CHEMICAL REVIEWS

Review

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Catalytic Enantioselective Transformations Involving C−H Bond Cleavage by Transition-Metal Complexes

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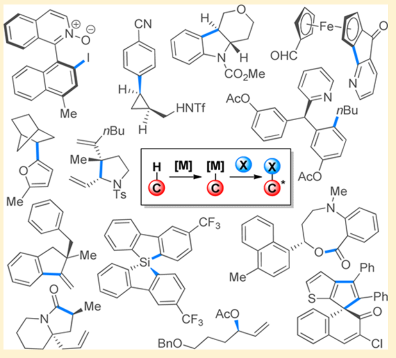
ABSTRACT: The development of new methods for the direct functionalization of unactivated C−H bonds is ushering in a paradigm shift in the field of retrosynthetic analysis. In particular, the catalytic enantioselective functionalization of C−H bonds represents a highly atom- and step-economic approach toward the generation of structural complexity. However, as a result of their ubiquity and low reactivity, controlling both the chemo- and stereoselectivity of such processes constitutes a significant challenge. Herein we comprehensively review all asymmetric transition-metal-catalyzed methodologies that are believed to proceed via an inner-sphere-type mechanism, with an emphasis on the nature of stereochemistry generation. Our analysis serves to document the considerable and rapid progress within in the field, while also highlighting limitations of current methods.



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1. INTRODUCTION

Synthetic strategies toward the enantioselective construction of carbon−carbon (C−C) and carbon−heteroatom (C−X) bonds have traditionally relied upon the presence of either a heteroatom or unsaturation to facilitate the transformation.[1−3] Transition-metal-catalyzed cross-coupling approaches are among the most powerful methodologies in the field, and over the past several decades, the development of new reactions, ligand families, and metal complexes have enabled myriad elegant and creative applications in both academic and industrial settings.[4−9] However, despite their enormous utility, this class of reaction is not without limitation. At least one of the coupling partners requires prefunctionalization; thus, multistep preparative sequences are often necessary. In addition, many of the organometallic reactants (and their byproducts) are highly toxic, air and moisture sensitive. Conceptually, the direct functionalization of carbon−hydrogen (C−H) bonds represents an elegant, atom- and step-economic solution,[10−13] with the

Special Issue: CH Activation

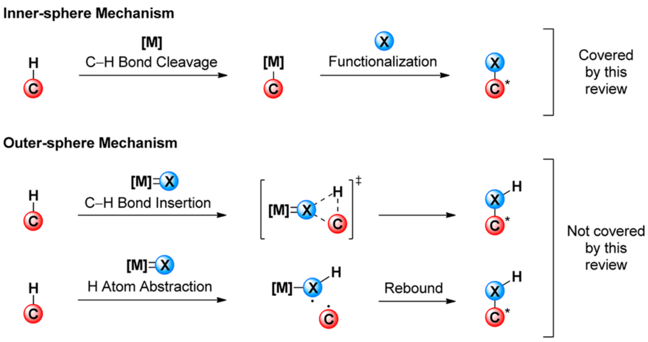
Received: October 8, 2016
Published: February 17, 2017

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

potential to fundamentally alter the logic of retrosynthetic analysis. In particular, the burgeoning field of enantioselective transition-metal-catalyzed C−H functionalization holds great promise as an enabling methodology for the rapid generation of structural complexity from simple precursors.[14−17]

A variety of systems for enantioselective transition-metal-catalyzed C−H functionalization reactions have been developed, and each can be classified by the general mechanism in operation (Scheme 1).[18] Reactions that proceed via a C−H bond cleavage event that leads to the formation of a discrete organometallic intermediate can be considered "inner-sphere" mechanisms. In contrast, "outer-sphere" processes do not involve direct interaction between the C−H bond and the metal center, but rather, association with a coordinated ligand facilitates C−H bond cleavage. These processes can proceed via either a concerted insertion process, such as in the case of metal−carbenoid and −nitrenoid insertions,[19] or via an H atom abstraction/rebound sequence, as is observed for iron porphyrin C−H hydroxylation.[20] As a result of the fundamental differences between these mechanisms, the innate selectivity between each methodology differs. Generally speaking, inner-sphere processes are particularly sensitive to the steric environment of the C−H bond, whereas outer-sphere are usually selective for the weakest C−H bonds.[18]

Scheme 1. Mechanistic Classification of Transition-Metal-Catalyzed Enantioselective C−H Functionalization Reactions



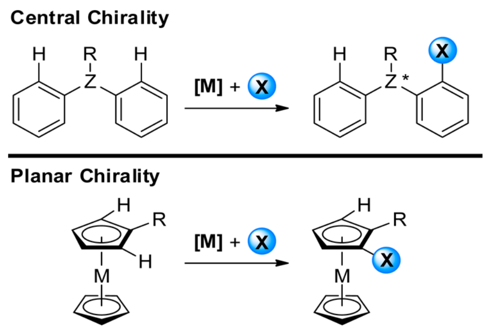
The scope of this review is limited to those examples that are believed to proceed via an inner-sphere mechanism and involve activation of a C−H bond with a pK_a greater than 25, thus best enabling a comparative analysis between related methodologies. Accordingly, reactions that represent a formal C−H functionalization (e.g., the Mizoroki−Heck,[21] Wacker−Tsuji oxidation,[22] Friedel−Crafts,[23] etc.) will not be discussed, although in cases where the mechanism is ambiguous or debated we have erred on the side of caution, and these examples are included. With the exception of the Kharasch−Sosnovsky reaction, which has been well-covered elsewhere,[16,24,25] we have made all attempts to comprehensively review this area of research up until November 2016, and we have primarily organized the literature according to the nature of the stereochemistry-generating step in each methodology.

2. STEREOCHEMISTRY-GENERATING C−H ACTIVATION

2.1. C(sp^2)−H Functionalization

C(sp^2)−H bonds are typically more sterically accessible and acidic than their sp^3-hybridized counterparts. Although these inherent biases can be overcome, for example, via the employment of directing groups, the asymmetric C−H functionalization of C(sp^2)−H bonds remains a considerably more common process. To the best of our knowledge, all methodologies that proceed via a stereochemistry-generating C(sp^2)−H activation involve desymmetrization of a prochiral starting material via the selective C−H activation of an enantiotopic aryl C−H bond, followed by either an inter- or intramolecular functionalization to generate a molecule with either central or planar chirality (Scheme 2).

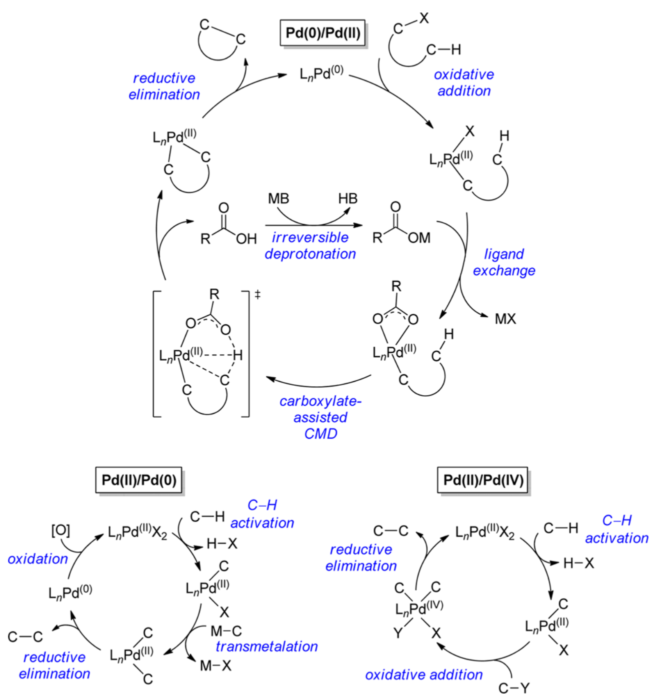
Scheme 2. Nature of Chirality Generated by Stereochemistry-Generating C(sp^2)−H Activations



2.1.1. Palladium Catalysis.

Palladium is the most commonly employed transition metal for reactions that proceed through a stereochemistry-generating C−H activation, and within this area there are three general mechanistic scenarios (Scheme 3). The Pd(0)/Pd(II) catalytic cycle initiates with oxidative addition of a Pd(0) complex into a carbon−(pseudo)halogen bond, followed by a C−H activation event that typically proceeds via a reversible carboxylate-assisted concerted metalation−deprotonation (CMD) mechanism.[26,27]

Scheme 3. General Mechanisms of Palladium-Catalyzed Reactions Involving a Stereochemistry-Generating C−H Activation

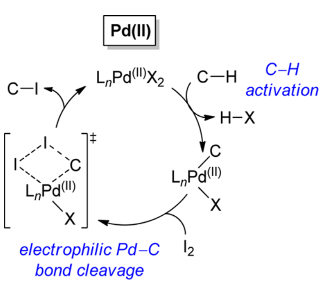


DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Irreversible deprotonation of the released carboxylic acid by an inorganic base renders the CMD enantiodetermining and regenerates the carboxylate cocatalyst.[28] Finally, reductive elimination serves to release the coupled product and regenerate the active Pd(0) catalyst. To date this process has only been realized in an intramolecular sense, likely highlighting the difficulty of controlling the enantioselectivity of an intermolecular C−H activation event with today's methodologies. Conversely, enantioselective reactions proceeding via Pd(II)/Pd(0) or Pd(II)/Pd(IV) catalysis have been conducted in both an intra- and intermolecular sense. Both catalytic cycles begin with a directed C−H activation, facilitated by a Pd(II) complex, before bifurcation of the two processes. The former proceeds via a transmetalation/reductive elimination sequence, providing the coupled product and a reduced form of the palladium catalyst. In this case, reoxidation via an external oxidant closes the catalytic cycle. The Pd(II)/Pd(IV) cycle continues via an oxidative addition process to generate an electron-poor Pd(IV) species that reductively eliminates to complete the catalytic cycle.[29]

Although the three mechanistic pathways described above are the most common, a recent combined experimental and computational study by Yu, Musaev, and their co-workers indicates that for C−H iodination reactions employing molecular iodine as the sole oxidant, a switch in mechanism can occur depending on the nature of the Pd-directing group interaction and the hybridization of the C−H bond.[30] More specifically, $C(sp^2)$−H bonds typically react via a Pd(II) redox-neutral mechanism (Scheme 4). In this case, following C−H activation, a

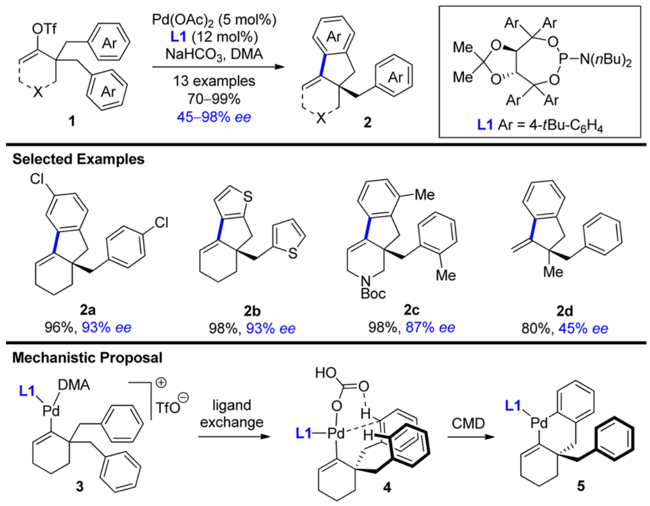
Scheme 4. Redox-Neutral Pd(II)-Catalyzed $C(sp^2)$−H Iodination



concerted electrophilic Pd−C bond cleavage provides the iodinated product and regenerates the active catalyst. Notably, $C(sp^3)$−H iodination reactions tend to proceed through the Pd(II)/Pd(IV) catalytic cycle described above; however this preference can be reversed via the employment of weak directing groups (currently only achieved in an achiral fashion).

2.1.1.1. Pd(0)/Pd(II). The first example of an enantioselective Pd(0)/Pd(II) $C(sp^2)$−H functionalization reaction was disclosed by the Cramer research group in 2009 and involved intramolecular arylation of vinyl triflates **1**, providing access to chiral indanes **2** bearing an all-carbon quaternary stereocenter (Scheme 5).[31] At the time only one example of a palladium-catalyzed enantioselective reaction involving a stereochemistry-generating C−H activation had been reported, by Yu and co-workers, who in a pioneering study had successfully applied mono-*N*-protected amino acids (MPAA) as ligands in a Pd(II)/Pd(0)-catalyzed process (presented later in Scheme 15).[32] In efforts directed toward the development of complementary reaction pathways and the expansion of suitable ligand families for enantioselective C−H functionalization, Cramer et al. discovered that monodentate phosphine ligands displayed high

Scheme 5. First Pd(0)/Pd(II) Enantioselective $C(sp^2)$−H Functionalization



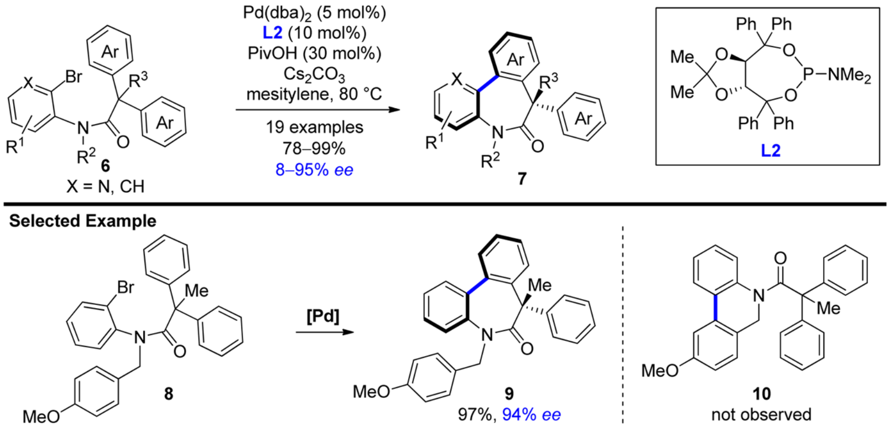
reactivity in the envisioned transformation and that TADDOL-derived phosphoramidites, in particular, provided excellent enantiocontrol. Under optimized conditions, a room-temperate C−H functionalization, facilitated by 4-*t*Bu-C_6H_4 substituted ligand **L1**, yielded the desired indanes in high enantiopurity. A variety of functionalities were tolerated in the reaction, including aryl chlorides (**2a**), substituted thiophenes (**2b**), and Boc-protected amines (**2c**). Although reaction of acyclic alkenyl triflates was also tolerated (**2d**), a significant reduction in enantioselectivity was observed. The working mechanistic model for the reaction was based on proposals by Fagnou,[23−25] and a collaborative study from Maseras, Echavarren, and their co-workers[33,34] in which the oxidative addition intermediate **3** undergoes ligand exchange with sodium bicarbonate to provide **4**, followed by an enantiodetermining carboxylate-assisted CMD to palladacycle **5**.

In 2013, Saget and Cramer extended this methodology to the arylation of amides **6**, providing highly functionalized dibenzazepinones **7** (Scheme 6).[35] In this case, the C−H activation generates a rare eight-membered palladacycle, which at the time was an unprecedented process in asymmetric catalysis. Protection of the amide was determined to be necessary for reactivity, and except for in the case of substituted pyridines (e.g., when X = N), all examples proceeded with high levels of enantiocontrol. Notably, even when 4-methoxybenzyl-substituted amide **8** was employed, dibenzazepinone **9** was generated in 97% yield, and no competing C−H functionalization to dihydrophenanthridine **10** was detected (in this case via a seven-membered palladacycle).

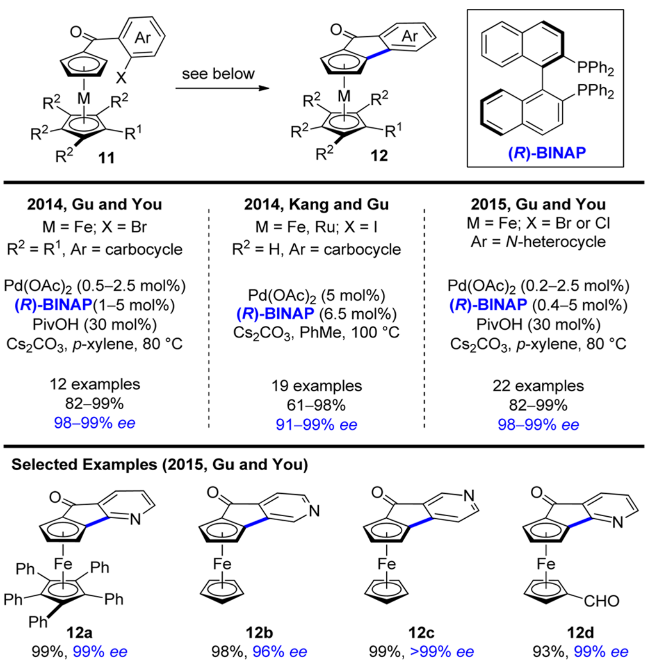
Several methodologies proceeding via a stereochemistry-generating C−H activation event to generate planar chiral compounds have also been disclosed. All involve the functionalization of metallocenes, enabling efficient access to valuable chiral scaffolds with potential application as new ligands or catalysts.[36] Early Pd(II)/Pd(0)-catalyzed studies on substituted ferrocenes required external oxidants for catalytic turnover (presented later in Scheme 17),[37−39] creating the potential for undesired ferrocenium generation. In early 2014, the You[40] and Gu[41] groups independently and concurrently circumvented this potential problem via the development of an intramolecular Pd(0)/Pd(II)-catalyzed arylation of aryl halides **11** (Scheme 7). This methodology was later extended by the You

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 6. Synthesis of Dibenzazepinones via an Intramolecular C−H Arylation



Scheme 7. Pd(0)/Pd(II)-Catalyzed Routes to Fluoreno- and Pyridylmetallocenes

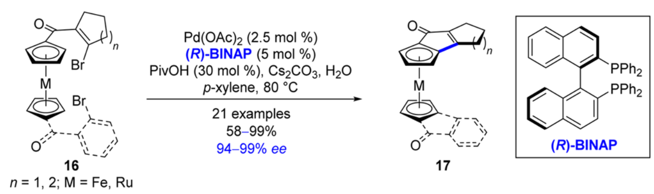


group to tolerate *N*-heterocyclic derivatives, allowing for the synthesis of a small library of chiral metallocenes in excellent yield and enantioselectivity (**12a**−**12d**).[42] Notably, all three of these methodologies employ $Pd(OAc)_2$ as a precatalyst, cesium carbonate as an inorganic base, and the readily available (*R*)-BINAP as ligand, demonstrating the generality of these conditions.

