing a modified *N*-Boc group and the 2,6-difluorobenzyl as the α-substituent led to the optimal asymmetric induction of the C–H/R–BX_n cross-coupling reactions (Scheme 51). The substrate scope of this transformation was general. Various alkyl and aryl groups bearing functional groups such as ethers and protected amines could be tolerated at the α-position of amide directing group of **176** (R^1), affording the corresponding products **177** in up to 81% yield and 92% ee under mild conditions.

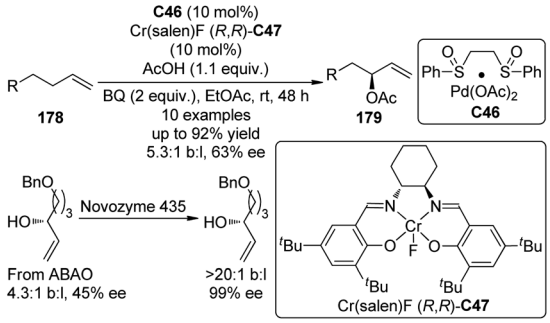
Another type of promising $C(sp^3)$–H bond functionalization occurs at the allylic position[172] and it can be viewed as an atom-economical alternative of the traditional Tsuji–Trost allylic substitution reactions which employs allylic halides, esters or carbonates as the substrates.[173] In 2008, Shi and co-workers[174] reported the formal asymmetric allylic C–H bond functionalization *via* Pd(0) catalyzed allylic and homoallylic diamination



Scheme 50 The Pd-catalyzed synthesis of heterobiaryls reported by Yamaguchi and Itami.



Scheme 51 The Pd-catalyzed asymmetric C–H bond functionalization reactions of cyclopropanes reported by Yu.

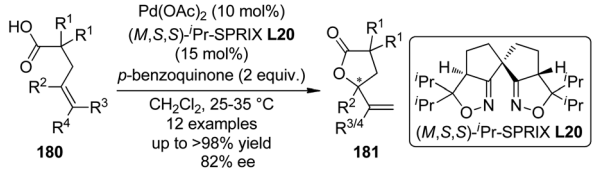


Scheme 52 The Pd-catalyzed asymmetric allylic C–H bond oxidation reactions reported by White.

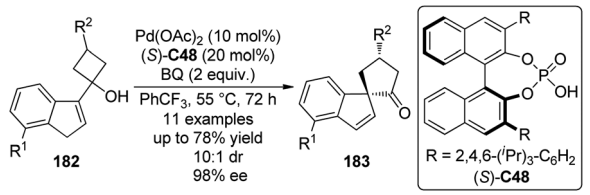
reactions between terminal olefins and *N*,*N*′-di-*tert*-butyldiaziridinone. On the other hand, Covell and White[175] achieved the asymmetric branched allylic C–H bond oxidation (ABAO) of terminal olefin substrates **178** using the serial ligand catalysis strategy by Pd(II)/sulfoxide catalyst **C46** in combination with a chiral Lewis acid Cr(Salen)F (*R*,*R*)-**C47** to furnish the enantioenriched allylic alcohol derivatives **179** (Scheme 52). Since the enantioselectivities are modest (43–63% ee), the same authors[176] were able to combined the ABAO approach with enzymatic and/or small molecule catalyst based resolutions for the construction of chiral polyoxygenated motifs with high enantiopurity.

In 2011, Sasai and co-workers[177] reported an enantioselective cyclization of 4-alkenoic acids **180** *via* Pd(II)-catalyzed oxidative allylic C–H bond esterification. Among various ligands with quite different chiral backbones tested, only spiro bis(isoxazoline) ligand (*M*,*S*,*S*)-^{i}Pr-SPRIX **L20**[178] exhibited satisfactory activity and asymmetric induction. Under the optimized conditions, the desired γ-lactone products **181** were afforded in up to >98% yield and 82% ee (Scheme 53). Preliminary mechanistic studies prefer the mechanism that involves a π-allyl Pd intermediate over oxypalladation/β-hydride elimination sequence.

In 2012, Chai and Rainey[179] described the Pd(II)/chiral phosphoric acid catalyzed asymmetric allylic C–H bond activation/semipinacol rearrangement[180] protocol for the construction of spirocyclic compounds from indene derivatives **182**. Although various chiral oxazoline ligands failed to give satisfactory results, adding chiral phosphoric acids was found to have a dramatic effect on the reactivity and stereoinduction with (*S*)-**C48** as the optimal one. The corresponding ketones **183** with an all-carbon quaternary α-chiral center were obtained in up to



Scheme 53 The Pd-catalyzed asymmetric allylic C–H bond esterification reactions reported by Sasai.



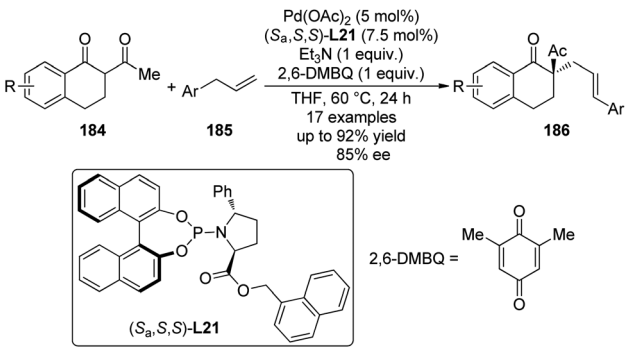
Scheme 54 The Pd-catalyzed asymmetric allylic C–H bond functionalization reactions reported by Rainey.

78% yield (up to quantitative yield based on recovered starting material) and 98% ee (Scheme 54). A primary kinetic isotope effect (KIE) value of 2.82–3.39 confirmed that the cleavage of the allylic C–H bond is prior to or during the rate-limiting step.

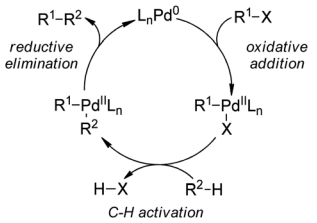
Recently, Trost and co-workers[181] reported the Pd(II)-catalyzed asymmetric allylic alkylation reactions through C–H bond activation.[182] With catalytic amount of $Pd(OAc)_2$ and the newly synthesized chiral phosphoramidite ligand (S_a,*S*,*S*)-**L21**, the asymmetric allylic alkylation reactions between the cyclic α-substituted β-diketones **184** went smoothly with a series of allylarenes **185** to generate their corresponding alkylation products **186** bearing an all-carbon quaternary chiral center in good yields and ee's (Scheme 55).

5.1.2. Pd(0)/Pd(II) catalytic cycle. Paralleled to the aforementioned Pd-catalyzed asymmetric C–H bond functionalization reactions that feature a Pd(II)/Pd(0) catalytic cycle, another category of C–H bond functionalizations that involve a conceptually different Pd(0)/Pd(II) catalytic cycle have also received considerable developments in recent years.[183] Mechanistically, these reactions start with the oxidative addition of Pd(0) catalyst to the organic halides (or equivalents) to afford the organopalladium(II) species that cleaves the C–H bonds of the other reaction component that can be regarded as the nucleophile. After the following reductive elimination, the Pd(0) catalyst was regenerated. Since the organic halides (or equivalents) work as the internal oxidants, the external oxidants are therefore not needed (Scheme 56).

The first Pd(0)-catalyzed enantioselective C(sp^2)–H bond functionalization reaction was reported by Albicker and Cramer[184] in 2009. The asymmetric desymmetrization of prochiral substrates **187** was expected to occur by the C–H bond



Scheme 55 The Pd-catalyzed asymmetric allylic C–H bond functionalization reactions reported by Trost.



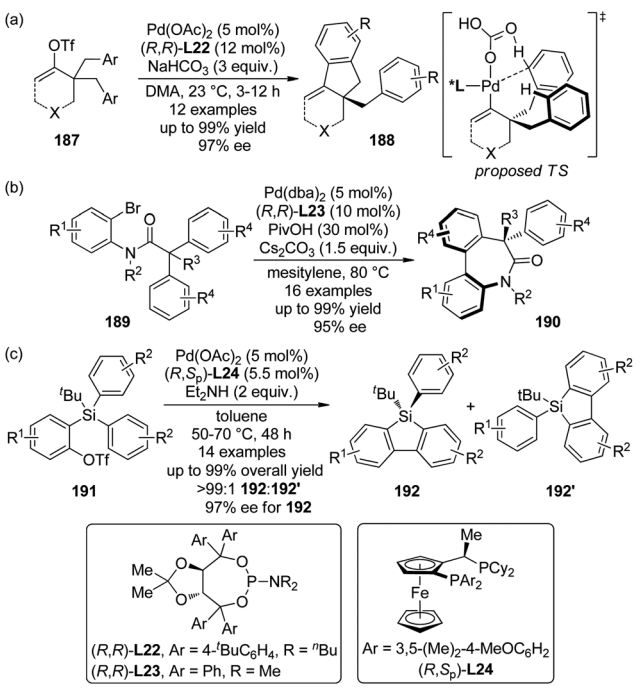
Scheme 56 The schematic mechanistic scenarios of the Pd(0)-catalyzed C–H activation/C–C coupling reaction.

functionalization *via* the transition state shown in Scheme 57(a). Thus only one coordination site on the Pd center was left for the external chiral ligands. In this context, a series of bulky monodentate phosphorus-based ligands were screened. While cyclohexyl-MOP ligand and Feringa-type ligands only led to moderate level of ee's, some TADDOL-based phosphoramidite ligands could result in enhanced enantioselectivity, with (*R*,*R*)-**L22** as the optimal one. The desired indane derivatives **188** were obtained in up to quantitative yields and 97% ee under mild conditions. Very recently, the Cramer group[185] extended this method to the enantioselective synthesis of functionalized dibenzazepinones **190** from the prochiral substrates **189**. The simplest TADDOL-based phosphoramidite ligand (*R*,*R*)-**L23** gave the best results and a bulky carboxylate ($PivO^-$) was critical for the chirality relay during the C–H bond cleavage (Scheme 57(b)). Quite a lot of functional groups such as amide, chloride and heteroaromatic rings were well tolerated. Remarkably, this reaction proceeded through a challenging eight-membered palladacyclic transition state. This pathway was still preferred even when other reaction site were available on the amide protecting groups (**189**, R^2 = Bn or ^{i}Pr) for the C(sp^2)–H or C(sp^3)–H bond functionalization through seven- or six-membered ring transition states.