Recently, Guiry and co-workers applied this methodology to the synthesis of a new family of chiral ferrocenyl diols from dibromide **13** (Scheme 8).[43] Both the prior reports from the groups of Gu and You[40] and Kang and Gu,[41] had disclosed the synthesis of the C_2 symmetric dione **14** in excellent enantioselectivity via a double cyclization event. Further optimization by Guiry et al. enabled a multigram, chromatography-free synthesis of this key intermediate, while simultaneously decreasing catalyst and ligand loadings. These products were derivatized via a stereoselective double nucleophilic addition to provide diols **15**, and studies exploring the application of these new scaffolds as organocatalysts in an asymmetric Diels−Alder reaction were reported.

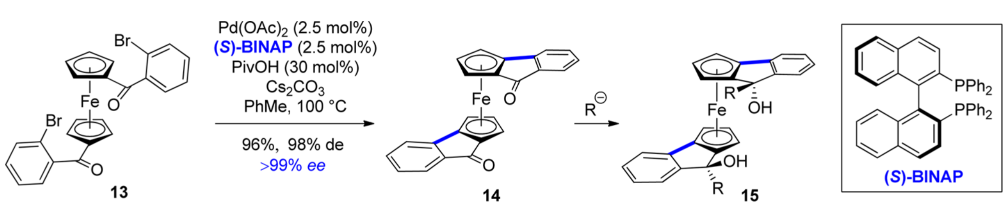
In 2016, the Gu and You groups demonstrated that the intramolecular C−H alkenylation of metallocenes **16** is also possible under Pd(0)/Pd(II) catalysis, again employing BINAP as the stereocontrolling element (Scheme 9).[44] A range of functional groups were well-tolerated, and notably, the reaction could be combined with an intramolecular C−H arylation, enabling a diastereo- and enantioselective synthesis of planar chiral ferrocenes **17**.

Scheme 9. Pd(0)/Pd(II)-Catalyzed C−H Alkenylation of Ferrocenes



Chiral phosphoric acids are also suited for the enantioselective construction of planar chiral ferrocenes (Scheme 10).[45] In 2016, Ye, Duan, and their co-workers reported an intramolecular asymmetric C−H arylation of ketones **18** with BINOL-derived phosphoric acid **L3**, delivering chiral ferrocenes **19** in up to 83% ee. The authors hypothesize that in situ deprotonation of **L3** with cesium carbonate forms the corresponding chiral phosphate,

Scheme 8. Synthesis of Novel Ferrocenyl Diol Catalysts via a Double C−H Functionalization Strategy



DOI: 10.1021/acs.chemrev.6b00692
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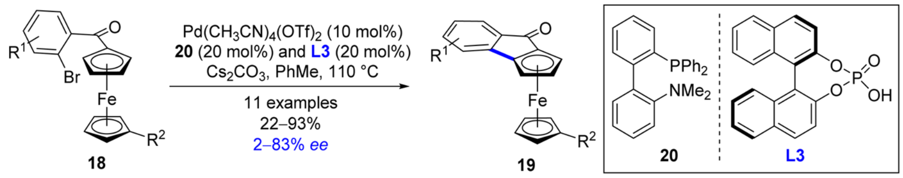
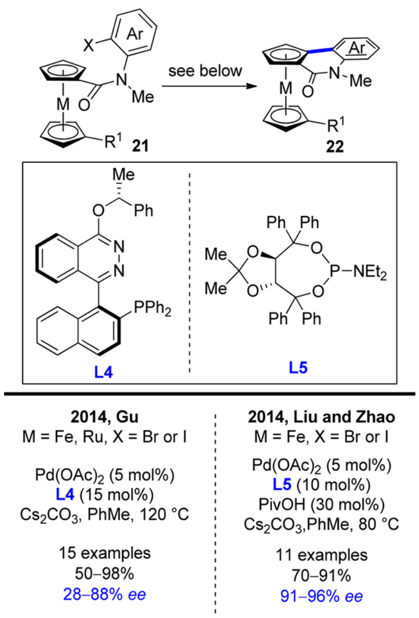
Scheme 10. Pd(0)/Pd(II)-Catalyzed Enantioselective Synthesis of Ferrocenes Using a Chiral Phosphoric Acid



which serves as a coordinated base to the Pd center and facilitates an enantioselective C−H activation through a CMD mechanism.

The synthesis of chiral quinilino-metallocenes has also been achieved via a closely related enantioselective Pd(0)/Pd(II) C−H functionalization, as reported by both the research groups of Gu[46] and of Liu and Zhao[47] (Scheme 11). In these studies,

Scheme 11. Synthesis of Quinilino−Metallocenes by Gu, and Liu and Zhao

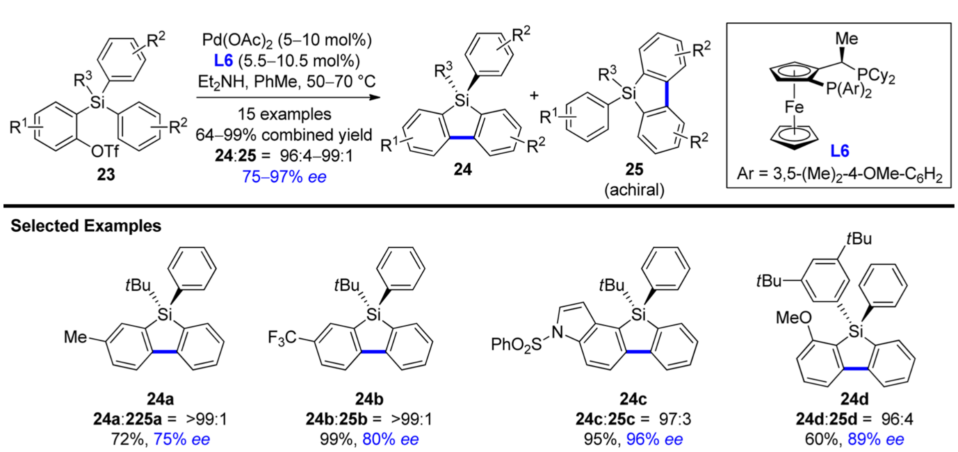


carboxamides **21** were converted to planar chiral derivatives **22** using Pd$(OAc)_2$ and cesium carbonate, with either Carreira's *O*-PINAP derivative **L4** (Gu) or TADDOL-derived phosphoramidite **L5** in the presence of pivalic acid (Liu and Zhao). The latter system provided superior enantioselectivities (including examples with identical substrates). Interestingly, the addition of pivalic acid to Gu's reaction with *O*-PINAP **L4** had no effect on enantioselectivity, suggesting that phosphoramidite **L5** is the primary contributor to the greater level of enantiocontrol in Liu and Zhao's work.

C−H functionalization strategies have also been employed to access heteroatom-chiral molecules. The earliest enantioselective approach toward *Si*-stereocenters, reported by Shintani, Hayashi, and their co-workers in 2012,[48] is an extension of Shimizu's[49] Pd(0)-catalyzed synthesis of achiral *Si*-bridged biaryls (Scheme 12). Desymmetrization of triarylsilanes **23** with Pd$(OAc)_2$, an amine base, and the electron-rich Josiphos-type ligand **L6** proceeded with high chemo- and enantioselectivity, to yield *Si*-stereogenic dibenzosiloles **24**. Formation of the undesired isomer **25** was largely retarded with all chiral ligands screened, and enantioselectivities ranged from 75−97%. Alkyl (**24a**), trifluoromethyl (**24b**), and indole (**24c**) triflates were all well-tolerated, and differentiation between appropriately substituted aryl groups proved possible (**24d**). Competition experiments between the triflate precursors **24a** and **24b** demonstrated that electron-poor substrates reacted significantly faster; these studies in conjunction with kinetic isotope experiments led the authors to propose that oxidative addition is likely the rate-determining step.

Intramolecular Pd(0)/Pd(II) C−H functionalization reactions have also been employed to access *P*-stereogenic compounds. *P*-Chiral ligands have played a significant role in the development of asymmetric catalysis,[50,51] and their efficient construction is of great importance.[52,53] The cyclization of prochiral phosphinic amides **26** to azaphosphinine oxides **27** was reported concurrently by Duan and co-workers[54] and by Liu, Ma, and their co-workers[55] via almost identical protocols (Scheme 13). Both research groups screened a variety of chiral phosphine ligands, observing that TADDOL-derived tetraphenyl phosphoramidites **L2** and **L5** provided the highest levels of enantioselectivity. Good yields were observed for various aryl substituents,

Scheme 12. An Intramolecular C−H Functionalization Route to *Si*-Stereogenic Dibenzosiloles



DOI: 10.1021/acs.chemrev.6b00692
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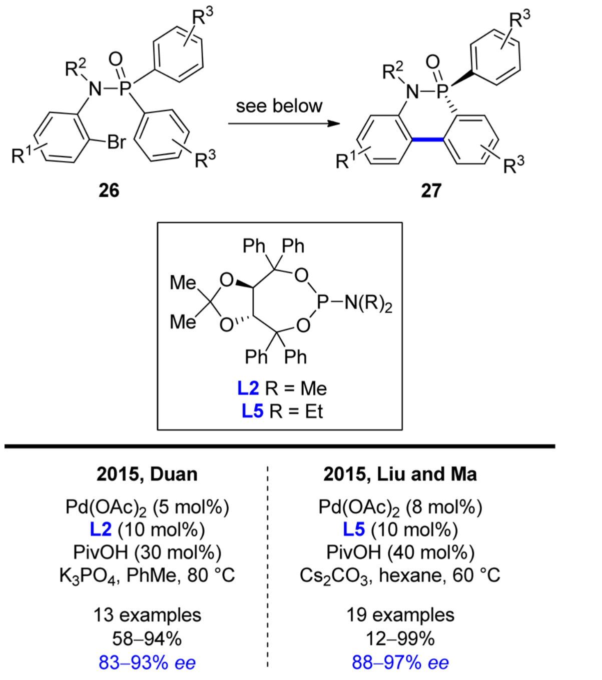
Scheme 13. Intramolecular Arylation of Phosphinic Amides by the Groups of Duan and of Liu and Ma



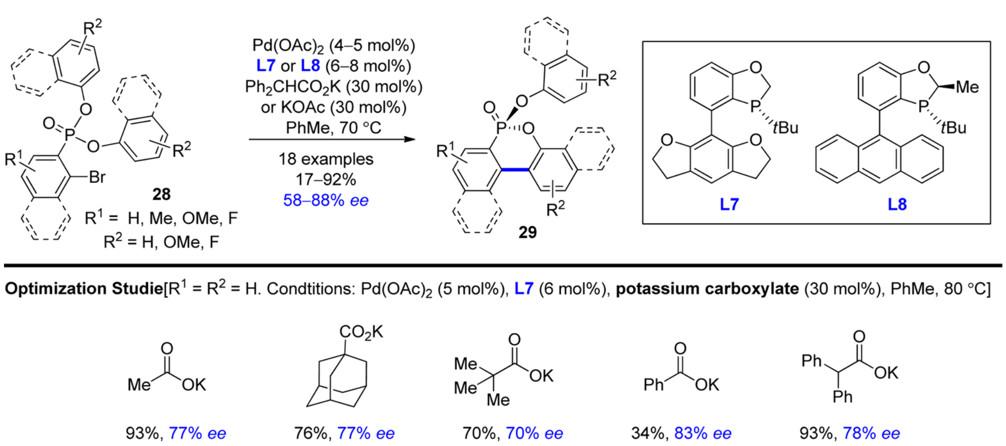
such as OMe, F, CF_3, CN, and Cl;[54,55] however, alkyl substitution ortho to phosphorus significantly decreased the yield (without impacting enantioselectivity).[55] Notably, *P*-chiral phosphonates have also been accessed via a Pd(II)/Pd(0) reaction pathway (see Scheme 18).[56]

In 2015, Tang and co-workers reported the desymmetrization of Me-, OMe-, and F-substituted aryl bromides **28**, utilizing their newly developed *P*-chiral ligand **L7**, to provide *P*-chiral phosphonates **29** in moderate to good enantioselectivity (Scheme 14).[57] A dramatic base effect was observed during optimization studies: increasing steric bulk near the carboxylate functionality reduced yields, and in the case of potassium pivalate, a reduction in enantioselectivity was also observed. Potassium benzoate was found to improve enantioselectivity, but at the expense of yield. Ultimately, potassium 2,2-diphenylacetate provided the best balance, and was used in further optimization studies. In the case of naphthyl bromide substrates, Antphos derivative **L8**, in combination with potassium acetate, provided the highest selectivity. The authors subsequently demonstrated that the aryloxy substituents of **29** could be displaced stereospecifically, thus enabling the synthesis of potential ligand precursors.

2.1.1.2. Pd(II)/Pd(0). In a landmark study published in 2008, Yu and co-workers reported the first palladium-catalyzed enantioselective C−H functionalization methodology incorporating a stereochemistry-generating C−H activation event,[32] importantly introducing MPAAs as viable ligands for this class of transformation (Scheme 15). Under optimized conditions, prochiral pyridines **30** were coupled with alkylboronic acids **31** in the presence of a Pd(II) source and (−)-menthyl-substituted amino acid ligand **L9**, yielding triarylmethane derivatives **32** in modest to high enantioselectivities (absolute configuration determined in a subsequent publication[58]). Benzoquinone proved to be an essential additive, critical for both the C−H activation and reductive elimination steps, and Ag_2O was employed to reoxidize Pd(0) to Pd(II). A small selection of electron-rich and electron-deficient aryls were tolerated, as well as several alkylboronic acids (see selected examples **32a**−**32d**). Ligand optimization studies assisted in the elucidation of some key mechanistic features of the transformation: butylation with cyclopropyl amino acid **L10** provided the target in 46% yield and 46% ee; however, when the less conformationally restricted Boc-protected amino acid **L11** was employed, an improved 63% yield and 90% ee was observed. It was confirmed that an electron-poor nitrogen, free carboxylic acid, and secondary amine were all necessary for good reactivity (**L12**, **L13**, and **L14**) and that bulkier *N*-protecting groups were superior, ultimately identifying (−)-menthyl derivative **L9** as the optimal ligand. The Yu group also demonstrated that $C(sp^3)$−H functionalization was also viable with this methodology (Scheme 36).

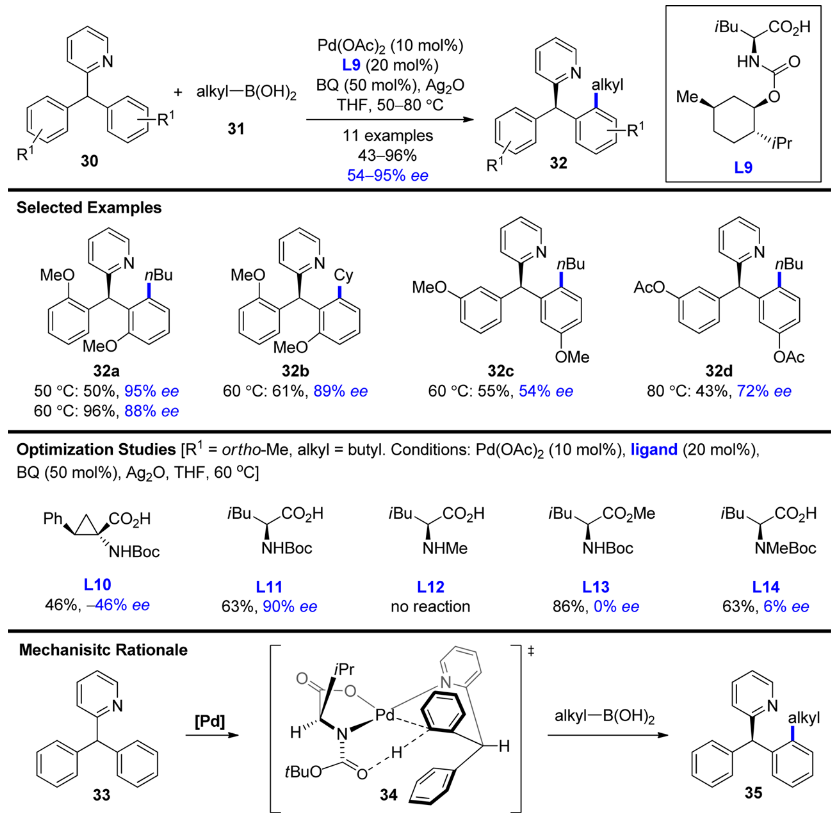
A number of studies concerning the mechanism and origin of enantiocontrol with MPAA ligands in Pd(II)-catalyzed C−H functionalization reactions have since been reported.[58−68] An insightful historical account has been published by Engle,[69] and as such, we present here only the most recent (and currently accepted) model. A collaborative effort between the laboratories of Houk, Yu, and Wu, combining both mass spectrometry experiments with DFT calculations, demonstrated that MPAA ligands play a dual role as both an internal base in a novel CMD event, in addition to stabilizing monomeric Pd complexes.[63] This mechanism has been supported by further experimental and computational data from Musaev et al.[70] and from Zhang, Yu, Wu, and their co-workers.[60] In the latter report, the alkylation of