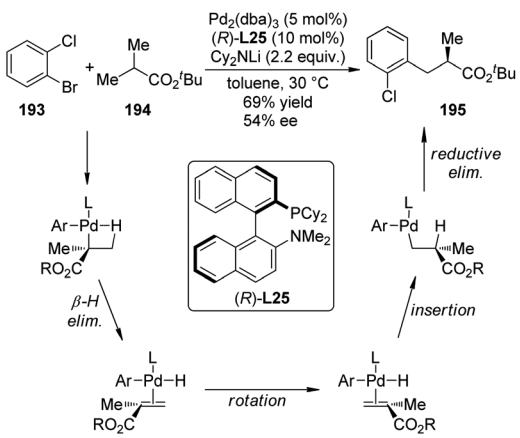
Similar strategy was applied by Shintani, Hayashi and co-workers[186] to construct enantioenriched silicon-stereogenic dibenzosiloles[187] *via* Pd(0)-catalyzed C–H bond functionalization. Different from Cramer's results, The Josiphos-type bisphosphine ligand (*R*,S_p)-**L24** was the most effective to promote the reactions of **191** with satisfactory outcomes. The corresponding products **192** were afforded with up to 97% ee (Scheme 57(c)). Kinetic studies suggested that the initial oxidative addition of aryl triflates was likely the turnover-limiting step and the following C–H bond cleavage occurs fast. The formation of the side product **192′** involving a [1,5]-Pd migration was effectively suppressed by using the bisphosphine ligand.

Much success has been achieved in recent years in the area of Pd(0)-catalyzed asymmetric C(sp^3)–H bond functionalization reactions. In 2010, Clot, Baudoin and co-workers[188] realized the Pd-catalyzed β-arylation of carboxylic esters **194** with aryl halides **193**. The electronegative group in the *ortho* position of the aryl halide was crucial to obtain the β-arylation products. Mechanistic investigations indicated that the β-arylation was not directed by the carbonyl group, but occurred *via* the β-hydride elimination of the initially formed palladium-C-enolate that was followed by rotation, re-insertion and the final reductive elimination (Scheme 58). Moderate level of enantioselectivity (up to 54% ee) could be achieved when BINOL-derived KenPhos (*R*)-**L25** was utilized as the chiral ligand.

Several groups have been engaged to the Pd(0)-catalyzed asymmetric C(sp^3)–H bond functionalization reactions of inert methyl or methylene moiety for the synthesis of enantioenriched indoline derivatives (Scheme 59). In 2011, Kündig and co-workers[189] found that the asymmetric C–H bond functionalization reactions of *N*-cycloalkyl substituted carbamates **196** (PG = CO_2Me) could be promoted by the chiral Pd complex (either preformed or generated *in situ*) ligated by bulky NHC ligand (*S*,*S*)-**L26**. Fused indolines **197** bearing *trans* [3.4.0]- or [3.5.0]-bicyclic backbones could be delivered with up to 95% ee



Scheme 57 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by (a) and (b) Cramer and (c) Shintani and Hayashi.



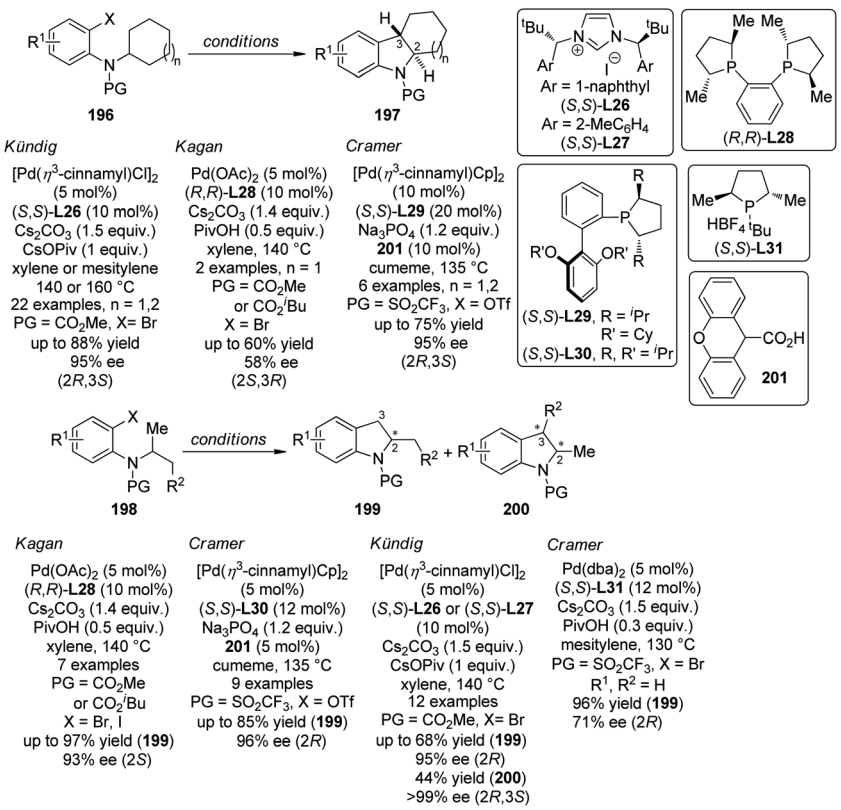
Scheme 58 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by Clot and Baudoin.

even at the elevated temperature (140 or 160 °C). Later, the Kündig group[190] showed that the regiodivergent C(sp^3)–H bond functionalization was possible for substrates **198** ($R^2 \neq H$). When NHC ligand (*S*,*S*)-**L26** or (*S*,*S*)-**L27** were employed, the C–H bond functionalizations both at the terminal methyl and methylene group of **198** could happen, leading to 2-substituted indoline **199** and 2,3-disubstituted indoline **200**. The matched/mismatched effect exhibited between the chiral catalyst and a series of racemic substrates. The (2*R*)-**199** were produced in higher yields but moderate level of ee's whereas the (2*R*,3*S*)-**200** were the minor products but with excellent ee's. The highest selectivity was observed when R^2 = Ph. In this case both (2*R*)-**199** and (2*R*,3*S*)-**200** were afforded with >95% ee when (*S*,*S*)-**L26** was used. Recent mechanistic studies by Kündig and co-workers[191] revealed that the ligand exchange (bromide for acetate/pivalate) appeared to be the rate-limiting step with the chiral catalysts and the C–H bond cleavage occurred fast but determined the enantioselectivity of the reaction.

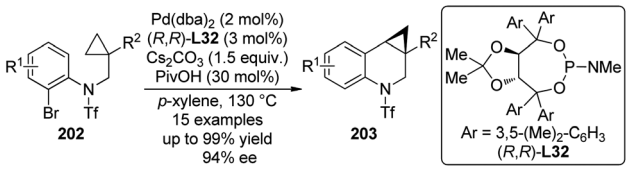
Almost at the same time as Kündig's first report in 2011, Kagan and co-workers[192] found that the chiral bisphosphine ligand Me-DuPhos (*R*,*R*)-**L28** could also be utilized in Pd-catalyzed C–H bond functionalization reactions (Scheme 59). Several 2-substituted indolines **199** could be generated with up to 93% ee from the corresponding substrates **198** (R^2 = H) by the catalytic system comprised of $Pd(OAc)_2$ and (*R*,*R*)-**L28**. In addition, two examples of such reactions involving substrates **196** were described, albeit the ee's of the products were only moderate.

In 2012, Cramer and co-workers[193] synthesized a new class of modular monodentate phosphine ligands SagePhos by incorporating the electron-rich C_2-symmetric phospholane moieties into the Buchward-type biphenyl backbone. With the novel sterically demanding ligands such as (*S*,*S*)-**L29** and (*S*,*S*)-**L30**, the asymmetric C–H bond functionalization reaction of the substrates **196** and **198** bearing either cyclic or acyclic *N*-substituents were accomplished (Scheme 59). It was also disclosed that adding bulky acid like **201** to the reaction was crucial for enhancing the enantioselectivity, probably because it could help to relay the chiral information from the ligand to the reactive center. The significant cooperative effects were observed in that a pair of enantiomers of chiral acids in combination with the same chiral catalyst could result in the products in reversed absolute configuration respectively. The utilization of an enantiopure acid as the only chirality source also led to a moderate level of asymmetric induction. Recently, the Cramer group[194] developed a series of chiral monodentate trialkylphosphine ligands like (*S*,*S*)-**L31**, and found that their Pd complexes could also catalyze the asymmetric C–H bond functionalization reaction for the synthesis of 2-substituted indolines **199** although the enantioselectivity was not high.

Besides the enantioselective synthesis of indoline derivatives *via* Pd catalyzed C–H bond functionalization reactions, the Cramer group[195] also communicated the efficient access to functionalized tetrahydroquinolines through the direct functionalization of the cyclopropane C–H bond of substrates **202**. After screening various reaction conditions, The use of catalytic



Scheme 59 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by several groups.

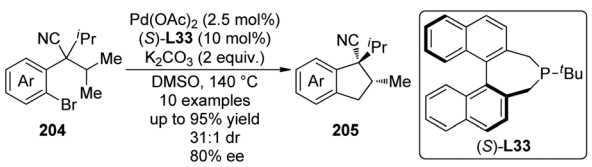


Scheme 60 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by Cramer.

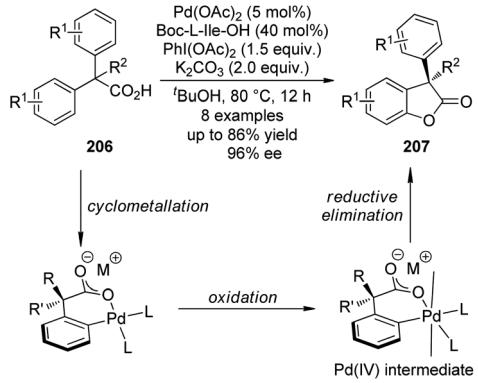
amounts of $Pd(dba)_2$, TADDOL-based phosphoramidite ligand (*R*,*R*)-**L32** in conjunction with pivalic acid presented the optimal enantioselectivity (Scheme 60). Remarkably, the reaction could be performed on a gram-scale with the loading of Pd salts as low as only 1 mol%. The enantioenriched tetrahydroquinolines **203** were readily transformed to the corresponding tetrahydrobenzoazepines *via* the enantiospecific cyclopropane cleavage.

Baudoin and co-workers[196] applied the strategy of direct functionalization of inert C–H bonds to the asymmetric synthesis of fused cyclopentane compounds. Compared with the aforementioned synthesis of indolines, the use of substrates **204** posed an additional challenge since the replacement of nitrogen atom by a quaternary benzylic carbon atom causes the existence of both diastereotopic and enantiotopic C–H bonds. An extensive survey of various Pd sources and chiral ligands indicated the combination of $Pd(OAc)_2$ and binepine ligand (*S*)-**L33** could give the best results. An array of desired products **205** was afforded in up to 95% yields with reasonable stereoselectivity (up to 31 : 1 dr and 80% ee) (Scheme 61).