Scheme 14. Synthesis of *P*-Stereogenic Phosphonates

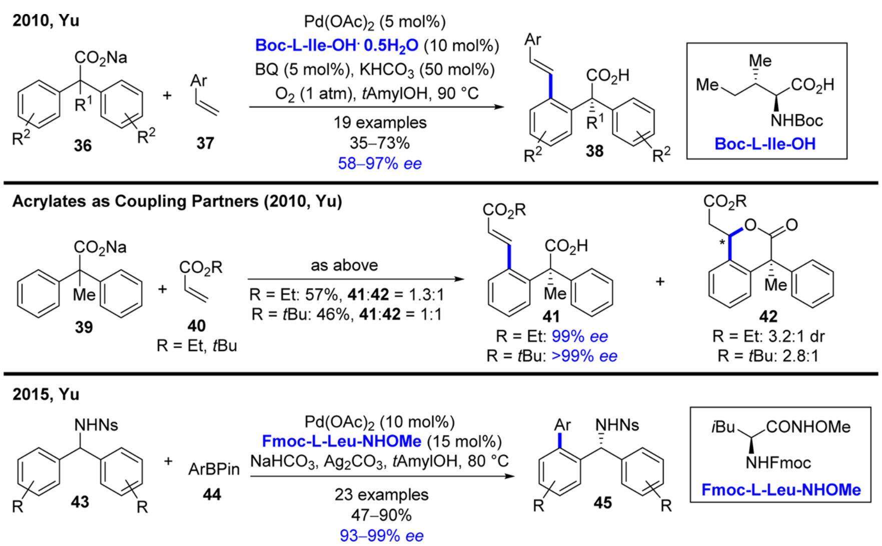


DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 15. First Report of a Palladium-Catalyzed Enantioselective C(sp²)−H Functionalization Reaction



Scheme 16. Pd(II)/Pd(0)-Catalyzed C−H Functionalization Employing Carboxylate and *N*-Nosyl Directing Groups

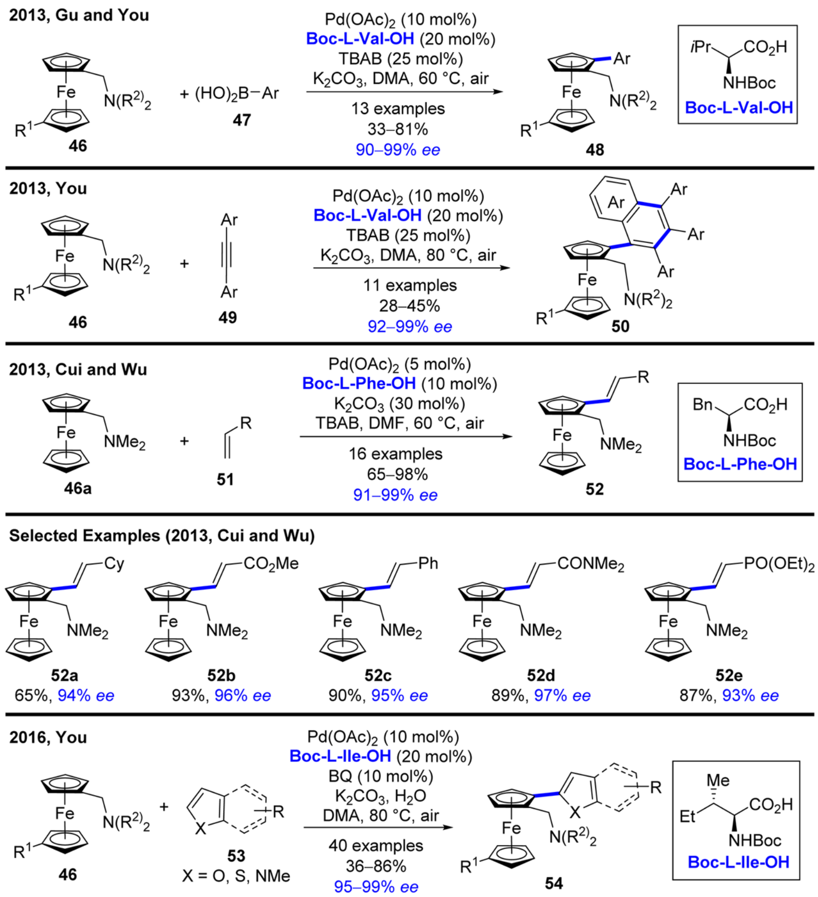


2-benzhydrylpyridine (**33**) was studied and is believed to proceed first via N−H activation, followed by an enantiodetermining CMD of the aryl C−H bond, facilitated by the carbonyl oxygen of the amidate moiety (see DFT-calculated transition state **34**). In this model, the *i*Pr substituent forces the Boc group below the Pd plane. For C−H activation to occur, the activated C−H bond must be directed toward the Boc carbonyl oxygen, and as a result of these conformational requirements, the nonparticipating aryl group prefers the less sterically crowded axial position, ultimately leading to the (*R*)-configured products **35**.

This methodology was later extended by the Yu group to accommodate both carboxylate[71] and *N*-nosyl[72] directing groups in dehydrogenative Mizoroki−Heck reactions[73] (Scheme 16). In the former case, the preformed sodium salts **36** were reacted with styrenes **37**, employing oxygen as the stoichiometric oxidant, potassium bicarbonate as base, and Boc-L-Ile-OH·0.5H_2O as ligand, enabling access to chiral diphenylacetic acids **38** in moderate to excellent enantioselectivity. Curiously, the selection of metal counterion for both the diaryl substrate and base was crucial, and alternate combinations were detrimental for both the enantioselectivity and yield. Acrylates were also found to be competent reaction partners, as demonstrated by the coupling of

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 17. Synthesis of Planar Chiral Ferrocenes via Pd(II)/Pd(0) C−H Functionalization



sodium 2,2-diphenylpropanoate (**39**) with ethyl or *t*Bu acrylates **40**. However, in this case a mixture of the desired olefin products **41** and their intramolecular oxa-Michael addition products **42** was observed.

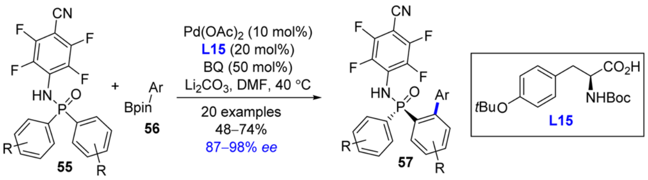
In 2015, Yu et al. published the first *N*-nosyl-directed C−H functionalization reaction. In this study, diarylmethylamines **43** were coupled with arylboronic pinacol esters **44**, providing the desymmetrized products **45** in high ee.[72] Sodium bicarbonate is necessary to deprotonate the sulfonamide for coordination to palladium, likely also facilitating organoboron transmetalation,[74] while Ag_2CO_3 acts as both a reoxidant and a promotor for coupling. During ligand optimization, replacement of the typical MPAA carboxylic acid moiety with *N*-methoxyamide and of the *N*-Boc protecting group with Fmoc both proved beneficial. The synthetic utility of this transformation was demonstrated through the removal of the directing *N*-nosyl group in good yield and under mildly basic conditions.

Building upon reports from the groups of Sokolov[75] and Richards[59] regarding the stoichiometric enantioselective palladation of aminomethylferrocenes with MPAA ligands, in conjunction with the subsequent catalytic advancements introduced by Yu and co-workers, several groups have now developed enantioselective syntheses of planar chiral ferrocenes using Pd(II)/Pd(0) catalysis (Scheme 17). In 2013, Gu, You, and their co-workers disclosed an enantioselective arylation of aminomethylferrocenes **46** with arylboronic acids **47**, employing the commercially available Boc-L-Val-OH with $Pd(OAc)_2$, TBAB (likely to limit Pd(0) agglomeration[76]), and K_2CO_3, in DMF under air.[37] The resulting products **48** were isolated in 33−81% yield and up to 99% ee. Later that year the You group demonstrated that the Cui and Wu groups' racemic dehydrogenative annulation with diarylethynes[77] could be conducted in an enantioselective fashion under these same reaction conditions.[38] Thus, ferrocenes **46** were coupled with symmetrical alkynes **49** to yield highly enantioenriched naphthyl-substituted ferrocene derivatives **50**, albeit in moderate yield. Notably, very similar conditions were also used by Cui, Wu, and their co-workers, in their dehydrogenative Heck coupling of dimethylaminomethylferrocene (**46a**).[39] In this methodology, various monosubstituted olefins **51** were well-tolerated, including alkyl derivatives (**52a**), acrylates (**52b**), styrenes (**52c**), acrylamides (**52d**) and phosphonates (**52e**). The most recent Pd(II)/(Pd(0)-catalyzed C−H functionalization of ferrocenes was disclosed by You, in 2016, and represents the first example of a catalytic enantioselective biaryl coupling that proceeds via C−H activation of both coupling partners.[78] The first (stereochemistry-generating) C−H activation of the ferrocene backbone is directed by the dimethylamino group of **46**, while the regioselectivity of the second C−H activation is governed by the heteroatom of **53**. As with the previous studies, an MPAA ligand was employed, and air was used as the stoichiometric oxidant. Various functionalized heteroaromatic-substituted derivatives of general structure **54** were accessed with excellent regio- and enantioselectivity. Notably, in addition to being a highly atom and step economic transformation, this protocol produces H_2O as the sole byproduct.

Pd(II)/Pd(0) catalysis has also been used to synthesize *P*-stereogenic phosphinamides (Scheme 18).[56] Expanding upon their own racemic studies,[79] Han and co-workers found that MPAA ligand **L15** provided high levels of enantiocontrol in the

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

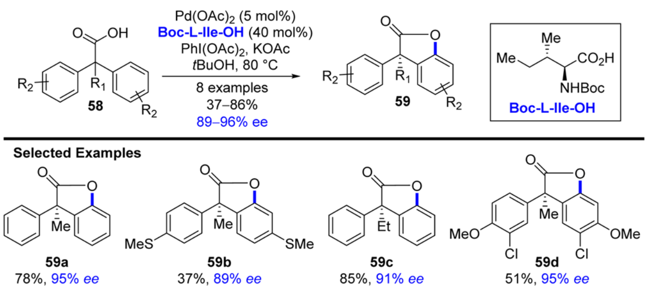
Scheme 18. Enantioselective Synthesis of *P*-Chiral Phosphinamides



directed desymmetrization of **55**. The 2,3,5,6-tetrafluoro-4-cyanophenylamino directing group, in conjunction with boronic esters **56** as an aryl source, proved the best combination. The reaction could be successfully conducted on a gram scale, and further derivatization of the products **57** to potential new ligands was demonstrated, without significant erosion in enantiopurity. This intermolecular approach to *P*-chiral phosphinamides is complementary to Duan's[54] and Liu and Ma's[55] intramolecular Pd(0)/Pd(II)-catalyzed methodology described earlier (Scheme 13).

2.1.1.3. Pd(II)/Pd(IV) and Pd(II). The first report of a Pd(II)/Pd(IV) enantioselective C–H functionalization was disclosed by Wang, Yu, and their co-workers in 2013 (Scheme 19).[80] In this

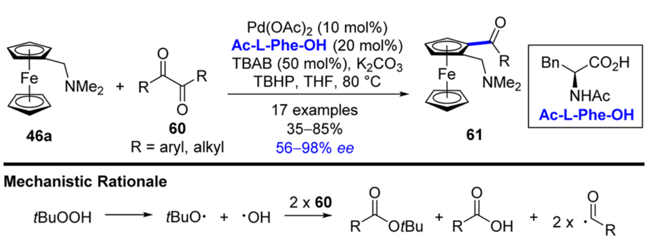
Scheme 19. Desymmetrization of Biaryls through Pd(II)/Pd(IV) C(sp^2)–H Functionalization



study, diphenylacetic acids **58** were converted to chiral benzofuranones **59**, employing (diacetoxyiodo)benzene as a bystanding oxidant[81] to promote the challenging reductive elimination via oxidation of the Pd(II) metallacycle to a Pd(IV) intermediate. Although most examples were achiral in nature, a small number of asymmetric reactions were reported. Good enantioselectivities were observed in all cases (e.g., **59a**–**59d**); however, yields were highly variable.

In 2014, the first catalytic and enantioselective C–H acylation of ferrocenes was reported by the groups of Cui and Wu.[82] Dimethylaminomethylferrocene (**46a**) was reacted with various diaryl and dialkyl 1,2-diketones **60**, providing the acylated targets **61** in up to 85% yield and 98% ee (Scheme 20). These could be derivatized in one step by the nucleophilic addition of

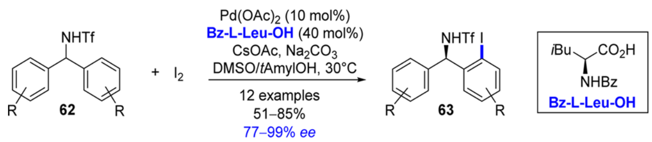
Scheme 20. Catalytic Enantioselective C–H Acylation of Dimethylaminomethylferrocene



phenyllithium, to provide efficient access to known planar–chiral *N*,*O*-ligands. A mechanism for the oxidation of the intermediate Pd(II) [to either a Pd(III) or a Pd(IV) species] via addition of acyl radicals generated from reaction of TBHP with 1,2-diketones **60**[83] was proposed on the basis of the observation that the addition of TEMPO inhibited the reaction.

In 2013, Yu and co-workers reported the first enantioselective C–H iodination reaction (Scheme 21).[84] Various diaryl

Scheme 21. Palladium-Catalyzed Enantioselective C–H Iodination

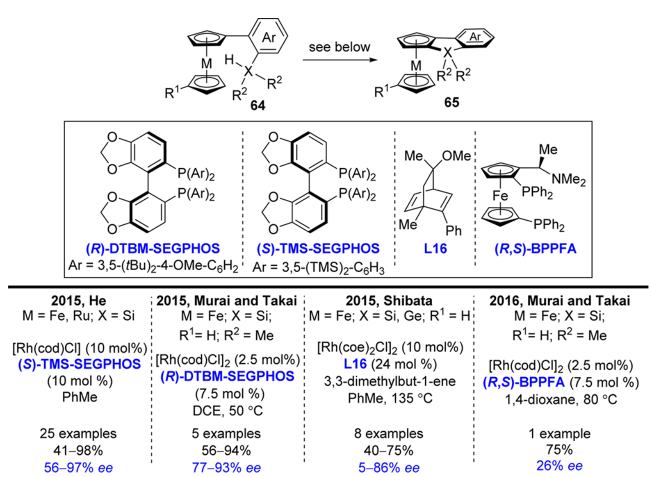


triflamides **62** were reacted with iodine (as the sole oxidant), in the presence of $Pd(OAc)_2$ and Bz-L-Leu-OH. The metal counterion of the base had a large impact on both the yield and enantioselectivity, and a 1:1 mixture of CsOAc and Na_2CO_3 gave the best results. Addition of DMSO as cosolvent increased the enantioselectivity further, and the authors suggest that perhaps it sequesters any Pd(II) not bound to Bz-L-Leu-OH, avoiding any racemic reaction. On the basis of Yu, Musaev, and their co-workers' recent computational study,[30] it is assumed that this reaction proceeds via a Pd(II) redox-neutral mechanism.

2.1.2. Rhodium Catalysis. Rhodium and iridium catalysis has most commonly been employed in methodologies that incorporate a stereochemistry-generating migratory insertion, and as such, a more detailed mechanistic discussion is reserved for section 3. Only a small number of applications involving a Rh-catalyzed stereochemistry-generating C(sp^2)–H activation have been reported, most commonly directed toward the synthesis of planar or heterochiral compounds.

Several research groups have disclosed rhodium-catalyzed intramolecular C–H silylation and/or germanylation protocols of metallocenes **64** to generate planar chiral scaffolds **65** (Scheme 22). The two more closely related protocols, published by He and co-workers[85] and Murai, Takai, and their co-workers[86] in 2015, both employed a Rh(I) catalyst and a SEGPHOS derivative as ligand. He and co-workers discovered that higher

Scheme 22. Rh-Catalyzed Approaches to Planar Chiral Metallocenes

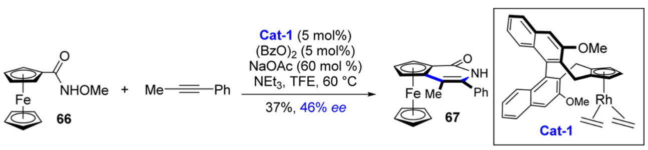


DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908–8976

temperatures were required with larger substituents on Si (*i*Pr not tolerated), and in all cases, a change from Me to Et resulted in a significant increase in enantioselectivity. This methodology was amenable to both ferrocenes and ruthenocenes, as well as various electron-poor, electron-rich, and halogenated arylsilanes. That same year the laboratory of Shibata[87] reported a Rh(I)-catalyzed C−H silylation and germanylation of ferrocenes, utilizing Carreira's [2.2.2]bicyclooctadiene ligand **L16**[88] and 3,3-dimethylbut-1-ene as hydrogen acceptor. In 2016, Murai, Takai, and their co-workers disclosed one additional example, as part of an unrelated mechanistic study, demonstrating that (*R*,*S*)-BPPFA also facilitated the reaction but provided a significantly lower level of enantiocontrol.[89]

An intermolecular C−H functionalization approach to racemic fused ferrocenylpyridinones was disclosed by You and co-workers in 2016 (Scheme 23).[90] In this study, one example

Scheme 23. Catalytic Enantioselective C−H Functionalization of Ferrocenecarboxamides



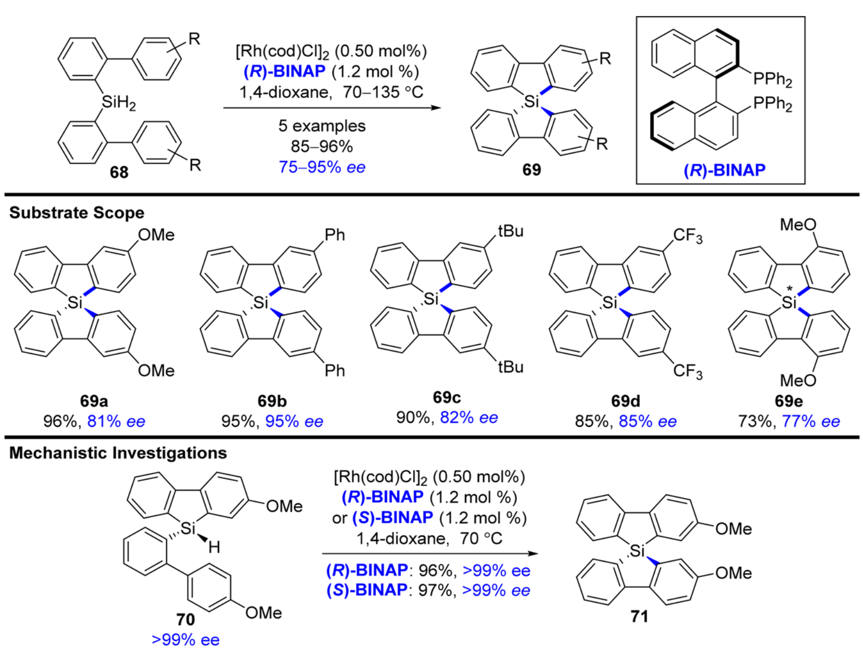
demonstrated that enantioinduction was possible via employment of chiral cyclopentadienyl Rh(I) complex **Cat-1** (this ligand class was originally developed in the laboratory of Cramer; see section 3.1.1.1.2 for details regarding their inception). Under unoptimized conditions, annulation of carboxamide **66** with phenylpropyne in the presence of benzoyl peroxide [to generate the active Rh(III) catalyst], proceeded in moderate yield (37%) and with moderate enantioselectivity (46% ee).