5.1.3. Pd(II)/Pd(IV) catalytic cycle. The third class of general mechanistic scenario for the Pd-catalyzed direct C–H bond functionalization reactions is characterized by a Pd(II)/Pd(IV) catalytic cycle.[197,198] Wang and co-workers[199] envisioned that the enantioselective synthesis of chiral benzofuranones **207** could be achieved by Pd(II)-catalyzed asymmetric C–H bond activation/C–O bond formation reactions of α,α-disubstituted phenylacetic acids **206** that involves the reductive elimination facilitated by the oxidation of the Pd(II) metallacycle to a transient Pd(IV) intermediate with a bystanding oxidant. This idea was indeed realized by utilizing the catalytic system of $Pd(OAc)_2$/Boc-L-Ile-OH in combination with $PhI(OAc)_2$, a widely used oxidant for the Pd(II)/Pd(IV) catalysis (Scheme 62). The reactions of several prochiral substrates went smoothly to give the corresponding desymmetrization products in up to 86% yield and 96% ee. The absolute configuration of the final products suggested that the previously proposed stereochemical model[145,148] for the $Pd(OAc)_2$/mono-*N*-protected amino acid ligand system



Scheme 61 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by Baudoin.



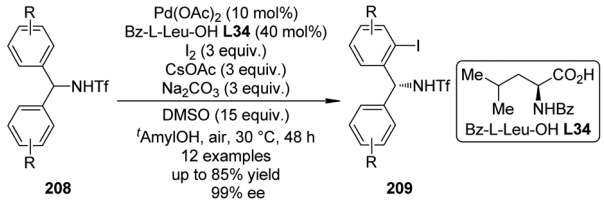
Scheme 62 The Pd-catalyzed asymmetric C–H bond functionalization reactions reported by Wang.

still worked in this case even if the reaction proceeded through a different redox course.

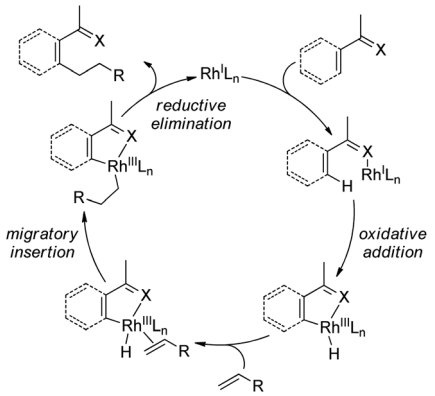
Very recently, Yu and co-workers[200] developed a Pd(II)-catalyzed enantioselective C–H bond iodination reaction of prochiral substrates **208** with molecular I_2 as the sole oxidant.[201] After careful evaluation of the reaction conditions, it was finally found that Bz-L-Leu-OH **L34** is the optimal ligand, and the combination of CsOAc and Na_2CO_3 as the base effectively promotes the reaction. Higher enantioselectivity could be obtained using a binary solvent system of ^{t}AmylOH with DMF or DMSO, probably due to DMF or DMSO could avoid racemic background reaction by sequestering the small amount of free Pd(II) species not coordinated to the chiral ligands. Thanks to this novel strategy, an array of chiral diarylmethylamines **209** could be synthesized in up to 85% yield and 99% ee under quite mild conditions (30 °C, air) (Scheme 63). However, whether a Pd(IV) intermediate is involved in this reaction is not clear at this stage.

5.2. Rh-Catalyzed reactions

5.2.1. Rh(I) catalysis. Rh is another transition metal of significant importance in catalyzing direct C–H bond functionalization reactions. These reactions can be further classified into two subgroups according to their mechanisms: Rh(I) catalysis and Rh(III) catalysis. The catalytic cycle of Rh(I) catalysis[202] starts with the oxidative addition of the Rh(I) catalyst to the aromatic or olefinic C–H bond. This step is often assisted with an *ortho* chelating group. Subsequently, the formed C–Rh species inserts into an unsaturated functionality such as alkene, alkyne, or imine intra- or intermolecularly to deliver a new C–Rh



Scheme 63 The Pd-catalyzed asymmetric C–H bond iodination reactions reported by Yu.

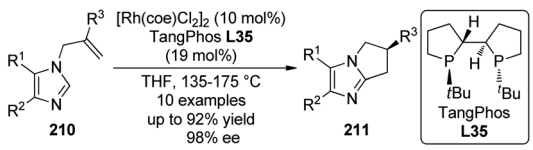


Scheme 64 The schematic mechanistic scenarios of the Rh(I)-catalyzed C–H bond functionalization reactions.

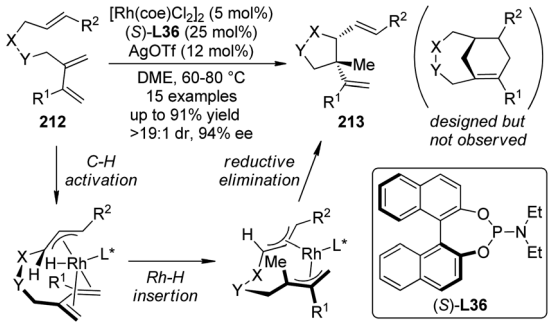
species. The final reductive elimination offers the product and at the same time regenerates the Rh(I) catalyst (Scheme 64). The group of Bergman and Ellman[203] made important contributions to the field of asymmetric Rh(I) catalyzed direct C–H bond functionalization reactions.[204] Several important natural products as well as molecules of biological activity have been synthesized based on this methodology.[205]

In 2009, Bergman, Ellman and co-workers[206] disclosed the Rh(I)-catalyzed enantioselective cyclization of *N*-allylic imidazoles **210** *via* C–H bond functionalization reactions. Among the structurally diverse chiral ligands that were screened, only TangPhos **L35** was highly active and at the same time exhibited superior asymmetric induction. Typically, with 19 mol% of **L35** and 10 mol% of $[Rh(coe)Cl_2]_2$, an array of cyclized products **211** was afforded in up to 92% yield and 98% ee even at remarkably high temperature (135–175 °C) (Scheme 65). In some cases, comparable results could be achieved with prolonged reaction time where the loadings of the Rh precursor and the ligand were lowered to 2.5 mol% and 4.9 mol%, respectively. The superb performance of **L35** was probably the consequence of its highly electron-rich nature and the potential to partially dissociate from the metal center, liberating a vacant coordinating site during the catalytic cycle.

During the attempts to develop the Rh-catalyzed type II Diels–Alder reactions,[207] Li and Yu[208] serendipitously discovered the cyclization reactions of ene-2-diene substrates **212** to afford the *cis* disubstituted five-membered carbo- or heterocyclic compounds **213** *via* Rh-catalyzed allylic C–H bond functionalization. Later, by employing the chiral phosphoramidite ligand (*S*)-**L36** in combination with a cationic Rh(I) catalyst, Li and Yu[209] demonstrated the enantioselective variant of this reaction. The desired products bearing two consecutive chiral centers



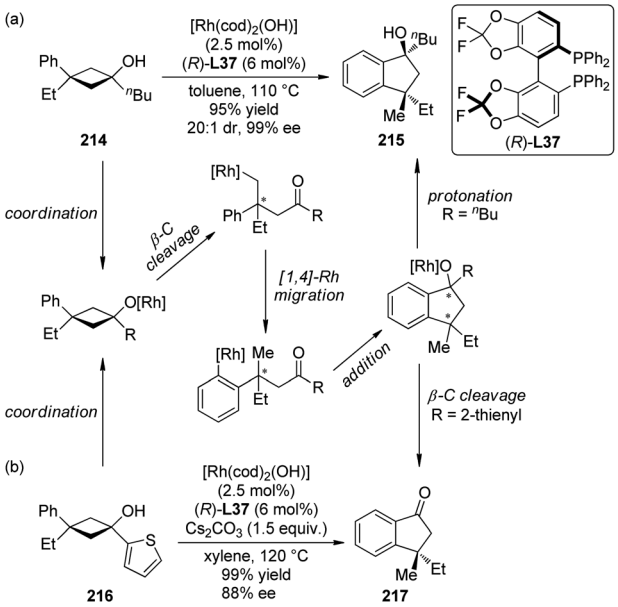
Scheme 65 The Rh-catalyzed asymmetric C–H bond functionalization reactions reported by Bergman and Ellman.



Scheme 66 The Rh-catalyzed asymmetric C–H bond functionalization reactions reported by Yu.

could be synthesized in up to 91% yields and excellent stereocontrol (up to >19 : 1 dr and 94% ee) (Scheme 66). Detailed DFT calculations[210] suggested that the conjugated diene moiety is very critical for this allylic C–H bond activation reaction and the originally designed type II Diels–Alder reaction was disfavored by the bridgehead double-bond distortion. Notably, the chiral diene compounds obtained with this method could be used as efficient ligands in Rh-catalyzed asymmetric conjugated addition reactions between aryl boronic acids and α,β-unsaturated keones.[211]

The group of Cramer systematically studied the versatile transformations of cyclobutanols for the construction of quaternary chiral centers induced by the β-carbon elimination.[212] In 2009, Cramer and co-workers[213a] found that the substrates **214** could be used to synthesize multi-substituted chiral indanol derivatives **215** under Rh(I) catalysis (Scheme 67(a)). This reaction starts with the β-carbon cleavage by the initially formed Rh alkoxide species to form the primary alkyl Rh intermediate. The subsequent [1,4]-Rh migration[214] leads to



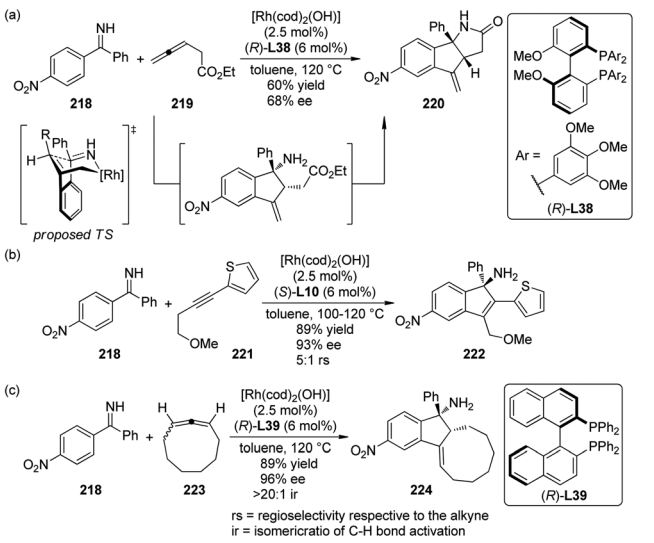
Scheme 67 The Rh-catalyzed β-carbon cleavage induced asymmetric C–H bond functionalization reactions reported by Cramer.

the aryl Rh intermediate that undergoes the addition to the formed ketone moiety. The catalytic cycle ends up with the protonation, affording the desired product. Shortly after Cramer's work, Murakami and co-workers[213b] reported similar results on the asymmetric synthesis of indanol derivatives. Later, Cramer and co-workers[215] envisioned that if the α-substituent of the cyclobutanol was replaced with an electron-rich aromatic ring such as 2-thienyl (**216**), the final step of the catalytic cycle might shift from the protonation to the β-aryl cleavage, giving rise to the corresponding indanones **217**. This idea was realized with the same catalytic system (2.5 mol% of $[Rh(cod)_2OH]$ and 6 mol% of (*R*)-**L35**), in the presence of an inorganic base Cs_2CO_3, which probably worked as an inhibitor to the protonation (Scheme 67(b)).

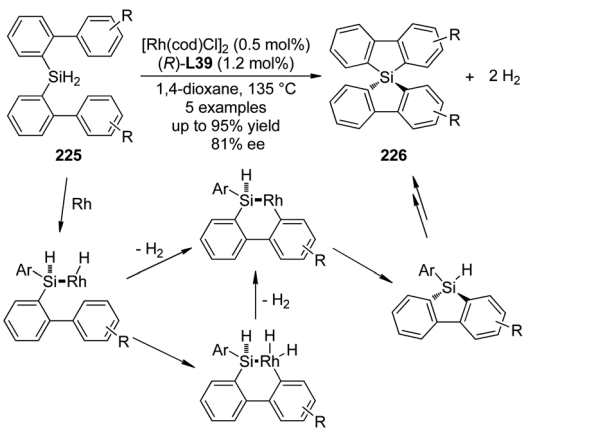
The C–Rh species generated from the aryl C–H bond activation/carborhodation sequence are also capable of enantioselectively adding to ketimines. This type of reactions was realized by Tran and Cramer[216] who used *N*-unsubstituted aryl imine **218** and terminal allene **219** as the substrates with the Rh(I) catalyst. One enantioselective example was described by employing very bulky and electron-rich bisphosphine ligand (*R*)-**L38** (Scheme 68(a)). It was suggested that the initial carborhodation occurred from the sterically less hindered face of the allene leading to the allyl-Rh intermediate that underwent the subsequent allylation *via* a chair-like transition state. Therefore the substituent on the allyl moiety and the free primary amine group adopted the *syn* configuration and the final condensation delivered the γ-lactam products **220**. By replacing the terminal allenes with the internal alkynes as the reaction components, Tran and Cramer[217] accomplished enantioselective Rh(I)-catalyzed annulation reactions of aromatic ketimines triggered by direct C–H bond functionalization. Another electron-rich bisphosphine ligand of increased steric bulk (*S*)-**L10** led to the optimal results. Notably, when unsymmetrically substituted alkynes **221** was utilized, the carborhodation was highly regioselective, with the new C–C bond formed preferentially at the carbon atom proximal to the directing group (OMe). The desired product **222** was afforded in 89% yield with 93% ee and 5 : 1 rs (Scheme 68(b)). Very recently, Tran and Cramer[218] reported the Rh(I)-catalyzed annulation reactions between racemic allenes and aryl ketimines *via* dynamic kinetic asymmetric transformations (DYKAT)[219] in the presence of a similar catalytic system ($[Rh(cod)_2(OH)]$ + (*R*)-**L39**). In this reaction, the racemic 1,3-disubstituted allene **223** undergoes fast racemization through Rh–H insertion/β-H elimination and σ–π–σ isomerization of the allyl-Rh intermediates. The cyclometallated intermediate generated by the C–H bond activation reacts selectively with the matching allene enantiomer, leading to the desired product **224** after downstream transformations (Scheme 68(c)).

Kuninobu, Takai and co-workers[220] demonstrated the Rh-catalyzed asymmetric synthesis of spirosilabifluorene derivatives through double dehydrogenative intramolecular cyclization reactions. Under the optimized conditions (0.5 mol % of $[Rh(cod)Cl]_2$ + (*R*)-**L39**), several bis(biphenyl)silanes **225** were converted to the desired silicon-stereogenic products **226** in satisfactory yields and good ee's with the concomitant extrusion of H_2 (Scheme 69). It was suggested that the reaction proceeds in two consecutive cyclization steps, each of which starts with the insertion of the Rh center into a Si–H bond. The subsequent C–H bond functionalization might occur either *via* σ-bond metathesis or oxidative addition/reductive elimination sequence. The final reductive elimination gives rise to the desired C–Si bond.[221]

5.2.2. Rh(III) catalysis. A second general category of the Rh-catalyzed C–H bond functionalization reactions that is typically referred to as Rh(III) catalysis[222] shares a lot in common with the reactions catalyzed by the Pd(II)/Pd(0) cycle described in the Section 5.1.1. Of particular interests among the various Rh(III)-catalyzed C–H bond functionalization reactions are the ones employing CONH(OMe) or CONH(OPiv)[223] which were first utilized independently by the groups of late Fagnou,[224] and Glorius[225] as an oxidizing directing group.[226,227] The catalytic cycle of the Rh(III)-catalyzed C–H bond functionalization of *N*-pivalate benzamides and olefins[228] starts with the consecutive



Scheme 68 The Rh-catalyzed C–H bond functionalization/cyclization reactions reported by Cramer.

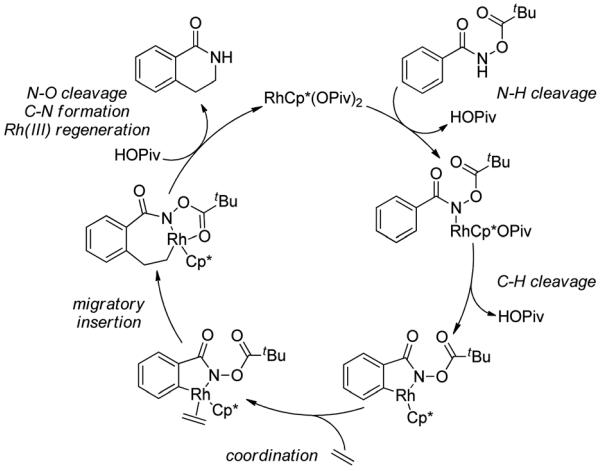


Scheme 69 The Rh-catalyzed asymmetric synthesis of spirosilabifluorene derivatives reported by Kuninobu and Takai.

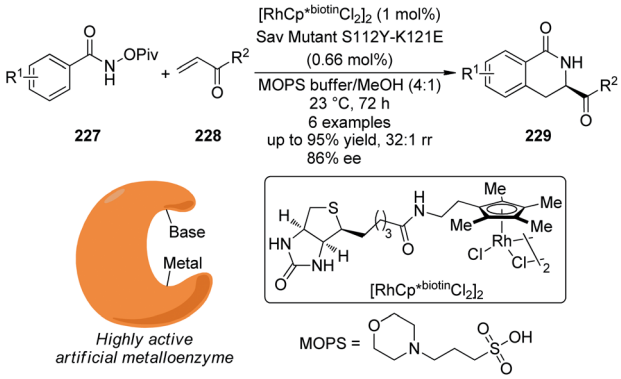
N–H bond and C–H bond cleavages assisted by the chelated base. Subsequently, the olefin coordinates to the Rh center and inserts into the C–Rh bond to afford the seven-membered rhodacycles. The following N–O bond cleavage/C–N bond formation sequence gives rise to the final lactam product with the concomitant regeneration of the Rh(III) catalyst (Scheme 70). Since the directing group here acts as an internal oxidant, the reactions can be conducted under very mild conditions (alcoholic solvents and room temperature).

However, it is pretty challenging to develop the enantioselective version of Rh(III)-catalyzed C–H bonds functionalization reactions in that the cyclopentadienyl (Cp) ligand is typically the only ligand that coordinates to the Rh center permanently throughout the catalytic cycle, and to design a chiral Cp ligand compatible with the late-transition metal-catalyzed reactions is of inherent difficulty.[229] Breakthroughs in this area were achieved very recently by the group of Ward and Rovis, as well as the group of Cramer *via* biochemical and chemical modifications of the Cp ligand respectively.[230]

Ward, Rovis and co-workers[231] were able to develop efficient artificial metalloenzymes[232] for Rh(III)-catalyzed asymmetric C–H bond functionalization reactions by applying the Biotin–Avidin technology.[233] In this study, a biotinylated Cp*Rh(III) complex named $[RhCp^{*biotin}Cl_2]_2$ was synthesized and incorporated to streptavidin (Sav) by taking advantage of the remarkable affinity between biotin and streptavidin. The *ortho* C–H bond functionalization reactions of benzhydroxamic acids **227** with acrylates or ethyl vinyl ketone **228** were selected as the model reactions (Scheme 71). By introducing basic residues in appropriate proximity to the metal center with the assistance of genetic engineering and computational modeling, high reactivity and enantioselectivity of the reactions were achieved. A double mutant (Ser[112] to Tyr and Lys[121] to Glu) of streptavidin S112Y-K121E could give the best results for a variety of substrates (up to 95% yield and 86% ee). Further mechanistic investigations showed that the C–H bond cleavage event is the turnover-limiting step and the metalloenzymes exhibit nearly 100-fold acceleration compared with the isolated Rh complex.



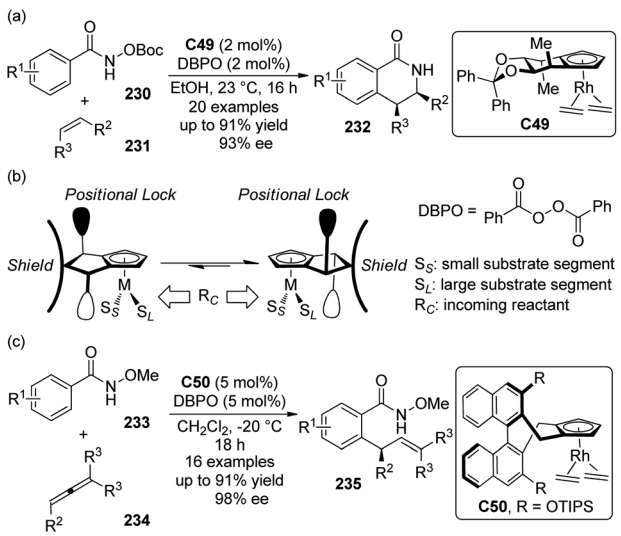
Scheme 70 The mechanism of the Rh(III)-catalyzed C–H bond functionalization with an oxidizing directing group.