Rh-catalyzed C−H silylation has also been employed to access spiro compounds. In 2013, Kuninobu, Takai, and their co-workers disclosed a double dehydrogenative cyclization of bis(biaryl) silanes **68** using $[Rh(cod)Cl]_2$ and (*R*)-BINAP (Scheme 24).[91] The absolute configuration of the products was determined in a subsequent optimization and mechanistic study done in collaboration with the Murai group,[92] enabling the synthesis of both para- and ortho-substituted spirosilabifluorenes **69a−69e** in up to 96% yield and 95% ee. The first and second cyclization events were determined to proceed at similar rates, enabling isolation of the monocyclized intermediate **70**. When a highly enantioenriched sample was submitted to the second C−H silylation reaction, with either (*R*) or (*S*)-BINAP, the axially chiral product **71** was obtained with no difference in selectivity, indicating that the absolute configuration is determined in the first silylative cyclization.

In 2015, Ryberg, Hartwig, and their co-workers disclosed an enantioselective silylation of arene C−H bonds, proceeding via an Ir-catalyzed hydrosilylation of diaryl ketones **72** to intermediate silanes **73**, followed by a Rh-catalyzed directed C−H silylation to generate chiral benzoaxasiloles **74** (Scheme 25).[93] Initial attempts to use Ir catalysis for both processes required temperatures higher than 80 °C and a 4 mol % catalyst loading to provide the desired products in good yield. Moreover, poor substrate scope was exhibited under these conditions when substituted aryls were employed. Eventually, it was discovered that a Rh(I) source, in combination with a chiral bisphosphine ligand and norbornene as a hydrogen acceptor, enabled reaction at 50 °C with only a 0.5 mol % catalyst loading. Ligands from the catASium (**L17** and **L18**) and Walphos (**L19**, **L20**, and **L21**) families proved complementary, providing products with the opposite absolute configuration, in 54−90% yield and 72−99% ee. This methodology also proved applicable to the parallel kinetic resolution of enantioenriched diarylmethanols via site-selective C−H silylation (Scheme 118). In addition, the researchers demonstrated the value of the enantioenriched benzoaxasiloles via functionalization of the aryl−Si bond through Hiyama arylation, Tamao−Fleming oxidation, and halogenation protocols.

The most recent Rh-catalyzed example comes from the Cramer lab and involves the desymmetrization of *P*,*P*-diaryl-lphosphinic amides **75** with internal alkynes **76**, generating *P*-

Scheme 24. Synthesis of Spirosilabifluorene Derivatives via Rh-Catalyzed C−H Silylation



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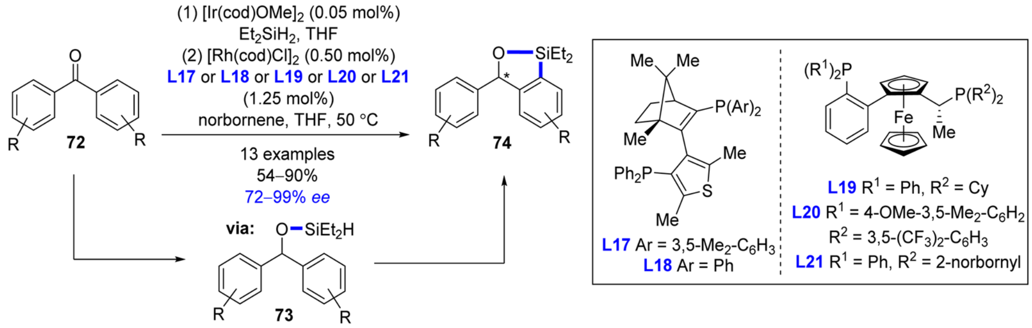
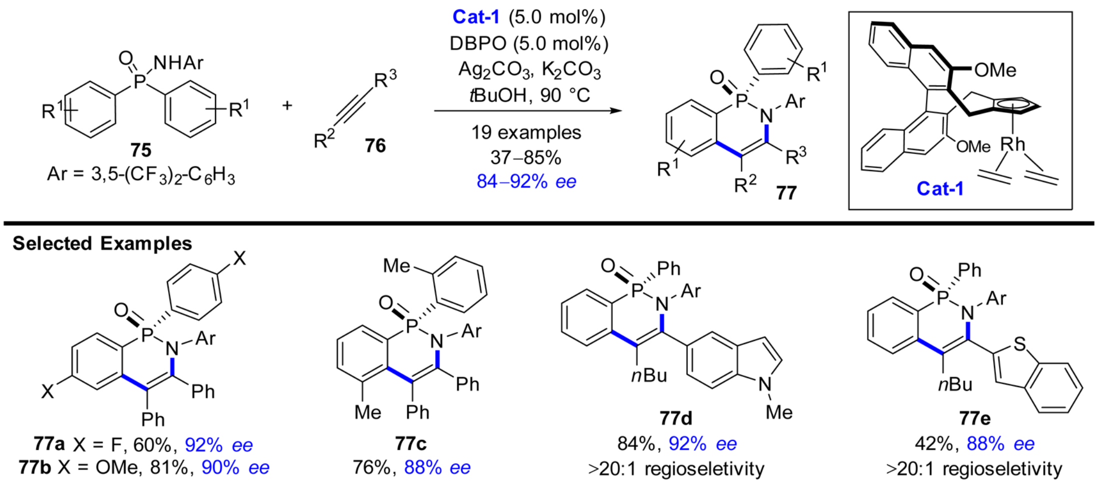
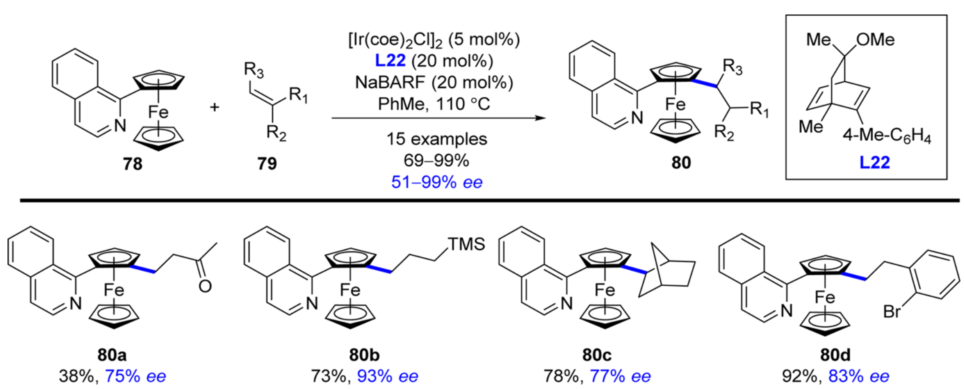
Scheme 25. Rh-Catalyzed Desymmetrization of Diarylmethanols



Scheme 26. Rh(III)-Catalyzed Synthesis of *P*-Chiral Cyclic Phosphinamides



Scheme 27. Ir(I)/Ir(III)-Catalyzed Enantioselective Alkylation of Ferrocene Derivatives



chiral cyclic derivatives **77** (Scheme 26).[94] Optimization and mechanistic studies determined the stereochemistry-generating C−H activation was reversible, resulting in poor levels of enantiocontrol, until K_2CO_3 was added as an inorganic base to mitigate the reversibility of the process. By employing their atropochiral **Cat-1** as catalyst and silver carbonate as a stoichiometric oxidant, a library of highly functionalized derivatives could be accessed in 84−92% ee. The substitution on the *P*-aryl groups had little effect on enantioselectivity (e.g., **77a**−**77c**), and unsymmetrical heteroaromatic-substituted alkynes were well-tolerated (e.g., **77d** and **77e**). Notably, the regioselectivity with all unsymmetrical alkynes was superior to reaction with the achiral pentamethylcyclopentadienyl (Cp*) ligand. The authors also demonstrated that under carefully selected conditions, reduction of the phosphine oxide moiety to the free phosphine proceeds with retention of configuration and with almost complete enantiospecificity.

2.1.3. Iridium Catalysis.

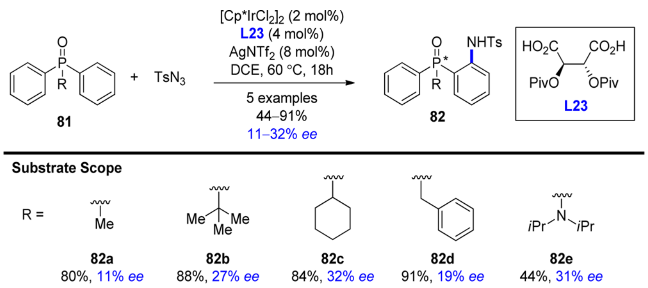
Only two iridium-catalyzed methodologies that incorporate a stereochemistry-generating C(sp^2)−H activation have been reported. In 2014, Shibata and Shizuno disclosed the first catalytic and enantioselective C−H alkylation of ferrocene derivatives via reaction of 1-ferrocenylisoquinoline (**78**) with various alkene and styrene coupling partners **79** (Scheme 27).[95] Earlier mechanistic studies in an achiral setting with $[Ir(cod)_2]BARF$ as catalyst revealed that 1,5-cyclooctadiene (cod) remained coordinated throughout the entire cycle and that the addition of phosphine ligands significantly lowered the reaction rate,[96] prompting the authors to screen chiral diene ligands in the development of an asymmetric variant. Optimization revealed that an analogue of

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Carreira's diene,[88] tolyl-substituted derivative **L22**, provided the highest level of enantiocontrol. The 1-isoquinolinyl group was determined to be the optimal for directing C−H activation, retarding the formation of double addition products while good levels of enantioselectivity were maintained. Methyl vinyl ketone (**80a**), allyl silane (**80b**), norbornene (**80c**), and 2-bromostyrene (**80d**) were all amenable to the reaction, although for styrene derivatives ortho-substitution is necessary to prevent the formation of branched analogues. The proposed mechanism proceeds via an Ir(I)/Ir(III)-catalyzed oxidative addition/reductive elimination pathway, with the latter being enantiodetermining.[96]

In 2015, Chang and co-workers reported a redox-neutral C−H amidation of phosphine oxides **81** with tosyl azide (Scheme 28).[97] Good yields were observed for alkyl (**82a**−**82c**) and benzyl (**82d**) substituted derivatives; however, the *N,N*-diisopropyl derivative (**82e**) reacted sluggishly, and in all cases, only low levels of asymmetric induction were observed with chiral acid **L23**. Mechanistic studies suggest that the acid participates in a rate-limiting CMD event and also facilities protodemetalation.

Scheme 28. Asymmetric C−H Amidation of Phosphine Oxides

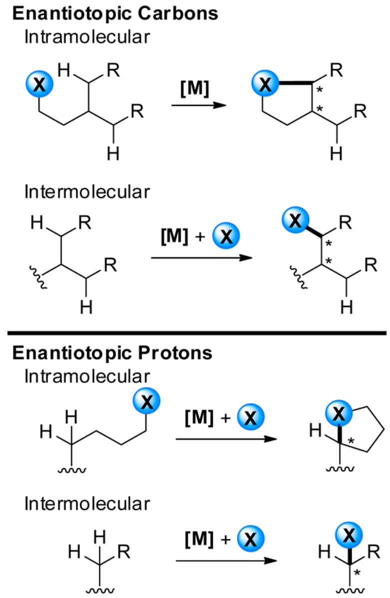


2.2. C(sp^3)−H Functionalization

The stereochemistry-generating activation of C(sp^3)−H bonds has only been used to access molecules with central chirality (Scheme 29). The most common mode of reactivity is the functionalization of C(sp^3)−H bonds on enantiotopic carbons, and this has been achieved in both an inter- and intramolecular sense. In comparison, only a handful of examples describing the functionalization of enantiotopic protons has been reported, most commonly in an intermolecular manner. Notably, the stereochemical implications of allylic C(sp^3)−H activation processes are generally more complex than that of their nonallylic counterparts, and as such, we have reserved discussion of such examples until section 5.2.

2.2.1. Palladium Catalysis. *2.2.1.1. Pd(0)/Pd(II).* The first stereochemistry-generating Pd(0)/Pd(II)-catalyzed C(sp^3)−H functionalization was disclosed in 2011 by the Kündig research group as part of an approach to chiral fused indolines.[98] Since then, the groups of both Kagan[99] and Cramer[100,101] have reported complementary methods, and the Kündig[102] laboratory has published a follow up study exploring the mechanism and expanding the scope of their original transformation (Scheme 30). Conceptually all approaches involve the intramolecular desymmetrization of aryl (pseudo)halides **83**, generating indolines **84** as a single diastereoisomer. Kündig's pioneering work employed 1-naphthyl-substituted NHC ligand **L24** and [Pd(η^3-cinnamyl)Cl]$_2$, in the presence of cesium pivalate and cesium carbonate, resulting in the generation of a Pd(0)−NHC

Scheme 29. Classification of Reactions Proceeding via a Stereochemistry-Generating C(sp^3)−H Activation

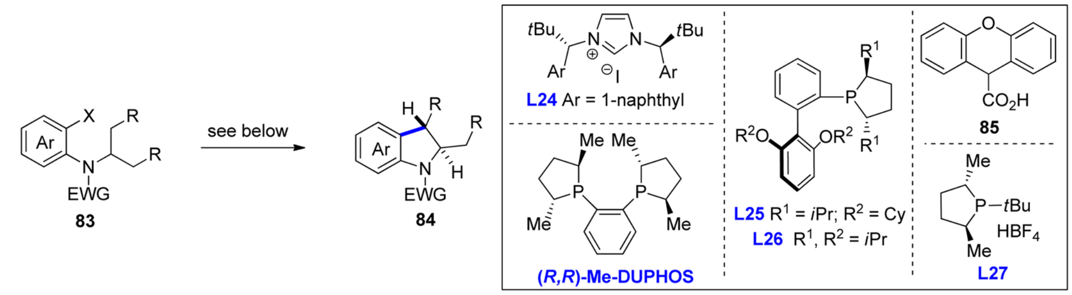


complex. The reaction is believed to proceed according to the general Pd(0)/Pd(II) mechanism described earlier (Scheme 3), and mechanistic studies indicate that a carboxylate-assisted CMD is in operation.[102] In this work, aryl bromides gave the best combination of yield and enantioselectivity, and indolines containing fused rings (**84a**−**84c**), electron-withdrawing substituents (**84d**), and amide directing groups (**84e**) could all be accessed. Extension of this methodology to a regiodivergent parallel kinetic resolution was also reported (Scheme 117).[103] Later that same year, Kagan and co-workers reported that the commercially available chiral diphosphine ligand (*R,R*)-Me-DuPhos could promote the same transformation under related conditions, and a small library of indolines was synthesized in moderate to good yields and enantioselectivities.[99] In 2012, Cramer and co-workers introduced a new class of chiral monodentate phosphine ligands (e.g., **L25** and **L26**),[100] successfully combining the properties of Buchwald-type ligands[104,105] with chiral phospholanes. This new scaffold provided indolines in up to 96% ee when used in combination with achiral acid **85**. Importantly, this study also demonstrated for the first time that a chiral carboxylic acid can interact with the chiral ligand in a cooperative manner (in a matched case), or even override the selectivity of the chiral ligand to reverse the sense of enantioinduction (in a mismatched case). Finally, in a proof-of-principle, the Cramer group demonstrated that a second new chiral ligand family, monodentate trialkylphosphines **L27**, could also catalyze the reaction, albeit with only moderate enantioselectivity.[101]

In addition to NHC and phosphine ligands, recent reports have demonstrated that chiral phosphoric acids can also be effective sources of asymmetric control for the synthesis of chiral indolines via the same retrosynthetic disconnection (Scheme 31). The first example, from the laboratory of Ye and Duan, employed BINOL-derived phosphoric acid **L3** as ligand, used in conjunction with either triphenylphosphine or CyJohnPhos.[45] Under these conditions, aryl bromides **86** were converted into the corresponding indolines **87** in moderate yields and enantioselectivities. Later that same year, the Baudoin group published a more detailed study of the same transformation.[106]

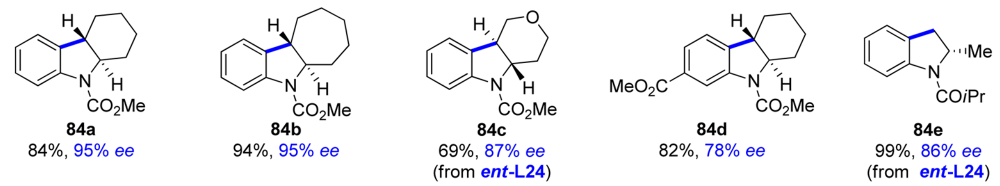
DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 30. Synthesis of Chiral Indolines via Pd(0)/Pd(II) Catalysis