Scheme 71 The biotinylated Rh(III) complex-catalyzed asymmetric C–H bond functionalization reactions reported by Ward and Rovis.

The engineered carboxylate residue is believed crucial to the highly efficient artificial "benzannulase".

On the other hand, Ye and Cramer[234] designed and synthesized a series of C_2-symmetric chiral Cp ligands. The Rh complexes of these ligands were successfully utilized in the enantioselective C–H bond functionalization reactions of hydroxamic acid derivatives **230** with various terminal and cyclic olefins **231** (Scheme 72(a)). The design of these novel chiral Cp ligands was according to the following considerations. The use of C_2-symmetric Cp derivatives could avoid the formation of undesired diastereoisomer due to the coordination of the metal to the other face of the Cp ring. The introduction of two positional locks on the Cp ligand restricted the rotation of the other two ligands on the metal center and thus fixed the conformation of metal–substrate complex. A sterically bulky substituent perpendicular to the Cp plane resulted in that the incoming reactant could only approach from just one side (Scheme 72(b)). Among the synthesized chiral Rh complex, **C49** led to the best results in terms of both yield and enantioselectivity, and the reaction featured a broad substrate scope. The



Scheme 72 The chiral Rh(III) complex-catalyzed asymmetric C–H bond functionalization reactions reported by Cramer.

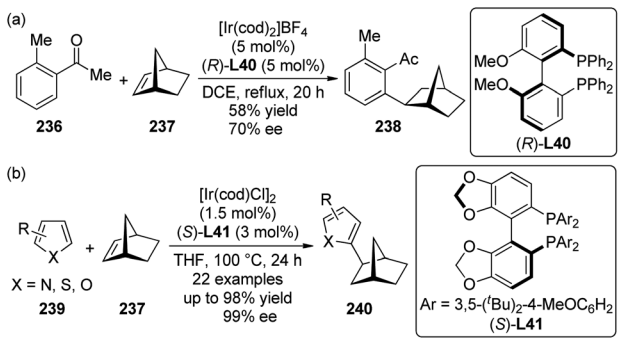
use of stable Rh(I) precursor and DBPO as the oxidant allowed the *in situ* generation of a competent Rh(III) catalyst. To be noted, the catalyst loading could be lowered to 1 mol%.

Based on the same strategy, Ye and Cramer[235] synthesized a tunable class of chiral Cp ligands derived from the BINOL skeleton and applied their Rh complexes to the C–H bond allylations of *N*–OMe protected benzamides **233** with trisubstituted allenes **234.**[236] In this case, the lower naphthyl portion of the ligand acts as the back wall and the *ortho* R group on the naphthyl ring has substantial influence to the shape of chiral pocket. After evaluation of a series of chiral Rh precursors, **C50** with a bulky *ortho* OTIPS substituent was identified as the optimal one (Scheme 72(c)). Under very similar conditions as the previously reported annulation reaction,[234] an array of allylated products **235** could be generated in up to 91% yield and 98% ee.

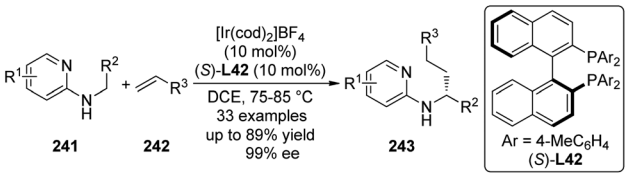
5.3. Ir-Catalyzed reactions

The history of iridium complexes being involved in the C–H bond activation reactions is quite long. However, the application of Ir-catalyzed functionalization of inert C–H bonds *via* a transient C–Ir species for the construction of C–C or C–X bonds in an enantioselective manner with high efficiency only emerges recently.[237] The successful reactions fall into the area of the asymmetric alkylation of C–Ir intermediates formed by the oxidative addition of Ir(I) precursors to the C–H bonds, which mechanistically resembles the reactions under Rh(I) catalysis presented in the Section 5.2.1.

In 2008, Shibata and co-workers[238] reported Ir-catalyzed asymmetric C–H bond alkylation reaction with norbornene **237** as the acceptor. The 2-methylacetophenone **236** was the only viable substrate. The *ortho* C–H bond alkylation product **238** was obtained in 58% yield and 70% ee (Scheme 73(a)). Sevov and Hartwig[239] recently expanded the substrate scope of this reaction to various heteroarenes. By using catalytic amount of $[Ir(cod)Cl]_2$ in combination with bisphosphine ligand (*S*)-DTBM-Segphos (*S*)-**L41**, the C–H bond adjacent to the heteroatoms of indoles, pyrroles, thiophenes and furans could add across norbronene to afford only one single constitutional isomer in both high yield and enantioselectivity (Scheme 69(b)). Preliminary mechanistic studies indicated that the oxidative addition of Ir(I) species to the heteroarene C–H bonds occurred prior to the turnover-limiting step.



Scheme 73 The Ir-catalyzed asymmetric C–H bond alkylation reactions reported by (a) Shibata and (b) Hartwig, respectively.



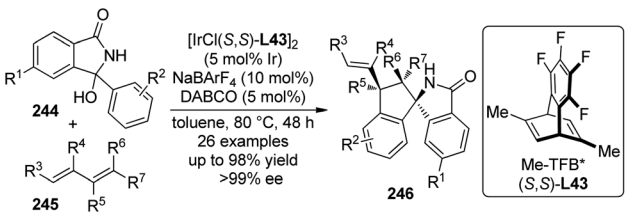
Scheme 74 The Ir-catalyzed asymmetric C–H bond alkylation reactions reported by Shibata.

The Shibata group[240] also realized Ir-catalyzed asymmetric secondary $C(sp^3)$–H bond alkylation reactions of 2-alkylaminopyridines with olefins. The cationic Ir(I) catalyst ligated by (*S*)-tolBINAP ligand (*S*)-**L42** could promote the reactions of the C–H bonds adjacent to the nitrogen atom of the substrates **241** with a large array of olefins **242** including styrenes and functionalized alkenes, leading to the desired chiral amine products **230** in up to 89% yield and 99% ee (Scheme 74). The nitrogen atom in the pyridine unit is likely acting as a directing group to facilitate the C–H bond cleavage through a six-membered ring transition state.

Nishimura *et al.*[241] achieved an asymmetric [3 + 2] annulation *via* Ir-catalyzed C–H bond functionalization to synthesize spiroaminoindane derivatives **246.**[242] With cationic Ir(I) catalyst generated from chiral diene ligand Me-TFB* (*S*,*S*)-**L43**,[243] the *in situ* formed cyclic *N*-acyl ketimines from the corresponding 3-aryl-3-hydroxyisoindolin-1-ones **244** react with 1,3-dienes **245** smoothly. The desired products were obtained with high yields and exceptional enantioselectivity (Scheme 75). The reaction also features relatively broad substrate scopes. An aryl–Ir(I) species formed by *ortho*-C–H bond functionalization is believed as the key intermediate of the reaction.

5.4. Kharasch–Sosnovsky reactions

The Kharasch–Sosnovsky reaction that refers to the Cu-catalyzed allylic oxidation reactions of alkenes with the *tert*-butyl peresters as the oxidant was first reported in the late 1950s.[244] The asymmetric variants of this reaction have been developed since mid-1990s.[245] Various nitrogen-based chiral ligands such as C_2-symmetric bis(oxazoline)s as well as proline-derived ligands were generally used. Although high level of enantioselective control could be reached, the viable substrates are mainly restricted to cyclic olefins and prolonged reaction time (up to several days at rt) is typically required. Thus, a general,

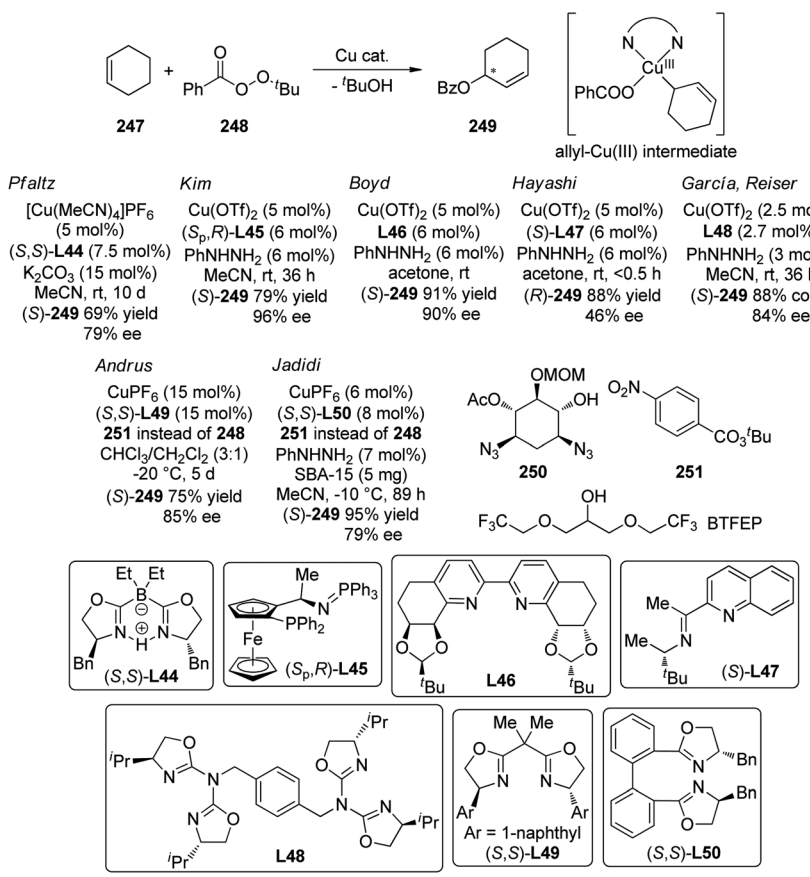


Scheme 75 The Ir-catalyzed asymmetric [3 + 2] annulation reaction reported by Nishimura.