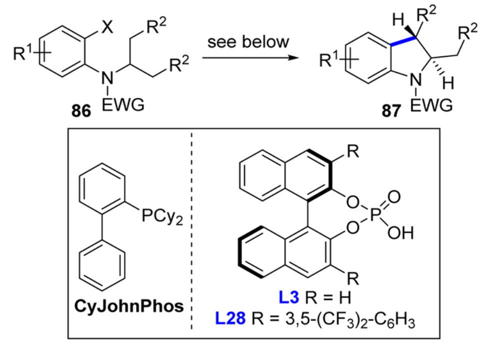


2011 and 2013, Kündig	2011, Kagan	2012, Cramer	2012, Cramer
EWG = CO_2R, COR; X = Br	EWG = CO_2R; X = Br, I	EWG = Tf; X = OTf	EWG = Tf; X = Br; R = H
[Pd(η^3-cinnamyl)Cl]$_2$ (2.5–5 mol%) L24 (5–10 mol%), CsOPiv Cs_2CO_3, xylenes or mesitylene 140 or 160 °C	$Pd(OAc)_2$ (5 mol%) (*R*,*R*)-Me-DUPHOS (10 mol%) Cs_2CO_3, PivOH xylenes, 140 °C	[Pd(η^3-cinnamyl)Cp]$_2$ (5 mol%) L25 or L26 (20 mol%) **80** (5 mol%), Na_3PO_4 cumeme or *p*-xylene, 135 °C	$Pd(dba)_2$ (5 mol%) L27 (12 mol%) PivOH (30 mol%), Cs_2CO_3 mesitylene, 130 °C
29 examples 13–94% 10–95% *ee*	7 examples 42–97% 23–93% *ee*	16 examples 54–85% 62–96% *ee*	1 example 96% 71% *ee*

Selected Examples (2011 and 2013, Kündig)



Scheme 31. Pd(0)/Pd(II)-Catalyzed Synthesis of Chiral Indolines Using a Chiral Phosphate and an Achiral Phosphine Ligand



2016, Ye and Duan	2016, Baudoin
EWG = CO_2Me; X = Br; R^1 = H	EWG = CO_2R^3; X = Cl, Br, I
$Pd(OAc)_2$ (5 mol%) **CyJohnPhos** or PPh_3 (10 mol%) L3 (10 mol%), Cs_2CO_3, *p*-xylenes, 130 °C	$Pd(PCy_3)_2$ (5 mol%) L28 (10 mol%) Cs_2CO_3, 4 Å MS DME, 120 °C
2 examples 39–47% 50–67% *ee*	27 examples 18–96% 59–96% *ee*

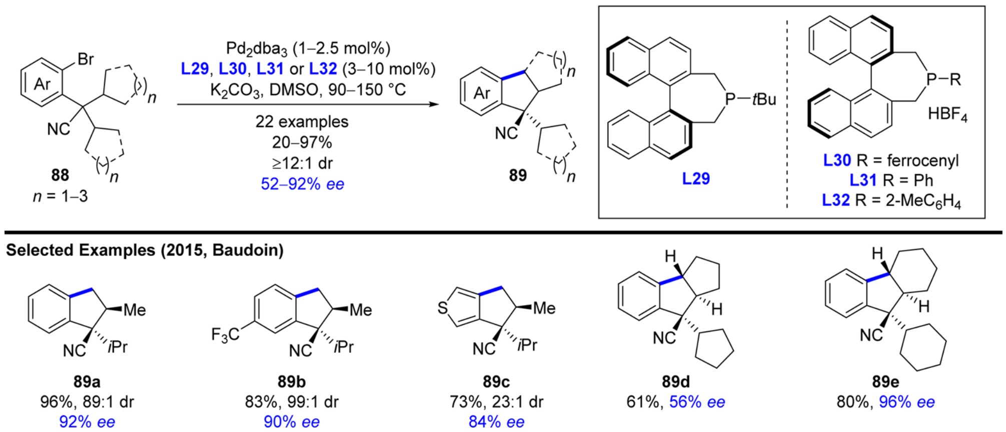
With the aid of DFT calculations, a range of 3,3′-disubstituated chiral phosphoric acids were examined, ultimately identifying the more elaborated BINOL-derived phosphoric acid **L28** as optimal. This reaction was also conducted in the presence of an achiral phosphine, allowing for the synthesis of a library of indolines in up to 96% ee. Notably, the Baudoin group also demonstrated the complementary behavior of their chiral phosphoric acid catalytic system versus Kündig's NHC system via application to the parallel kinetic resolution of racemic carbamates (see Scheme 117).

In 2012, Baudoin and co-workers successfully applied Pd(0)/Pd(II) catalysis to the synthesis of chiral indanes via an intramolecular C(sp^3)−H functionalization of aryl bromides **88** (Scheme 32).[107] Notably (*R*,*R*)-Me-DuPhos provided racemic products, despite its success for Kagan and co-workers in their related synthesis of indolines, shown above.[99] After extensive ligand screening, Baudoin et al. identified BINEPINE derivative **L29** as a suitable scaffold for enantioinduction. Further optimization in a follow-up paper improved the enantioselectivity through implementation of **L30**, **L31**, or **L32**, while concurrently expanding the scope of the reaction.[108] Excellent enantio- and diastereoselectivities were obtained for diisopropyl-substituted arenes (**89a** and **89b**), and only a minor reduction in selectivity was observed for the synthesis of fused thiophene **89c**. The arylation of cyclic secondary C(sp^3)−H bonds was completely diastereoselective; however, the enantioselectivity of the reaction was intimately linked to ring size (**89d** and **89e**).

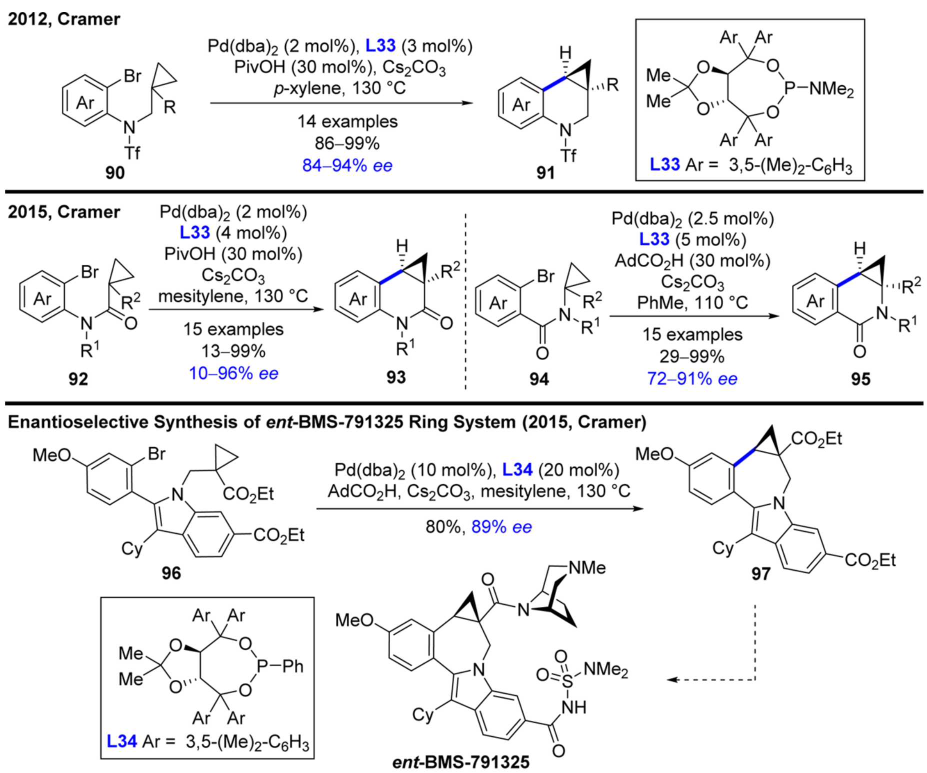
The synthesis of six- and seven-membered rings through the functionalization of cyclopropyl C(sp^3)−H bonds has also been achieved (Scheme 33). In 2012, the Cramer laboratory reported the highly enantioselective intramolecular functionalization of triflyl-protected anilines **90** to form the tetrahydroquinoline framework **91**.[109] In contrast to the indoline and indane syntheses described above, this reaction proceeds through a seven-membered palladacycle, and no Thorpe−Ingold bias by means of α-nitrogen substitution was required. Three years later, this methodology was extended to allow the synthesis of dihydroquinolones (**92** to **93**) and dihydroisoquinolones (**94** to **95**).[110] In this case, the same TADDOL-derived phosphoramidite ligand **L33** from their earlier study could be employed, and by simply inverting the amide connectivity in the reactants,

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

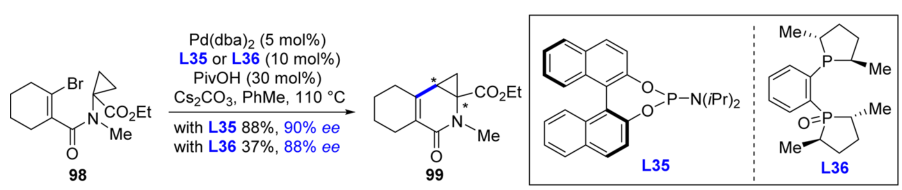
Scheme 32. C(sp^3)−H Functionalization Approach to Branched and Fused Indanes



Scheme 33. Enantioselective Synthesis of Six- and Seven-Membered Rings via Cyclopropyl C(sp^3)−H Functionalization



Scheme 34. Intramolecular Cyclopropyl C(sp^3)−H Alkenylation



either cyclopropyl-fused scaffolds could be accessed under closely related conditions. As part of the same study, this methodology was applied in a significantly more complex setting by means of an intramolecular cyclopropyl arylation of the highly substituted achiral indole **96**. The reaction was conducted using catalytic quantities of Pd(dba)$_2$ and TADDOL phosphinite **L34**, forging the seven-membered ring of **97** in 80% yield and in 89% ee. This framework constitutes the pentacyclic core of BMS-791325, a hepatitis C virus NS5B replicase inhibitor currently undergoing clinical evaluation.[111]

In 2016, the Charette group disclosed a racemic synthesis of cyclopropyl-fused azacycles via a Pd(0)/Pd(II)-catalyzed alkenylation of cyclopropyl C(sp^3)−H bonds.[112] Preliminary attempts at an enantioselective variant via the cyclization of amide **98** were also disclosed. Drawing inspiration from Cramer's success using TADDOL-phosphoramidite ligands in related

DOI: 10.1021/acs.chemrev.6b00692
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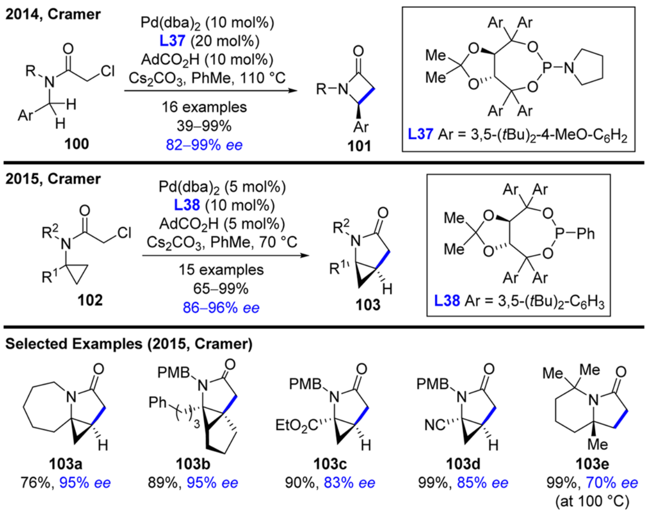
$C(sp^3)$−H functionalization reactions,[109,110] BINOL-derived phosphoramidite **L35** was employed as chiral ligand, providing **99** in 88% yield and 90% ee (Scheme 34). Further investigation also identified chiral bisphosphine monoxide **L36** as a promising ligand for this transformation, affording the cyclized product in 88% ee but a reduced 37% yield.

In 2014 and 2015, the Cramer group disclosed C−H functionalization methods for the formation of $C(sp^3)$−$C(sp^3)$ bonds, enlisting TADDOL-derived phosphoramidites as chiral ligands in both cases (Scheme 35).[113,114] Intramolecular

Scheme 35. $C(sp^3)$−$C(sp^3)$ Bond Formation via Intramolecular $C(sp^3)$−H Functionalization of Chloroacetamides

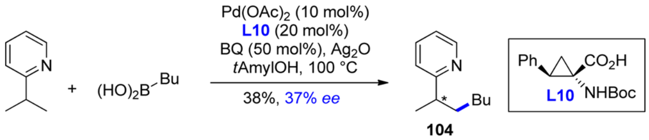


activation of chloroacetamides **100** at their benzylic C−H bond, followed by a challenging strain-inducing reductive elimination, delivered the valuable chiral β-lactam motif **101** in up to 99% ee.[113] Undesired nucleophilic substitution at the α-chloro position of **102** by the carboxylate cocatalyst, as well as aryl $C(sp^2)$−H functionalization, was mitigated via acid and ligand structure optimization. γ-Lactams could also be accessed in a similar manner via the intramolecular functionalization of cyclopropyl $C(sp^3)$−H bonds.[114] Several benzyl and alkyl substituents on nitrogen were tolerated (**103a**−**103e**); however, secondary amides do not react. Highly substituted cyclopropanes (**103b**), as well as adjacent ester (**103c**) and nitrile (**103d**) functionality, worked well, and the activation of methyl $C(sp^3)$−H bonds also proved possible, although inferior enantioselectivities were observed (**103e**).

2.2.1.2. Pd(II)/Pd(0). The first transition-metal-catalyzed enantioselective $C(sp^3)$−H functionalization was reported by Yu and co-workers in 2008, as part of a larger study concerning the reaction of $C(sp^2)$−H bonds [see Scheme 15 for $C(sp^2)$−H work].[32] The directed $C(sp^3)$−H butylation of 2-isopropylpyridine was demonstrated, employing cyclopropyl amino acid **L10** as ligand, under Pd(II)/Pd(0) catalysis (Scheme 36). Although the reaction provided **104** in only 38% yield and 37% ee, the enantioselectivity was highly dependent on ligand structure, leading the authors to correctly predict that $C(sp^3)$−H functionalization reactions could be rendered highly enantioselective with an appropriate ligand scaffold.

In 2011, the first highly enantioselective $C(sp^3)$−H functionalization methodologies began to appear in the literature. One such example, from the Yu group, focused on the amide-directed

Scheme 36. First Catalytic Enantioselective $C(sp^3)$−H Functionalization



intermolecular aryl-, alkenyl- and alkylation of cyclopropanes **105** with organoboron reagents, with yields ranging from 51 to 81% and enantioselectivities from 62 to 92% (Scheme 37).[115] The exact conditions for the synthesis of enantioenriched cyclopropyl derivatives **106** were tailored for each nucleophile (Ph−Bpin, 1-cyclohexenyl−Bpin, and *n*Bu−BF_3K), and the best results were obtained under batchwise addition of the reagents. Primary or secondary alkyl substitution at the α-position of the cyclopropane was well-tolerated for phenylation (**106a** and **106b**), as too was aryl substitution (**106c**); however, a lower yield and enantioselectivity was observed for butylation (**106d**). This methodology was later extended to allow for the arylation of cyclobutyl $C(sp^3)$−H bonds (**107** to **109**), and promising results concerning the functionalization of methyl $C(sp^3)$−H bonds were also disclosed (**110** to **112**).[116] As with their earlier study, a weakly coordinating electron-deficient amide served as directing group, and carbamate-bearing MPAA ligands controlled the enantioselectivity.

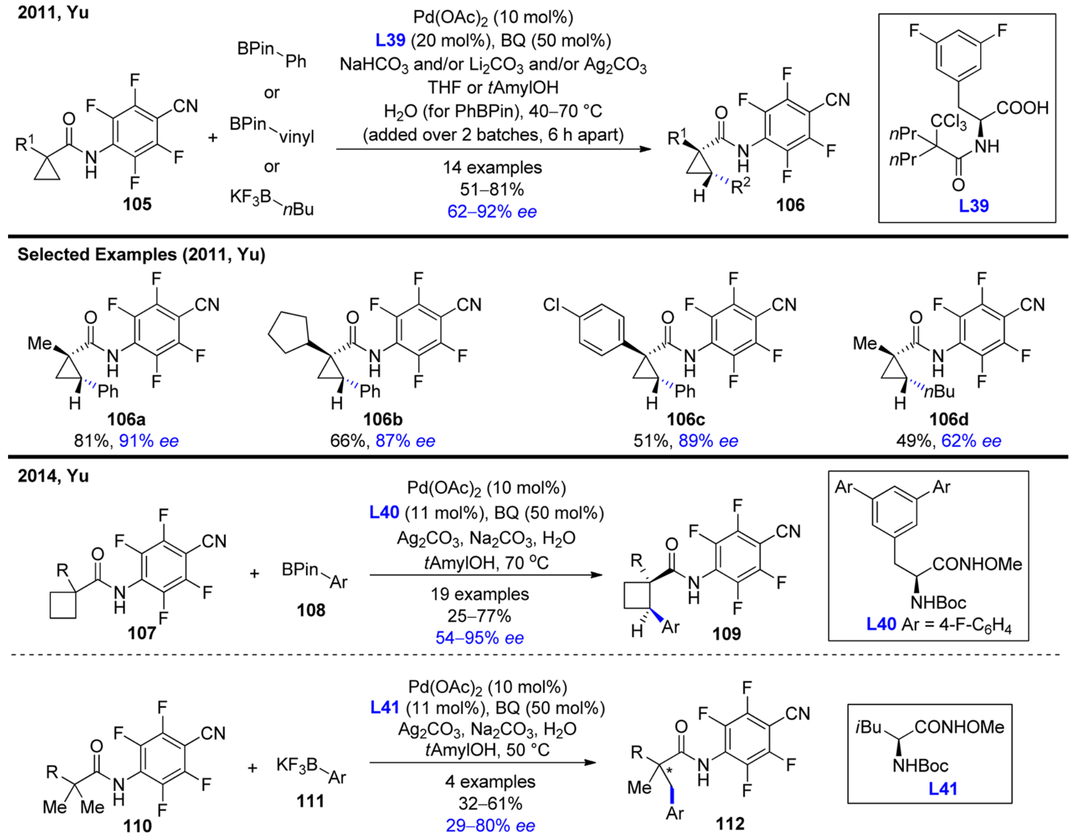
Recently, the Yu group reported a Pd(II)/Pd(0)-catalyzed enantioselective amine α-functionalization of thioamines **113** with boronic acids **114**, allowing efficient access to highly privileged enantioenriched motifs **115** (Scheme 38).[117] Among the ligands tested chiral phosphate **L42** performed best, affording the functionalized products **115** in 40−90% yield and 75−98% ee. Notably, their previously developed MPAA ligands[116,118] were ineffective and did not yield any of the desired products. The thioamide directing group proved crucial for reactivity (the corresponding amides were unreactive); however, the authors demonstrated their effective removal without erosion in enantiopurity. Both cyclic (**115a**−**115d**) and acyclic amines (**115e**), as well as a range of boronic acids (**115a**−**115e**), were well accommodated, and remarkably, regioselective C−H arylation was also demontrated (**115d** and **115e**).

2.2.1.3. Pd(II)/Pd(IV). The first Pd(II)/Pd(IV)-catalyzed enantioselective $C(sp^3)$−H functionalization was disclosed by Yu et al., in 2015 (Scheme 39).[118] In this report, triflyl-protected cyclopropylmethylamines **116** were coupled with a broad range of aryl iodides **117**, providing the functionalized products **118** in ≥95% ee in all cases (e.g., **118a**−**118e**). Silver carbonate served to promote both the oxidative addition and reductive elimination processes, and the reaction could be conducted on a gram scale without a significant decrease in yield or enantioselectivity. In addition, the authors demonstrated that triflyl deprotection could be conducted without impacting substrate enantiopurity.

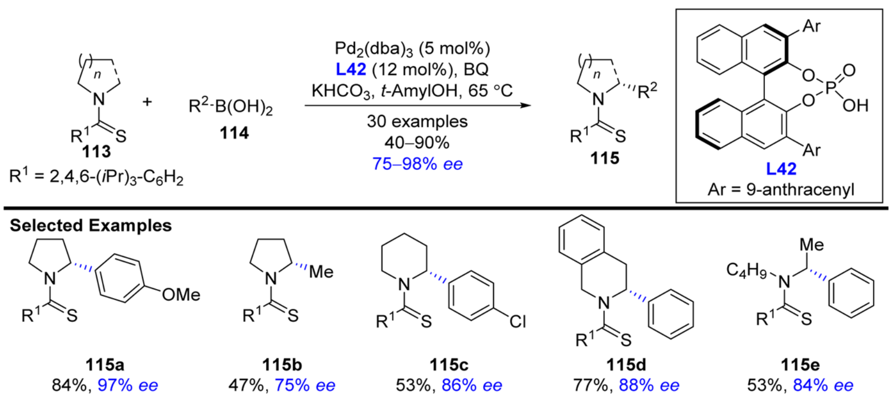
In 2015, Duan and co-workers demonstrated, for the first time, that chiral phosphoric acids and amides could successfully partake in a stereochemistry-generating C−H activation event and, more generally, that ligand families other than MPAA were suitable in enantioselective Pd(II)/Pd(IV)-catalyzed methodologies (Scheme 40).[119] The directed β-arylation of 8-aminoquinoline amides **119** with aryl iodides **120** was conducted using a Pd(II) source, cesium carbonate as base, and BINOL-derived ligand **L43** at 140 °C, providing the arylated products **121** in up to 80% ee. Notably, however, the functionalization of non-benzylic C−H bonds proceeded with low levels of enantiocon-

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

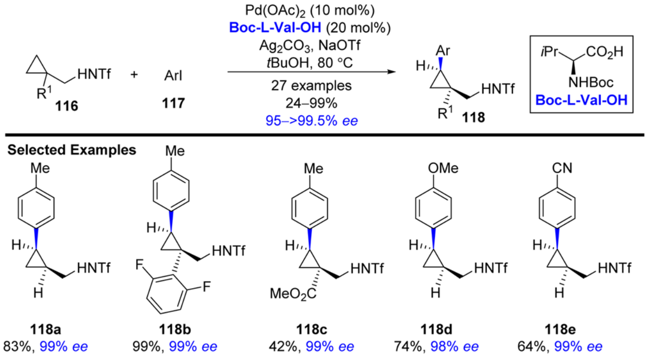
Scheme 37. *N*-(4-Cyano-2,3,5,6-tetrafluorophenyl)amide-Directed C(sp³)−H Functionalization



Scheme 38. Pd(II)/Pd(0)-Catalyzed Enantioselective Amine *α*-C(sp³)−H Functionalization



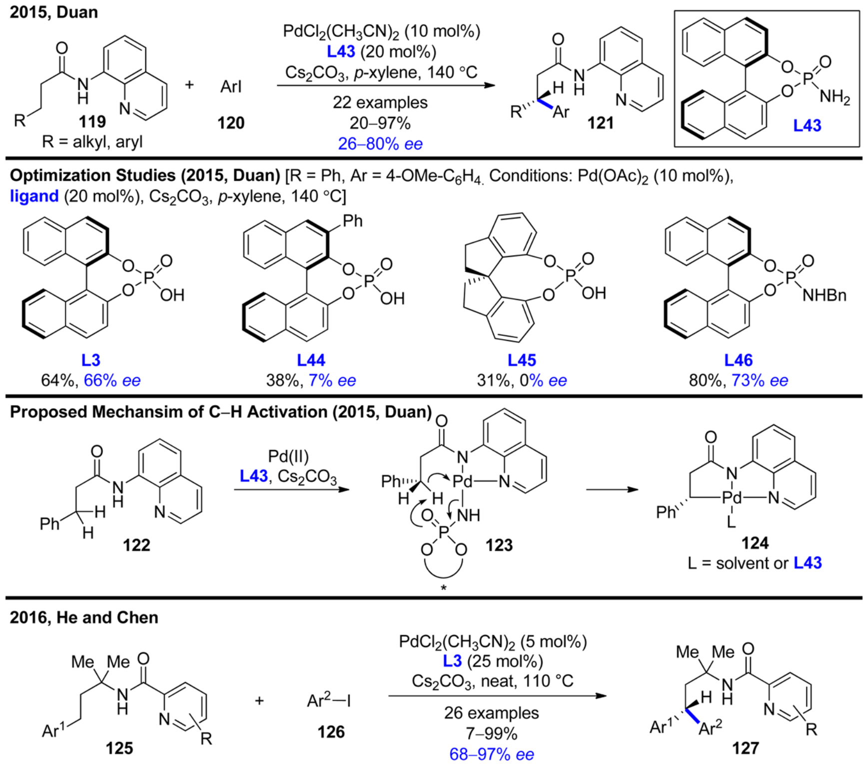
Scheme 39. Pd(II)/Pd(IV)-Catalyzed Enantioselective C(sp³)−H Functionalization



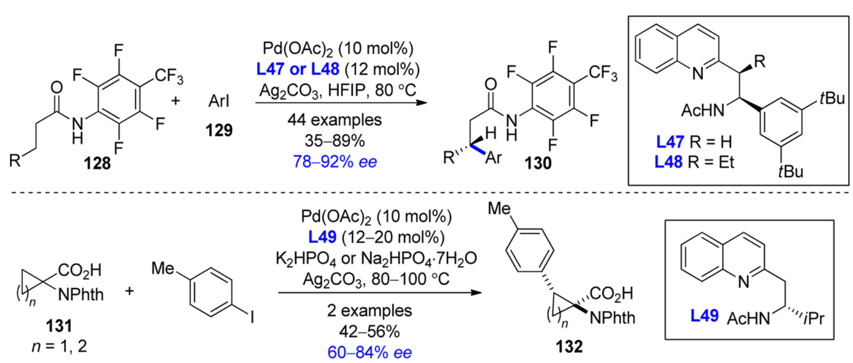
trol (26−28% ee). Ligand optimization studies conducted with chiral phosphoric acids revealed that the unsubstituted BINOL backbone was better suited for the transformation in terms of both yield and enantioselectivity (e.g., **L3** vs **L44**), and moving to the SPINOL framework resulted in a racemic transformation (**L45**). Ultimately, replacement of the phosphoric acid moiety in **L3** with a phosphoric amide (**L43**) provided the best result. Mechanistic investigations revealed that the rate of reaction with pivalic acid as ligand was 1.3 times faster than the blank reaction with no ligand, 2.6 times faster with **L46**, and 3.7 times faster with **L3**. Kinetic isotope experiments indicate that the C−H activation is rate-limiting, and the authors propose it proceeds via deprotonation and complexation of amide **122** with a Pd(II) species to generate intermediate **123**, followed by an amide-assisted C−H bond cleavage event to palladacycle **124**. One year later He, Chen, and their co-workers reported a closely related

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 40. Pd(II)/Pd(IV)-Catalyzed Benzylic C(sp^3)−H Arylation



Scheme 41. Pd(II)/Pd(IV)-Catalyzed Unactivated C(sp^3)−H Bond Arylation



picolinamide-directed benzylic γ-C−H arylation of amines **125** with aryl iodides **126**.[120] In the presence of a Pd(II) source, 25 mol % BINOL-derived phosphate **L3** as chiral ligand, and cesium carbonate as base, a variety of structurally diverse arylation products **127** could be generated in up to 99% yield and 97% ee.

In 2016, Houk, Yu, and their co-workers also reported a procedure for the arylation of amide β-methylene C(sp^3)−H bonds; however, in this study both benzylic and unactivated alkyl C−H bonds were well-tolerated (Scheme 41).[121] During the reaction development stages, monodentate quinoline or pyridine ligands, which had been shown in earlier achiral studies to accelerate C(sp^3)−H activation,[122,123] provided only low levels of enantiocontrol. Although MPAA ligands had proven ineffective for palladium insertion into acyclic methylene C−H bonds, the authors reasoned that combining structural motifs from both ligand families may improve the enantioselectivity of the reaction. Following ligand structure optimization, bidentate acetyl-protected aminoquinolines **L47** and **L48** were identified as excellent sources of enantiocontrol, enabling the coupling of electron-deficient amides **128** with aryl iodides **129**. The functionalized products **130** were isolated in 35−89% yield and 78−92% ee. The authors also demonstrated that free carboxylic acid derivatives **131** were competent substrates, in this case employing a phosphate buffer and **L49** as ligand, leading exclusively to *cis*-diastereoisomers **132**.

In efforts directed toward improving the efficiency and expanding the applicability of directed C−H functionalization reactions, Yu and workers reported an enantioselective C−H arylation of benzaldehydes **133** with aryl iodides **134** by means of a transient directing group, thus eliminating the need for its stoichiometric introduction and removal (Scheme 42).[124] Employing Pd(OAc)$_2$ and a catalytic quantity of L-*tert*-leucine, γ-arylated aldehydes **136** could be isolated in up to 88% yield and 96% ee. The reaction proceeds via in situ imine formation, followed by palladium complexation to generate intermediate **135**. Directed C(sp^3)−H arylation and then subsequent imine hydrolysis provide the desired products. A range of electron-deficient benzaldehydes were successfully coupled with a variety of meta- and para-substituted aryl iodides, including electron-

DOI: 10.1021/acs.chemrev.6b00692
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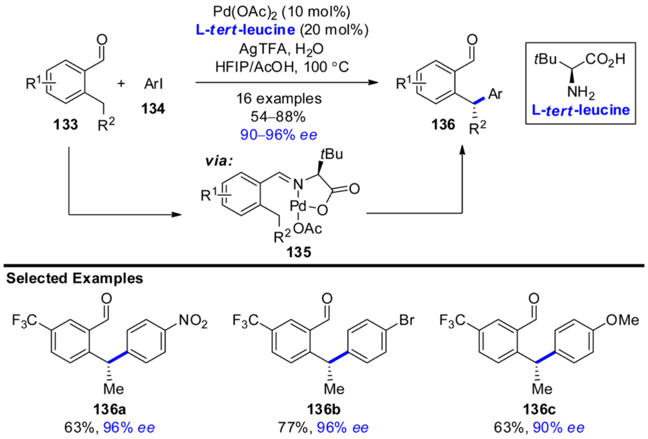
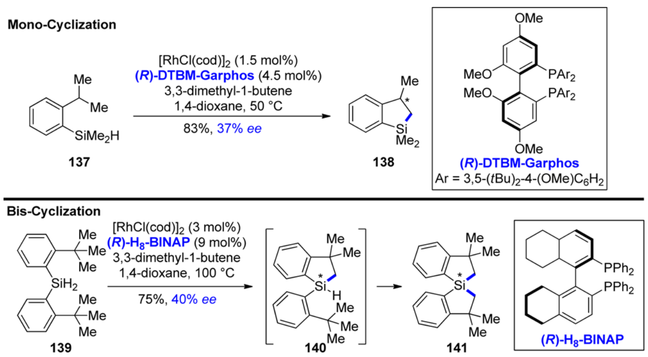
Scheme 42. Imine-Directed C(sp^3)−H Arylation of Benzaldehydes



poor (**136a**), halogenated (**136b**), and electron-rich derivatives (**136c**).

2.2.2. Rhodium Catalysis. Building upon their earlier Rh-catalyzed enantioselective silylation of C(sp^2)−H bonds (Scheme 24),[91] Murai, Takai, and their co-workers disclosed a related asymmetric dehydrogenative silylation, in this case proceeding via an enantioselective desymmetrization of a C(sp^3)−H bond (Scheme 43).[125] Employing diphosphine ligand

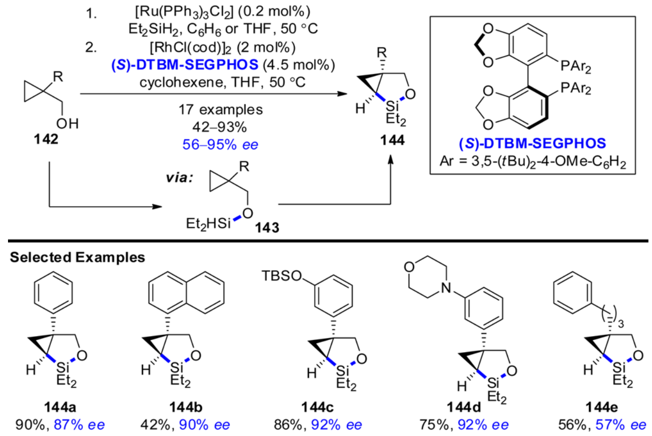
Scheme 43. Rh-Catalyzed Enantioselective Intramolecular Methyl C(sp^3)−H Silylation



(*R*)-DTBM-Garphos and 3,3-dimethyl-1-butene as hydrogen acceptor, (2-isopropylphenyl)dimethylsilane (**137**) was converted to 2,3-dihydro-1*H*-benzo[*b*]silole **138** in 83% yield and 37% ee. As part of the same study, this methodology was applied in the double C(sp^3)−H silylative cyclization of diarylsilane **139**, proceeding via monocyclized intermediate **140**. In this case, (*R*)-H_8-BINAP provided superior enantiocontrol compared to (*R*)-DTBM-Garphos, and the axially chiral 1,1′-spirosilabiindane **141** was synthesized in 75% yield and 40% ee. The stereochemistry of the product is thought to be determined in the first cyclization event, analogous to their related C(sp^2)−H functionalization studies.[91,92]

In mid-2016, the Hartwig group reported the first catalytic enantioselective silylation of methylene C(sp^3)−H bonds (Scheme 44).[126] In analogous fashion to their earlier reported silylation of C(sp^2)−H bonds (presented earlier in Scheme 25), the sequence begins with dehydrogenative coupling of cyclopropylmethanols **142** with dimethylsilane, in this case employing a Ru catalyst, to provide hydrosilyl ethers **143**. [RhCl(cod)]$_2$ and the bulky (*S*)-DTBM-SEGPHOS ligand were identified as the

Scheme 44. Rh-Catalyzed Enantioselective Silylation of Cyclopropyl C(sp^3)−H Bonds



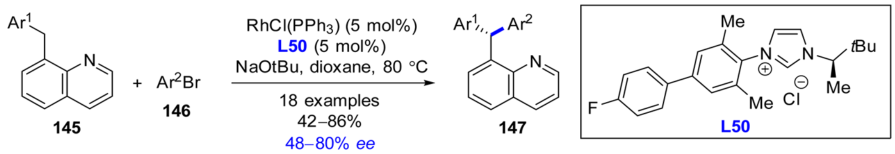
optimal combination for C−H functionalization, providing the silylated products **144** in up to 93% yield and 95% ee. The presence of cyclohexene as hydrogen acceptor proved critical for achieving high yields and enantioselectivity. Investigations into the substrate scope of the transformation revealed that aryl-substituted cyclopropanes provided higher levels of enantiocontrol than their corresponding alkyl derivatives (e.g., **144a**−**144d** versus **144e**). On the basis of this observation, and the fact that an almost identical selectivity was achieved for both primary and secondary alkyl substituents, the authors propose that a beneficial interaction between the aryl rings of the catalyst and the substrate is in operation. Kinetic isotope experiments suggest that C−H bond cleavage is rate-limiting and irreversible, indicating that the C−H activation is enantiodetermining, as opposed to the C−Si bond-forming reductive elimination.