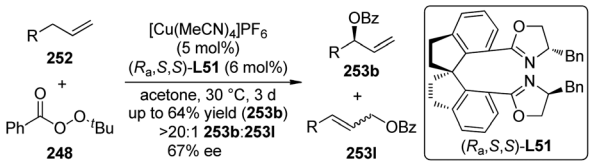
highly efficient catalytic system is still in great demand. Despite different mechanistic scenarios have been proposed, it is generally postulated that an allyl–Cu(III) intermediate is involved in the Kharasch–Sosnovsky reaction (Scheme 76).[246]

The Pfaltz group[247] synthesized chiral boron-bridged bisoxazoline ligand (*S*,*S*)-**L44** and evaluated their Cu complexes in the Kharasch–Sosnovsky reaction of cyclic olefins (Scheme 76). The enantioselectivity of the reaction was comparable with the previously reported best ones obtained using the BOX ligands.[248] Kim and co-workers[249] applied chiral (iminophosphoranyl)ferrocene ligands like (S_p,*R*)-**L45** in the same reactions. By using the *in situ* generated Cu(I) catalyst derived from the reduction of $Cu(OTf)_2$ with $PhNHNH_2$, the desired product **249** of the Kharasch–Sosnovsky reaction between cyclohexene **247** and *tert*-butyl perbenzoate **248** could be delivered in 79% yield and 96% ee. Boyd and co-workers[250] synthesized *cis*-dihydrodiol-derived 2,2′-bipyridine ligand **L46** and used it in the Kharasch–Sosnovsky reaction of **247**. The corresponding product was obtained in 91% yield and 90% ee with a similar protocol. Tan and Hayashi[251] reported the Kharasch–Sosnovsky reaction catalyzed by the Cu complex generated from novel *N*,*N*-bidentate Schiff base ligand (*S*)-**L47**. This catalytic system showed high reactivity in that the reaction of **247** completed in less than 0.5 h, although the ee of the product was only moderate. This protocol was further employed in the desymmetrization of 4,5-epoxycyclohexene for the synthesis of *O*-protected 2-deoxystreptamine precursor **250**.[252] García, Reiser and co-workers[253] developed an easily recoverable and reusable catalytic system based on a ditopic azabis(oxazoline) ligand **L48** for the Kharasch–Sosnovsky reaction. When the reaction was complete in MeCN or BTFEP, the ligand and Cu salt were able to form coordination polymers that could precipitate after extraction with hexane. The catalyst exhibited comparable activity after several successive recycles. Zhou and Andrus[254] found that the Cu complex derived from the naphthyl-substituted BOX ligand (*S*,*S*)-**L49** could promote the Kharasch–Sosnovsky reaction of **247** with *tert*-butyl *p*-nitroperbenzoate **251** as the oxidant, giving rise to the desired product **249** in 75% yield and 85% ee. Jadidi and co-workers[255] disclosed that in the presence of SBA-15 mesoporous silica as the additive, improved results (95% yield and 79% ee) could be observed for the Kharasch–Sosnovsky reaction catalyzed by the Cu complex derived from the atropisomeric chiral BOX ligand (*S*,*S*)-**L50**.

Apart from the recent development of the Kharasch–Sosnovsky reactions of cyclic olefins, the group of Zhu and Zhou[256] studied this reaction of acyclic terminal olefins using the chiral spiro bisoxazoline ligand (R_a,*S*,*S*)-**L51**.[257] A variety of the acyclic olefins **252** was investigated and the reactions of almost all the tested substrates led to the oxidation products with excellent regioselectivity (up to >20 : 1 b : l) favoring the branched allylic benzoates **253b** in up to 64% yield and 67% ee (Scheme 77). Functional groups such as ketone, ester and silyl were tolerated.



Scheme 76 The Cu-catalyzed asymmetric Kharasch–Sosnovsky reactions reported by several groups.

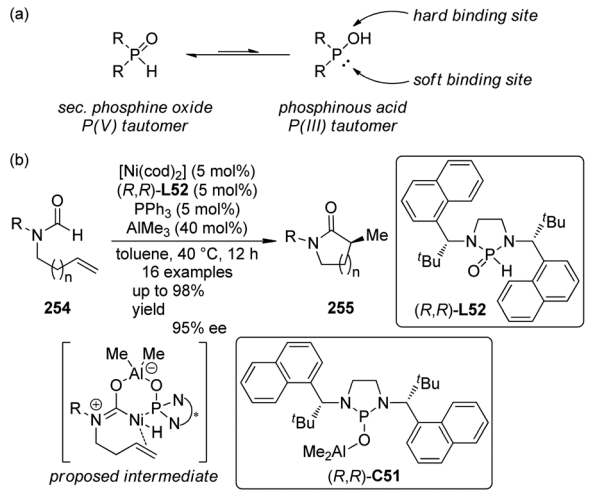


Scheme 77 The Cu-catalyzed asymmetric Kharasch–Sosnovsky reactions reported by Zhu and Zhou.

This report represented one of the best results for the Kharasch–Sosnovsky reactions of acyclic olefins.

5.5. Ni-Catalyzed reactions

Very recently, Donets and Cramer[258] reported a Ni-catalyzed asymmetric hydrocarbamoylation reactions of alkenes with diaminophosphine oxide ligands. It is known that secondary phosphine oxides are usually air-stable and robust preligand because of their unique tautomerization between the P(v) form and the P(iii) form.[259] In the presence of bases or transition metals, such equilibrium can be shifted to the trivalent phosphinous acid and thus provide the opportunity for the heterobimetallic catalysis where a late transition metal and an early transition metal can coordinate to the phosphorous atom and the oxygen atom, respectively (Scheme 78(a)). Bearing this idea in mind, the authors synthesized a class of chiral diaminophosphine oxide ligands[260] and tested them in the Ni-catalyzed intramolecular asymmetric hydrocarbamoylation reactions of formamides **254** with $AlMe_3$ as the other metal catalyst (Scheme 78(b)). The combination of $[Ni(cod)_2]$ and (*R*,*R*)-**L52** gave the optimal catalytic activity. Substrates with various substitution patterns were converted smoothly to the desired pyrrolidinones **255** in up to 98% yield and 95% ee under mild conditions. To be noted, a catalytic amount of PPh_3 was required to displace the cod from the Ni center for the generation of the competent catalytic species. In their mechanistic proposal, both $AlMe_3$ and $[Ni(cod)_2]$ coordinate to the chiral bridging ligand. The aluminum center activates the carbonyl group of the substrate, making the nickel center approximate to the formamide C–H bonds. The C–H bond cleavage takes place *via* a favorable six-membered heterocycle. The corresponding product is finally released after the subsequent migratory insertion and reductive elimination. In addition, the independently prepared aluminum complex (*R*,*R*)-**C51** could also be used. The loadings of this complex and the Ni precursor could be lowered to 0.25 mol% in this case. Interestingly, with (*R*,*R*)-**C51** as a catalyst, neither additional $AlMe_3$ nor PPh_3 was needed for achieving excellent results (97% yield and 94% ee).



Scheme 78 The Ni-catalyzed asymmetric hydrocarbamoylation reactions reported by Cramer.

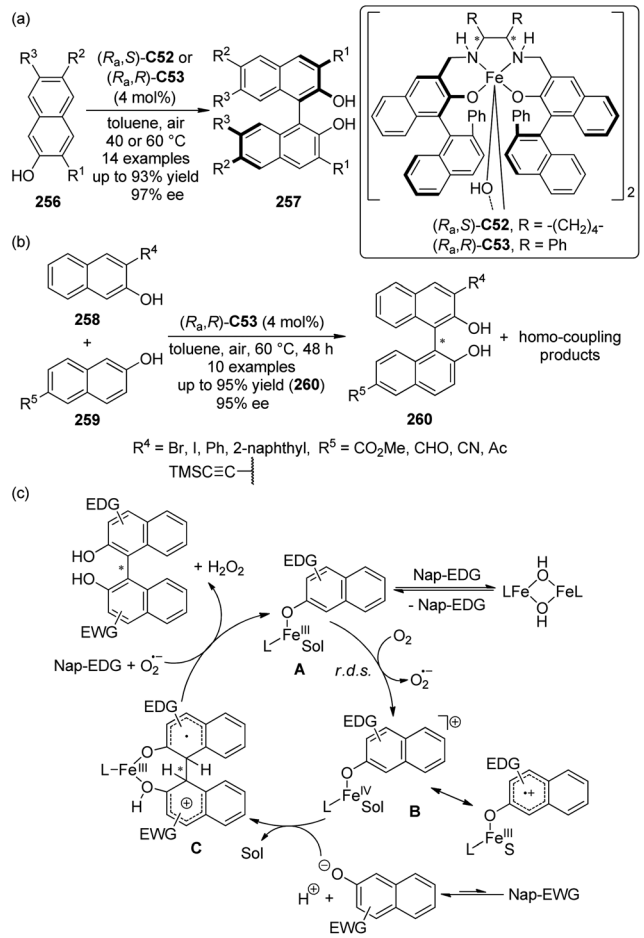
6. Miscellaneous reactions

6.1. Biaryl coupling reactions

The compounds possessing an axially chiral biaryl skeleton such as the BINOL derivatives[261] are among the privileged class of molecules for the application as ligands or catalysts in asymmetric catalysis.[262] Meanwhile, there are also numerous natural products that contain biaryl motifs.[263] Of various methods to construct this type of molecular architecture, the asymmetric oxidative coupling of 2-naphthols is probably the most straightforward and atom-economical way.[264]

In 2009, Egami and Katsuki[265] found that by using chiral di-μ-hydroxo dimeric Fe(iii)(salan) complex[266] (R_a,*S*)-**C52** or (R_a,*R*)-**C53** as the catalyst, various 2-naphthols **256** with different substitution patterns could undergo homo-coupling *via* asymmetric aerobic oxidation under mild conditions to afford enantioenriched BINOL-derivatives **257** (Scheme 79(a)). Notably, high level of enantioselectivity was observed when the C3-position of the naphthyl ring was substituted ($R^1 \neq H$). Functional groups such as halides, alkynes are well tolerated which allows further modification of the valuable BINOL skeletons. While an electron-withdrawing ester group is incorporated ($R^1 = CO_2Me$), no oxidative coupling reaction occurs. In their follow-up study, the Katsuki group[267] realized the Fe-catalyzed enantioselective synthesis of C_1-symmetric BINOLs[268] **260** through the cross-coupling of 2-naphthols (**258** and **259**) having sufficiently different redox potentials (Scheme 79(b)). Mechanistic investigations suggested that the radical–anion coupling mechanism might be operative (Scheme 79(c)). The dimeric Fe catalyst first dissociated to the monomeric species and reacts with the more electron-rich 2-naphthol (Nap-EDG) giving rise to the intermediate **A** that was oxidized to generate the radical cationic species **B**. On the other hand, the less electron-rich 2-naphthol (Nap-EWG) is more acidic and thus readily coordinates to the intermediate **B** in the anionic alkoxide form, yielding the intermediate **C**. The cross-coupling product is finally produced after the subsequent oxidation. Detailed X-ray diffraction analyses and cyclic voltammetry studies[269] revealed that the presence of the double hydrogen bonding in the Fe(salan) dimers, the oxidation potential of the monomeric Fe(salan) species as well as the location of the resulting radical cation have strong influence to the catalytic activity in this reaction.