The most recent Rh-catalyzed example comes from the lab of Glorius and involves a directed intramolecular C(sp^3)−H functionalization of 8-benzylquinolines **145** with aryl bromides **146** and was achieved using a Rh(I)/NHC catalytic system (Scheme 45).[127] Ligand structure optimization studies identified newly designed unsymmetrical NHC **L50** as providing moderate to good levels of enantiocontrol and site selectivity, enabling isolation of the enantioenriched triarylmethanes **147** in up to 86% yield and 80% ee.

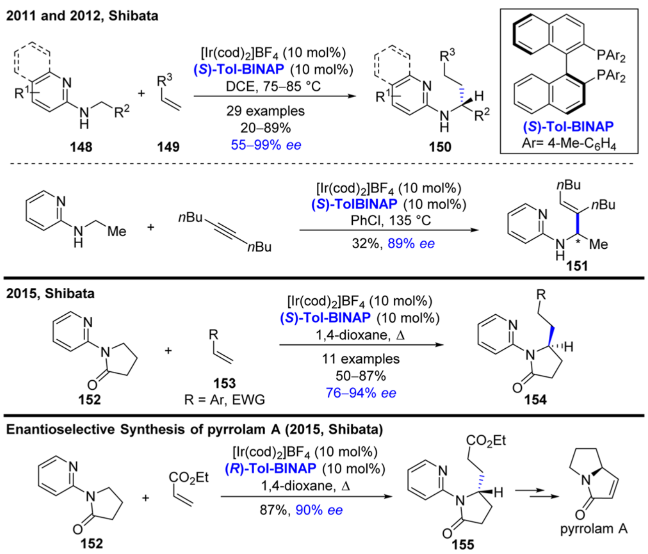
2.2.3. Iridium Catalysis. The Shibata group has reported several iridium-catalyzed C(sp^3)−H functionalization methodologies (Scheme 46). The first example, from 2011, involved a cationic Ir(I)-catalyzed enantioselective reaction of 2-(alkylamino)pyridines **148**.[128] These were alkylated with terminal alkenes **149** (usually styrenes), presumably proceeding via a 2-pyridal-directed C−H activation event, yielding chiral amines **150** in moderate to good yields and enantioselectivities. In a follow-up study, 2-quinoline was also identified as a suitable directing group, and the scope of alkene coupling partners was extended to include more functionalized derivatives.[129] In addition, one example describing the alkenylation of *N*-ethylpyridin-2-amine with dec-5-yne was disclosed, providing trisubstituted alkene **151** in 32% yield and 89% ee. This protocol was later applied to the C(sp^3)−H alkylation of *N*-(2-pyridyl)-γ-butyrolactam (**152**) with terminal alkenes **153**, in this case leading to chiral γ-lactams **154**.[130] Reaction with ethyl acrylate enabled the synthesis of functionalized ester **155** in 90% ee, which was subsequently converted to bacterial extract pyrrolam A.

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

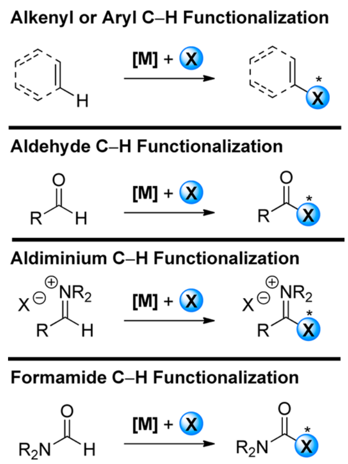
Scheme 45. Enantioselective Synthesis of Triarylmethanes via Rh-Catalyzed C(sp^3)−H Arylation



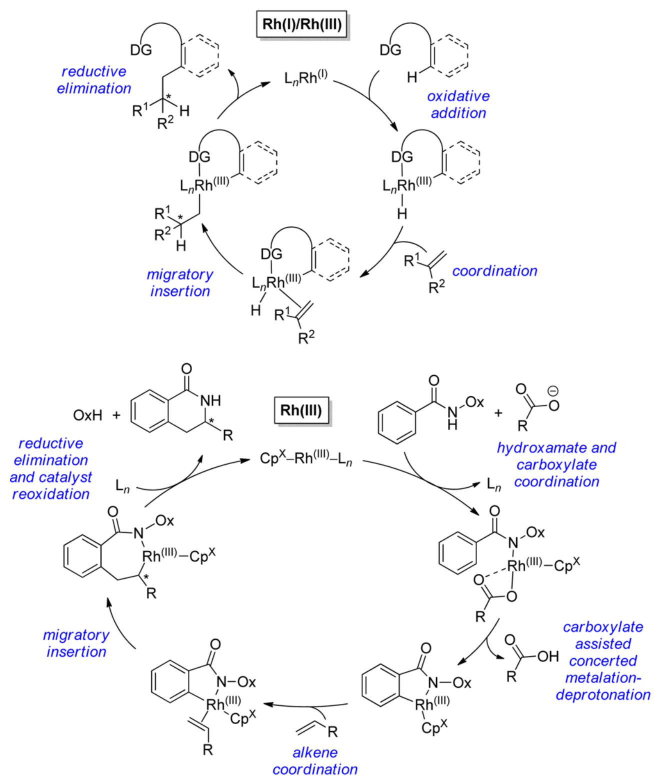
Scheme 46. Ir-Catalyzed Enantioselective C(sp^3)−H Functionalization



Scheme 47. Classification of Reactions Proceeding via a Stereochemistry-Generating Migratory Insertion



Scheme 48. General Mechanisms of Rhodium-Catalyzed C−H Functionalization Reactions Involving a Stereochemistry-Generating Migratory Insertion



3. STEREOCHEMISTRY-GENERATING MIGRATORY INSERTION

3.1. C(sp^2)−H Functionalization

In contrast to the previous section, which focused on the selective recognition of prochiral C−H bonds by a chiral catalyst, enantioselective methodologies incorporating a stereochemistry-generating migratory insertion require a chiral catalyst to control addition to one enantiotopic face of a coupling partner. The vast majority of enantioselective C−H functionalization strategies that proceed via a stereochemistry-generating migratory insertion involve activation of a C(sp^2)−H bond. This mode of reactivity has most commonly been realized with alkenyl, aryl, and aldehyde C(sp^2)−H bonds, although reports of enantioselective aldimine and formamide C(sp^2)−H bond functionalization have been disclosed (Scheme 47). These processes most typically proceed via a migratory insertion of a two-atom component (e.g., a π-bond) into a metal−carbon or metal−hydride bond, although carbenoid insertion has also been demonstrated.

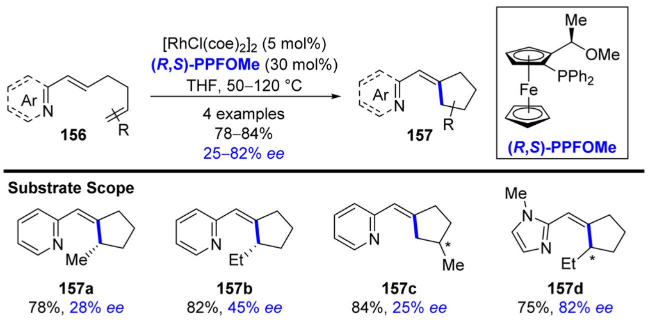
3.1.1. Alkenyl or Aryl C−H Functionalization. *3.1.1.1. Rhodium Catalysis.* To the best of our knowledge, all Rh-catalyzed enantioselective alkenyl and aryl C−H functionalization reactions that incorporate a stereochemistry-generating migratory insertion operate via either a Rh(I)/Rh(III) or a Rh(III) catalytic cycle. Although there are several variations on precisely how each proceeds, two relatively general pathways can be considered (Scheme 48). The Rh(I)/Rh(III) catalytic cycle initiates with a (usually nitrogen-directed) C−H activation, proceeding via oxidative addition of a Rh(I) species into the C−H bond. Following coordination of a π-bond coupling partner, most commonly a tethered olefin, a stereochemistry-generating migratory insertion into the Rh−hydride bond ensues. Finally, reductive elimination provides the coupled product and regenerates the active Rh(I) catalyst. In contrast, enantioselective Rh(III)-catalyzed reactions that proceed via a stereochemistry-generating migratory insertion are currently limited to the

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

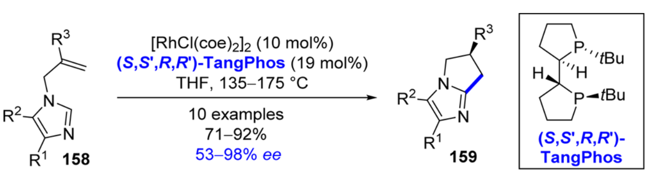
directed functionalization of aryl C−H bonds. In this case, the reaction begins with coordination of a hydroxamic acid derivative and carboxylate species to the active Rh(III) catalyst. This intermediate subsequently participates in a CMD event, followed by a stereochemistry-generating and enantiodetermining migratory insertion. Following reductive elimination of the coupled product, reoxidation of the catalyst to Rh(III) occurs via cleavage of the N−O bond of the internal oxidant.[131]

3.1.1.1.1. Rh(I)/Rh(III). The earliest enantioselective Rh(I)/Rh(III)-catalyzed C−H activation methodology was published by Murai and co-workers in 1997 (Scheme 49).[132] Four closely related *N*-heterocycle-directed transformations were described, each proceeding via an intramolecular olefin insertion pathway. In all cases, $[RhCl(coe)_2]_2$ was employed as a Rh(I) source, and the monodentate phosphine ligand (*R*,*S*)-PPFOMe provided the best levels of enantiocontrol. 2-Pyridyl-directed C−H functionalization required temperatures of 120 °C, enabling access to cyclopentanes **157a**−**157c** in good yields; however, only low enantioselectivities were observed (28−45% ee). Notably, when 2-imidazolyl was used as the directing group, the temperature could be lowered to 50 °C, resulting in a greatly improved level of enantiocontrol (**157d**, 82% ee).

Scheme 49. Pyridyl- and 2-Imidazoyl-Directed Rh(I)-Catalyzed Enantioselective C−H Alkylation



Scheme 50. Rh(I)-Catalyzed Enantioselective Intramolecular C−H Alkylation of *N*-Allylic Imidazoles



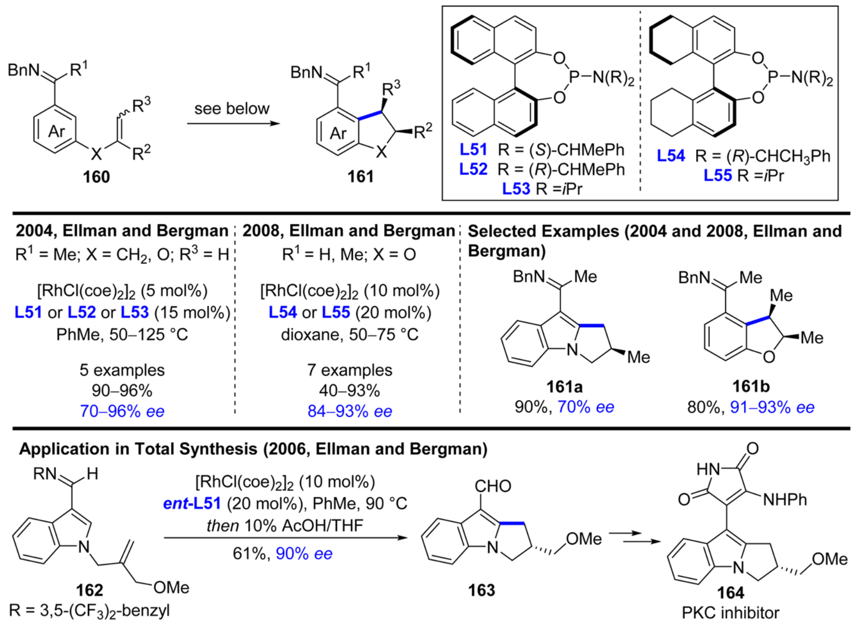
In 2009, Bergman, Ellman, and their co-workers reported the functionalization of imidazole substrates (Scheme 50).[133] In this case, the alkene was tethered at the 1-position, and bisphosphine (*S*,*S*′,*R*,*R*′)-TangPhos served as chiral ligand. Cyclization of *N*-allylic imidazoles **158** to the corresponding 5,5-fused ring system **159** proceeded in up to 92% yield and 98% ee, despite the high temperatures necessary for reaction. During optimization studies, electron-rich bidentate phosphines appeared to be necessary for high levels of enantiocontrol, and the authors speculate that partial ligand dissociation of (*S*,*S*′,*R*,*R*′)-TangPhos may occur, revealing an open coordination site necessary for catalytic activity.[134]

Imines have also been established as competent directing groups for intramolecular C−H functionalization reactions (Scheme 51). In 2004, Ellman, Bergman, and their co-worker reported the first highly enantioselective catalytic reaction involving aromatic C−H activation.[135] Hydroarylation of ketimines **160**, under Rh(I)/Rh(III) catalysis, provided chiral, fused aromatics **161** in 90−96% yield and 70−96% ee. Generally, the diastereomeric phosphoramidite ligands **L51** and **L52** provided the highest enantioselectivities, indicating that asymmetric induction was predominately controlled by the BINOL backbone. The optimal ratio of ligand to Rh was determined to be either 1:1 or 1.5:1. Higher ratios slowed the rate of reaction (without affecting enantioselectivity), suggesting only one phosphoramidite ligand is bound to Rh during the reaction. Four years later, Ellman, Bergman, and their co-workers extended the scope of the reaction to allow for nonterminal alkene coupling partners by employing H_8-BINOL-derived ligands **L54** and **L55**.[136] In all cases, the reaction was completely diastereoselective for the *syn*-diastereoisomer, irrespective of alkene configuration, indicating that an isomerization event precedes cyclization. Representative examples from these studies include *N*-fused tricyclic indole **161a** and dihydrobenzofuran **161b**, which were accessed in 70% and 91−93% ee, respectively. Ellman and Bergman have also applied this methodology in the enantioselective synthesis of a biologically active dihydropyrroloindole.[137] After a short screen of directing groups, bis(trifluoromethyl) benzyl imine **162** was identified as optimal, enabling a highly enantioselective cyclization. Key intermediate **163** was accessed in 61% yield and 90% ee following imine hydrolysis and was subsequently converted into PKC inhibitor **164**.

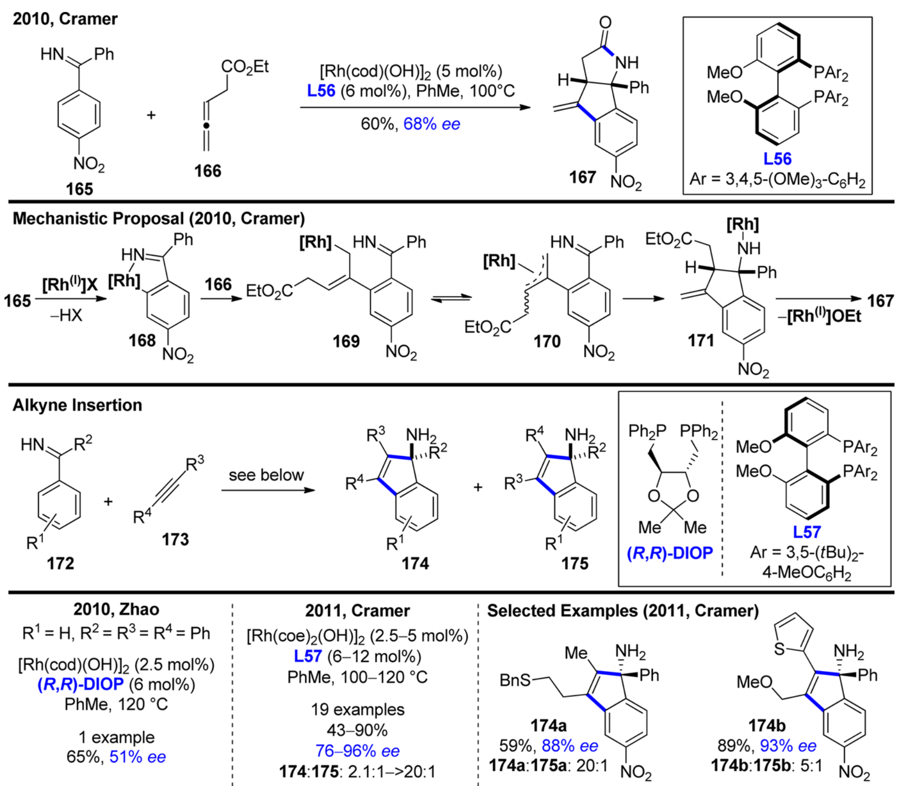
Imine directing groups have also been employed in intermolecular reactions (Scheme 52). As part of a larger study focused on the diastereoselective allylation of ketimines, Tran and Cramer reported a proof-of-concept for an enantioselective variant. Electron-poor ketimine **165** was reacted with the achiral ethyl penta-3,4-dienoate (**166**), under Rh(I)/Rh(III) catalysis and with the biaryl phosphine ligand **L56**, enabling the synthesis of lactam **167** in 60% yield and 68% ee.[138] In contrast to the previously described Rh(I)/Rh(III)-catalyzed reactions, the reaction does not involve migratory insertion into a Rh−hydride bond. Rather, the directed C−H activation of **165** is believed to proceed via either an oxidative addition/reductive elimination sequence or a σ-bond metathesis event, crucially removing the hydrogen atom from the Rh center. Formation of cyclometalated intermediate **168** is followed by a migratory insertion of the less substituted olefin of **166** in the Rh−aryl bond. The resulting allyl rhodium species, either as its σ- or π-bound complex **169** or **170**, can then participate in a stereochemistry-generating imine allylation, generating the 5,6-fused intermediate **171**. Finally, an intramolecular capture of the primary amine generates lactam **167** and releases a Rh(I) species. In early 2010, the Zhao lab reported a closely related Rh-catalyzed [3 + 2]-annulation approach to racemic indenamines.[139] One enantioselective example was reported, via coupling of diphenylmethanimine (where R^1 = H; R^2 = Ph) and 1,2-diphenylethyne (where R^3 = R^4 = Ph). (*R*,*R*)-DIOP was employed as a chiral ligand, providing the target in a modest 51% ee. One year later, Cramer et al. disclosed a highly enantioselective synthesis of indenamines **174**, in this case incorporating both symmetrical and unsymmetrical internal alkynes.[140] The C−H activation step proved highly site selective, and the regioselectivity of the migratory insertion could be controlled by the incorporation of potentially coordinating functional groups. In all cases the insertion occurred