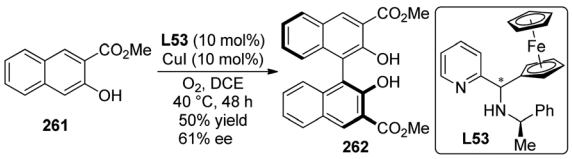
Prim and co-workers[270] synthesized a series of chiral *N*-heterocyclic pyridylmethylamine ligands and found their



Scheme 79 The Fe-catalyzed asymmetric biaryl coupling reactions reported by Katsuki.

corresponding Cu complexes could catalyze the oxidative coupling of electron-deficient 2-naphthol **261**. The complex of **L53** (diastereomerically pure but the absolute configuration of one chiral center not determined) showed the best asymmetric induction (61% ee) albeit the yield of the biaryl product **262** was only 50% (Scheme 80).

Sekar and co-workers[271] utilized a Cu(I) catalytic system comprised of CuCl and (*R*)-BINAM ((*R*)-**L54**, BINAM = 1,1′-binaphthyl-2,2′-diamine) to realize the asymmetric oxidative coupling of 2-naphthol derivatives **263**. Adding TEMPO as a co-oxidant was found to drastically increase the reaction rate as well as enantioselectivity. A series of enantioenriched BINOL products **264** bearing various ester groups at the 3,3′-positions

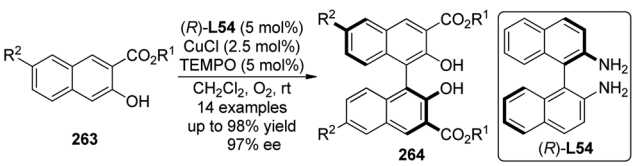


Scheme 80 The Cu-catalyzed asymmetric biaryl coupling reactions reported by Prim.

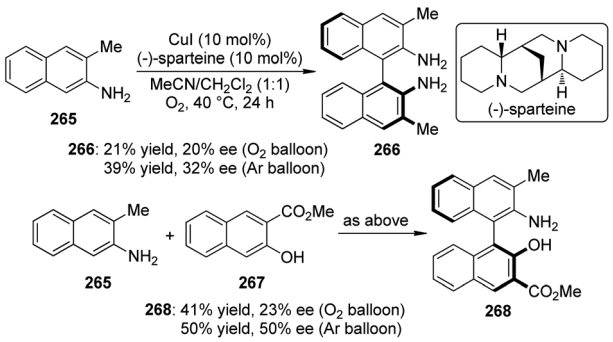
were obtained under very mild conditions (Scheme 81). A complex of CuCl·2**L54** was also isolated and characterized by single crystal X-ray diffraction analysis.

Mikami and co-workers[272] reported the Cu-catalyzed asymmetric homo-coupling reaction of 3-substituted naphthylamine **265** and its hetero-coupling reaction with 3-substituted naphthol **267**. By using (−)-sparteine as the chiral ligand, the desired products 3,3′-dimethyl-2,2′-diamino-1,1′-binaphthyl **266** (DM-DABN) and 3,3′-disubstituted 2-amino-2′-hydroxy-1,1′-binaphthyl **268** (NOBIN)[273] were afforded when O_2 was used as the oxidant. Interestingly, it was found that the enantioselectivity of the coupling products was relatively higher with lower concentration of O_2 (Ar balloon with O_2 gradually introduced to the reaction mixture through the balloon) (Scheme 82).

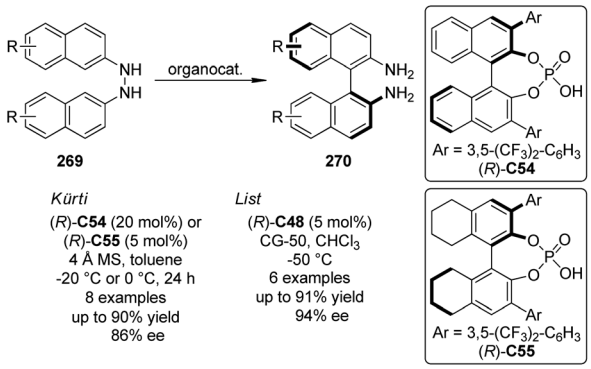
Very recently, the Kürti group[274] reported the asymmetric synthesis of BINAM derivatives *via* an atroposelective [3,3]-rearrangement reactions using *N*,*N*′-diaryl hydrazines **269** as the substrates. Various organocatalysts were evaluated and the chiral phosphoric acids (*R*)-**C54** and (*R*)-**C55** could give the optimal results in terms of both yields and ee's of the products **270** (Scheme 83). It was found that lowering the temperature and adding 4 Å molecular sieves (MS) were beneficial to improve the enantioselectivity. The reaction performed well on a 2–10 mmol scale (up to 2.8 g) and the catalysts could be recovered in nearly quantitative yield (99%) after flash chromatography. Based on DFT calculations, plausible transition states for the C–C bond forming step were postulated that the phosphate acts as a chiral counterion and creates a chiral pocket for the diastereoselective discrimination. Almost at the same time, List and co-workers[275] developed a very similar strategy for the asymmetric synthesis of BINAM derivatives.[276] In their cases, the chiral phosphoric acid (*R*)-**C48** was identified as the best



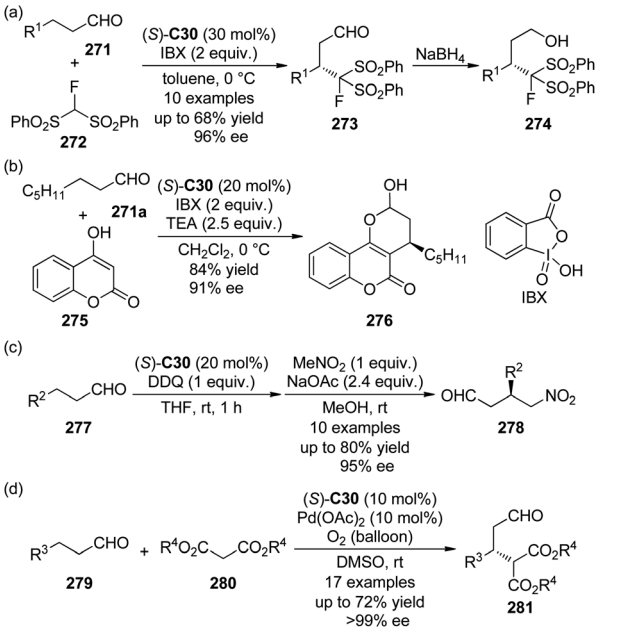
Scheme 81 The Cu-catalyzed asymmetric biaryl coupling reactions reported by Sekar.



Scheme 82 The Cu-catalyzed asymmetric biaryl coupling reactions reported by Mikami.



Scheme 83 The chiral phosphoric acid-catalyzed asymmetric [3,3]-rearrangement reactions reported by Kürti and List, respectively.



Scheme 84 The asymmetric β-functionalization reactions of aldehydes reported by (a) and (b) Li and Wang, (c) Hayashi, and (d) Xu, respectively.

catalyst and the weakly acidic CG-50 resin was a viable additive, allowing lower catalyst loading with full consumption of the substrates. Notably, a significant negative nonlinear effect was observed, which is consistent with a dicationic mechanism where two catalyst anions might be involved.

6.2. β-Functionalization of carbonyl compound

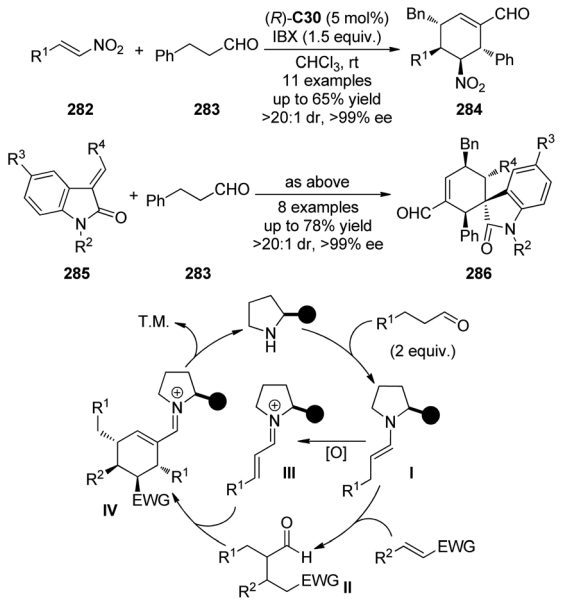
The asymmetric α-functionalization of carbonyl compounds has received considerable development in the past several decades and serves as prominent method for the enantioselective construction of C–C bonds in modern organic synthesis.[277] However, the direct asymmetric β-functionalization of simple saturated carbonyl compounds, on the other hand, still remains elusive. Given that the strategy involving the transformation of an iminium ion to an enamine in the "iminium catalysis" provides unique opportunity to functionalize the β- and α-position of aldehydes and ketones sequentially,[278] the group of Li and Wang as well as the group of Hayashi envisioned the reverse "enamine to iminium ion" process facilitated by proper oxidants could be capable to incorporate an nucleophile to the β-position of simple aldehydes and thus furnished the concept of "oxidative enamine catalysis" independently.[279]

In 2011, Li, Wang and co-workers[280] disclosed that by utilizing diphenylprolinol silyl ether (*S*)-**C30** as the catalyst, in combination with IBX as the oxidizing agent, simple aldehydes **271** could react with fluorobis(phenylsulfonyl)methane (FBSM) **272** smoothly to afford the β-functionalized aldehydes **273** in moderate yields and high ee's (Scheme 84(a)). In addition, this methodology could be further integrated to a variety of multiple cascade reactions to deliver versatile chiral targets such as coumarin-containing pyran **276** (Scheme 84(b)). Noticeably, relatively high catalyst loading (20–30 mol%) is required since the chiral amine catalyst can be oxidized by IBX. Almost at the same time, the Hayashi group[281] reported a very similar procedure employing DDQ as the oxidant and $MeNO_2$ as the nucleophile. A number of functionalized aldehydes **278** were obtained in a one-pot manner in up to 80% yield and 95% ee (Scheme 84(c)). Very recently, Xu and co-workers[282] developed an enantioselective β-functionalization reaction of aldehydes **279** with malonate diesters **280** by combining enamine/iminium ion catalysis and $Pd(OAc)_2$ catalyzed Saegusa oxidation.[283] Only O_2 (1 atm) was required to serve as the oxidant (Scheme 84(d)).

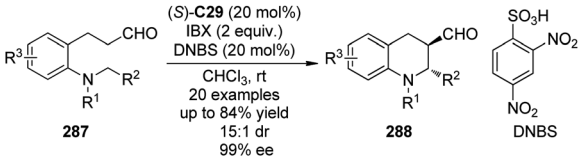
Enders and co-workers[284] integrated the asymmetric β-functionalization reactions of aldehydes into the organocatalytic two-component four-step "branched domino reaction" to synthesize polyfunctionalized cyclohexene derivatives. According to the proposed catalytic cycle (Scheme 85), two equivalents of β-substituted aldehydes are required. The enamine intermediate **I** generated from the aldehyde and secondary amine catalyst attacks a Michael acceptor leading to intermediate **II**. Simultaneously, **I** can be oxidized to the α,β-unsaturated iminium intermediate **III**. The following reaction between **II** and **III** gives the final product.[285] In the presence of catalytic amount of (*R*)-**C30** and 1.5 equiv. of IBX, the reactions of dihydrocinnamaldehyde **283** with nitroolefins **282** or oxindole derivatives **285** went smoothly to afford their corresponding products **284** and **286** in good yields and excellent dr's and ee's.

Kang and Kim[286] successfully applied the strategy of oxidative enamine catalysis into the [1,5]-hydride transfer/cyclization sequences.[130] By using the secondary amine catalyst (*S*)-**C29** in combination with IBX as the oxidant, a series of *ortho-tert*-amine-substituted dihydrocinnamaldehydes **287** were first oxidized to the corresponding α,β-unsaturated iminium intermediates that underwent the subsequent asymmetric [1,5]-hydride transfer/cyclization reactions to afford the desired tetrahydroquinoline derivatives **288** (Scheme 86).

Chi and co-workers[287] realized the NHC-catalyzed asymmetric β-functionalization reactions of aldehydes *via* the transformation of saturated aldehydes to formal Michael acceptors by the double oxidation.[288] By using the catalyst



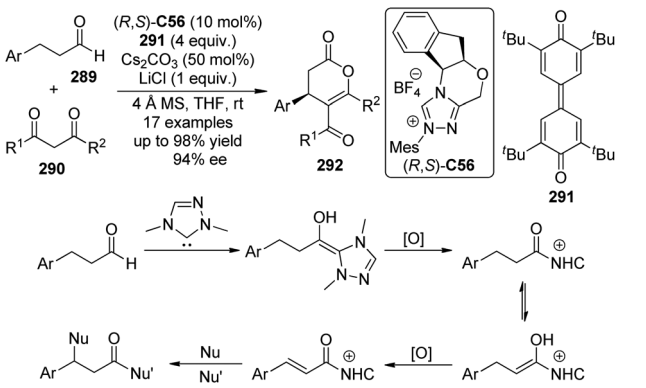
Scheme 85 The organocatalytic domino reactions involving β-functionalization of aldehydes reported by Enders.



Scheme 86 The asymmetric oxidative [1,5]-hydride transfer/cyclization reactions reported by Kim.

derived from chiral amino-indanol triazolium salt (*R*,*S*)-**C56** in combination with quinone **291** as the oxidant, the β-aryl substituted saturated aldehydes **289** were converted to the α,β-unsaturated acyl azolium intermediates which further reacted with 1,3-dicarbonyl compounds or β-keto esters **290** to generate the corresponding δ-lactones **292** (Scheme 87). It was found the use of LiCl and 4 Å MS as additives was beneficial to improve the ee's of the products. Notably, the β-alkyl substituted saturated aldehydes were not viable substrates, probably due to the reduced acidity of the β-C–H bonds.

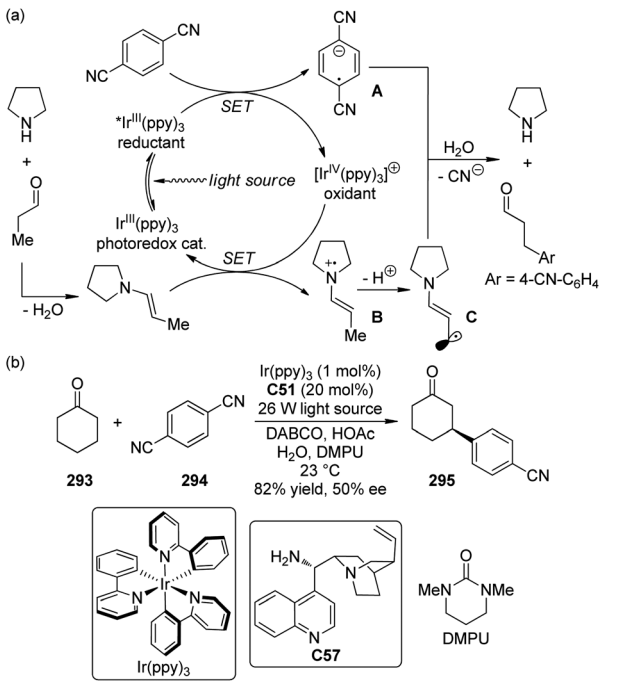
MacMillan and co-workers[289] envisioned that the β-functionalization of carbonyl compounds could be realized by combining the merging visible light mediated photoredox catalysis with the amine catalysis.[290] The designed dual catalytic cycle (Scheme 88(a)) starts with the formation of the excited state *Ir(III)(ppy)$_3$ upon the visible light irradiation of the well-known photoredox catalyst Ir(III)(ppy)$_3$. The high energy *Ir(ppy)$_3$ is readily oxidized to Ir(IV)(ppy)$_3$ by 1,4-dicyanobenzene *via* an SET process with the concomitant generation of radical anion **A**. Subsequently, the electron-rich enamine intermediate formed after the condensation of the carbonyl compounds and the amine catalyst is oxidized by Ir(IV)(ppy)$_3$ to afford the corresponding radical cation **B** which is further transformed to the



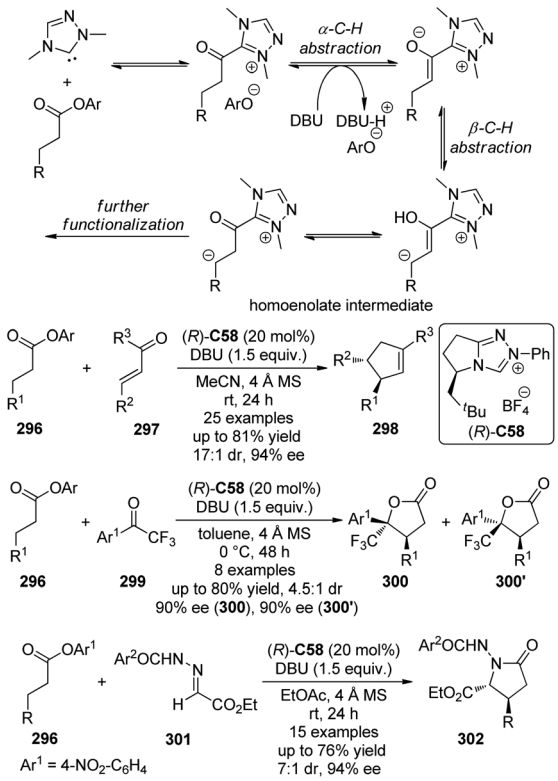
Scheme 87 The asymmetric β-functionalization reactions of aldehydes reported by Chi.

5πe$^-$ intermediate **C** *via* the allylic proton abstraction by a proper base. The desired products will be delivered after the radical coupling between intermediates **A** and **C** and following cyanide extrusion. This elegant transformation was realized for a large array of simple aldehydes and ketones with one enantioselective example (challenging inactivated ketone **293**) where cinchona-derived primary amine catalyst **C57** was employed although the ee of the product **295** was only moderate (Scheme 88(b)).

Very recently, the Chi group[291] achieved versatile enantioselective β-functionalization of esters through NHC catalysis.[7] In their postulated catalytic cycle (Scheme 89), the NHC catalyst first reacts with the ester to form the acyl azolium intermediate.[292] The subsequent α-C–H abstraction produced the enolate intermediate. Due to the electron-withdrawing ability of the



Scheme 88 The asymmetric β-arylation reactions of aldehydes and ketones reported by MacMillan.



Scheme 89 The asymmetric β-functionalization reactions of esters reported by Chi.

triazolium moiety and the conjugated nature of this intermediate, the β-proton of the ester could become acidic and the deprotonation could give rise to the corresponding homoenolate intermediate that is traditionally accessed *via* extended umpolung of α,β-unsaturated aldehydes under NHC catalysis.[293] Experimentally, the homoenolate intermediates generated from the β-activation of the esters **296** were found readily reactive to diverse electrophiles such as enones **297**, trifluoromethyl ketones **299** as well as activated hydrazones **301**. By utilizing chiral NHC catalyst (*R*)-**C58**, the desired highly functionalized cyclic olefins **298**, γ-lactones **300** and γ-lactams **302** were all produced in moderate to high yields and high level of stereocontrol under mild conditions.

7. Conclusion and prospective

Summarized and discussed in this review are the recent progresses in the field of direct asymmetric functionalization of inert C–H bonds. As a result of the fast and fascinating development achieved in the last several years, a large array of inert C(sp^2)–H and C(sp^3)–H bonds has been found possible to be directly functionalized in a highly enantioselective fashion. Various catalytic systems including well-defined organometallic complexes, small organic molecules and enzymes are applicable to promote this type of novel transformations that provide organic chemists alternative viewpoints to execute the disconnection strategy in modern organic synthesis. However, formidable challenges still remain in the following three major aspects: (1) limited substrate scope. Most asymmetric direct C–H bond functionalization reactions presented here only occurs at some specialized positions such as in proximity to a directing group, α to a heteroatom, and benzylic or allylic positions. Therefore, it will be of considerable value to expand the scope of the asymmetric functionalization to the more inert C–H bonds. (2) Relatively poor reactivity. Due to the inherent difficulty of the direct cleavage of C–H bonds, most current methodologies to this end still require relatively high catalyst loading and elevated reaction temperature. Thus, to develop novel highly efficient catalytic systems that can facilitate asymmetric C–H bond functionalization processes will undoubtedly be the primary direction of future contributions. (3) Complex reaction conditions. Various additives, stoichiometric oxidants are needed in the procedures of many asymmetric C–H bond functionalization reactions. Some catalysts are very sensitive and not easy to handle. Accordingly, most current asymmetric C–H bond functionalization methods are limited to laboratory scale and not feasible for industrial application. Hence, it is also important to enhance the operational simplicity of these methodologies.

Although there is still long way to realize the direct functionalization of arbitrarily specified C–H bonds of any chemical feedstock in high level of stereocontrol, the efforts devoted towards this ambitious goal will definitely stimulate further exciting advances of organic chemistry in the coming era.[294]

Acknowledgements

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