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 51. Rh(I)/Rh(III)-Catalyzed Intramolecular Cyclization via Imine-Directed C−H Activation



Scheme 52. Intermolecular C−H Functionalization of Aromatic Imines under Rh(I)/Rh(III) Catalysis

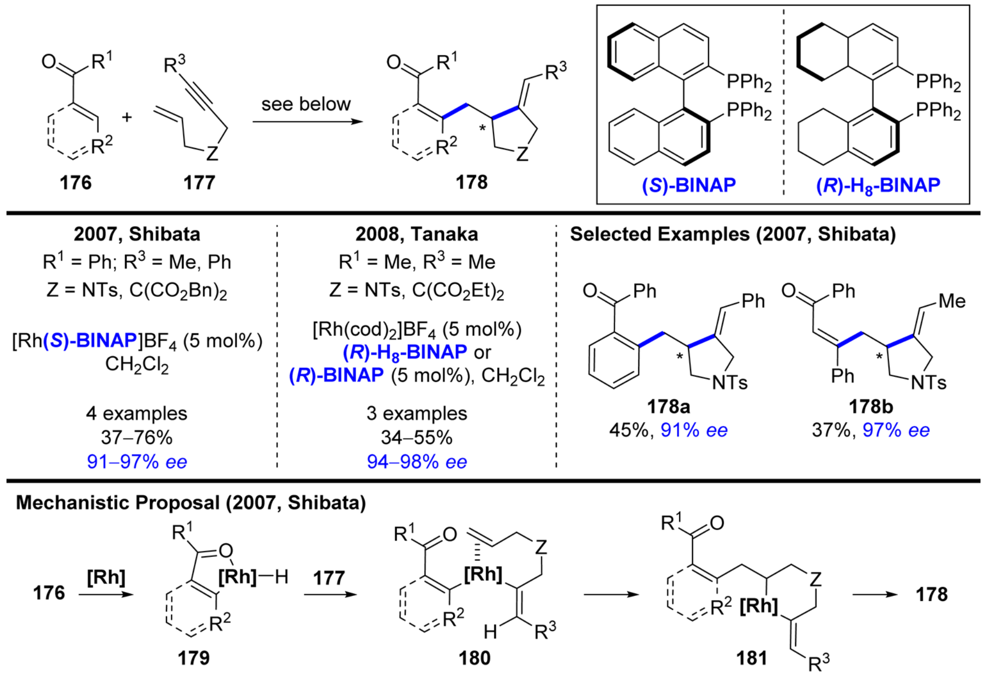


preferentially so that directing group ended up proximal to the aryl substituent (e.g., **174a** and **174b**).

In 2007 and 2008, the Shibata and Tanaka groups each disclosed a carbonyl-directed C(sp^2)−H functionalization of ketones **176** with enynes **177** (Scheme 53). The earlier report, from Shibata and co-workers, involved the functionalization of both aryl and alkenyl C−H bonds with a Rh−(*S*)-BINAP complex, providing the coupled products **178** in 91−97% ee.[141] Under related conditions, in this case using either (*R*)-H_8-BINAP or (*R*)-BINAP, three examples of aromatic ketone functionalization were described by Tanaka et al., also proceeding with high levels of enantiocontrol (94−98% ee).[142] Selected examples from Shibata's study include benzophenone-derived **178a** and (*E*)-chalcone-derived **178b**. Shibata and co-workers proposed that the reaction begins with a directed oxidative addition of Rh into the proximate C(sp^2)−H bond to generate intermediate **179**. This is followed by an intermolecular hydrorhodation of the alkyne moiety of **179** to yield **180**. A subsequent intramolecular carborhodation generates rhodacycle

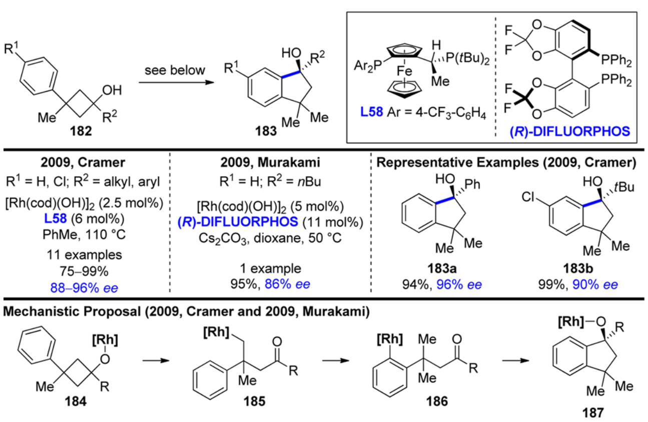
DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 53. Ketone-Directed Aryl and Alkenyl C−H Functionalization/Cyclization



181, which reductively eliminates to release the desired products 178.

Scheme 54. Rh(I)/Rh(III)-Catalyzed C−C/C−H Bond Activation Sequence of Achiral Cyclobutanols

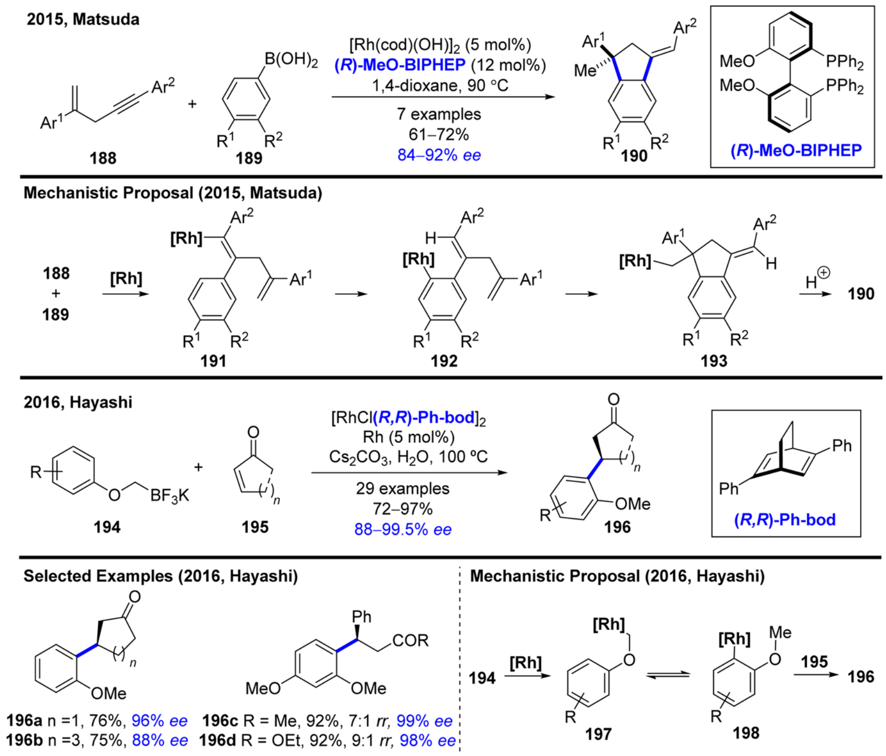


Two research groups have disclosed Rh(I)-catalyzed cascade C−C/C−H bond approaches to enantioenriched indanols (Scheme 54). In 2009, Cramer and co-workers demonstrated that *meso*-cyclobutanol **182** (used as an inconsequential mixture of diastereoisomers) could be converted to chiral indanols **183** in the presence of a Rh(I) source and Josiphos-type ligand **L58**.[143] Both alkyl and aryl substituents were well tolerated, and representative examples include indanols **183a** and **183b**. Later that same year, the Murakami group reported that the same transformation could be conducted using a Rh(I)/(*R*)-DIFLUORPHOS complex.[144] Both groups propose the same mechanistic pathway, beginning with β-carbon elimination of the rhodium alkoxide species **184** to generate primary alkyl−rhodium intermediate **185**. Following a 1,4-Rh shift to access the more stable aryl−Rh complex **186**, a stereochemistry-generating migratory insertion sets the quaternary stereocenter of **187**. This rhodium alkoxide then acts as a base, deprotonating another cyclobutanols molecule, while the target indanol is released. Both research groups also disclosed several diastereo- and enantioselective examples where the Me substituent in **182** is replaced with a different alkyl or aryl group. In this case, the β-carbon elimination becomes stereochemistry-generating (see Scheme 95).

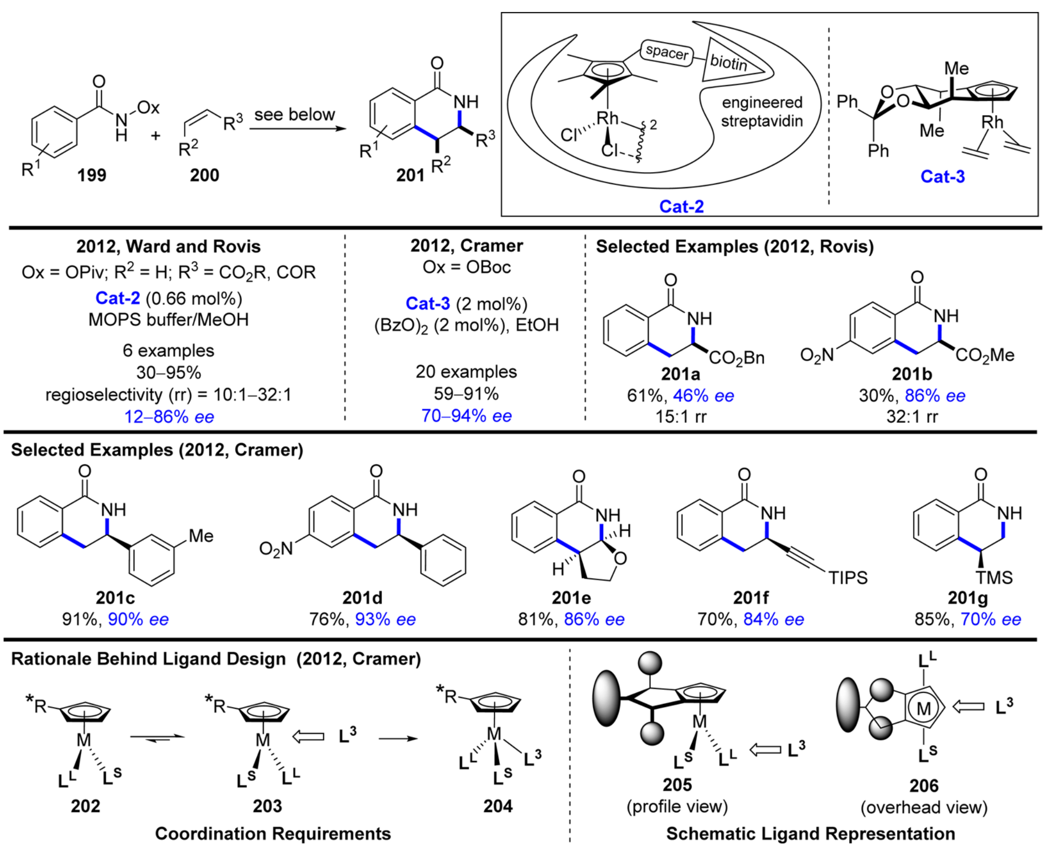
Two conceptually related methodologies, also incorporating 1,4-Rh shifts, were disclosed by the groups of Matsuda[145] and Hayashi[146] in 2015 and 2016, respectively (Scheme 55). The earlier report, from Matsuda and Watanuki, describes an arylative annulation of 1,4-enynes **188** with boronic acids **189**, under Rh(I) catalysis and using (*R*)-MeO-BIPHEP as ligand. Several enantioenriched functionalized indanes **190** bearing an all-carbon quaternary center were accessed in 61−72% yield and 84−92% ee. The reaction is believed to proceed via the generation of an arylrhodium species, followed by a regioselective addition to the alkyne of **188**, generating (*Z*)-arylalkenylrhodium(I) species **191**. A 1,4-Rh migration to the more sterically accessible site on the aromatic ring yields **192**, which is followed by migratory insertion of the 1,1-disubstituted alkene into the Rh−aryl bond. Finally, protonation of **193** releases the target **190**. In 2016, Ming and Hayashi disclosed a Rh(I)-catalyzed coupling of aryloxymethyltrifluoroborates **194** with enones **195** via a 1,4-Rh migration/arylation sequence.[146] By utilizing $[RhCl(R,R)\text{-Ph-bod}]_2$ as catalyst, the desired products **196** were delivered in high yields and with excellent enantioselectivities. Both cyclic (**196a** and **196b**) and linear (**196c** and **196d**) enones were well tolerated, as were meta-substituted aryloxymethyltrifluoroborates (**196c** and **196d**), which reacted preferentially at the less sterically hindered *o*-C−H site. On the basis of mechanistic studies, the authors propose that the reaction proceeds via transmetalation of the phenoxymethyl group of **194** from boron to rhodium, delivering intermediate **197**, which can then undergo a reversible 1,4-Rh migration through a Rh(III) species to form species **198**, followed finally by enone addition.

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 55. Intermolecular Rh(I)-Catalyzed Arylation Methodologies Proceeding via a 1,4-Rh Migration



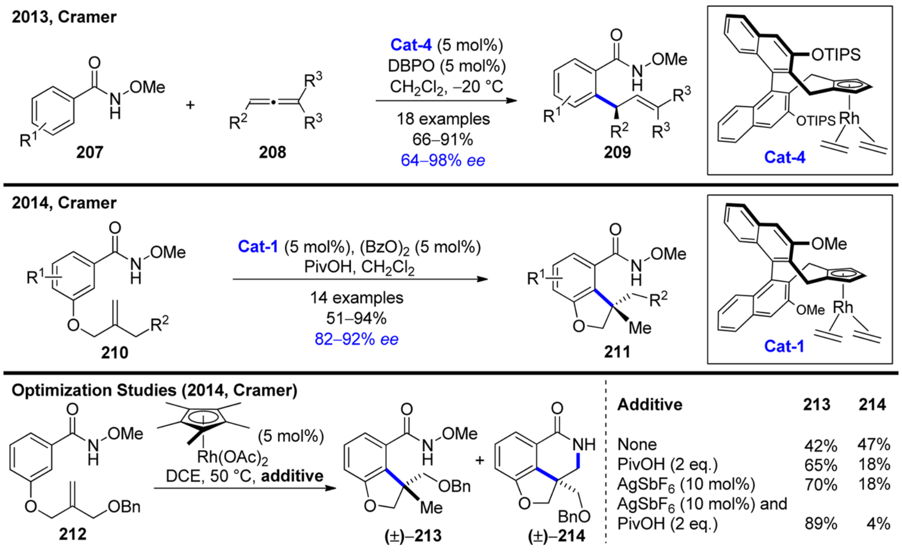
Scheme 56. Enantioselective C−H Functionalization of Hydroxamic Acid Derivatives with Chiral Rh(III)−Cyclopentadienyl Complexes



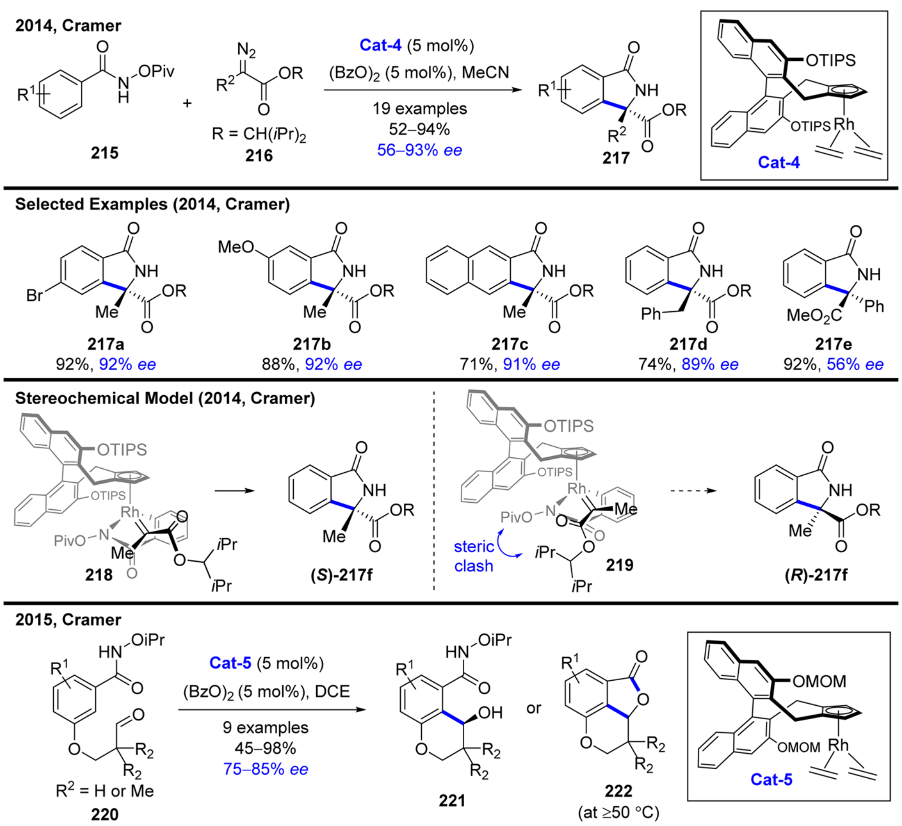
3.1.1.1.2. *Rh(III).* In studies directed toward the development of novel chiral cyclopentadienyl complexes,[147,148] the Cramer group[149] and a combined research effort by the Ward and Rovis groups[150] independently disclosed methodologies for the C−H

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 57. Rh(III)-Catalyzed Enantioselective C−H Functionalization of Aryl Hydroxamates with Allenes and Tethered Alkenes



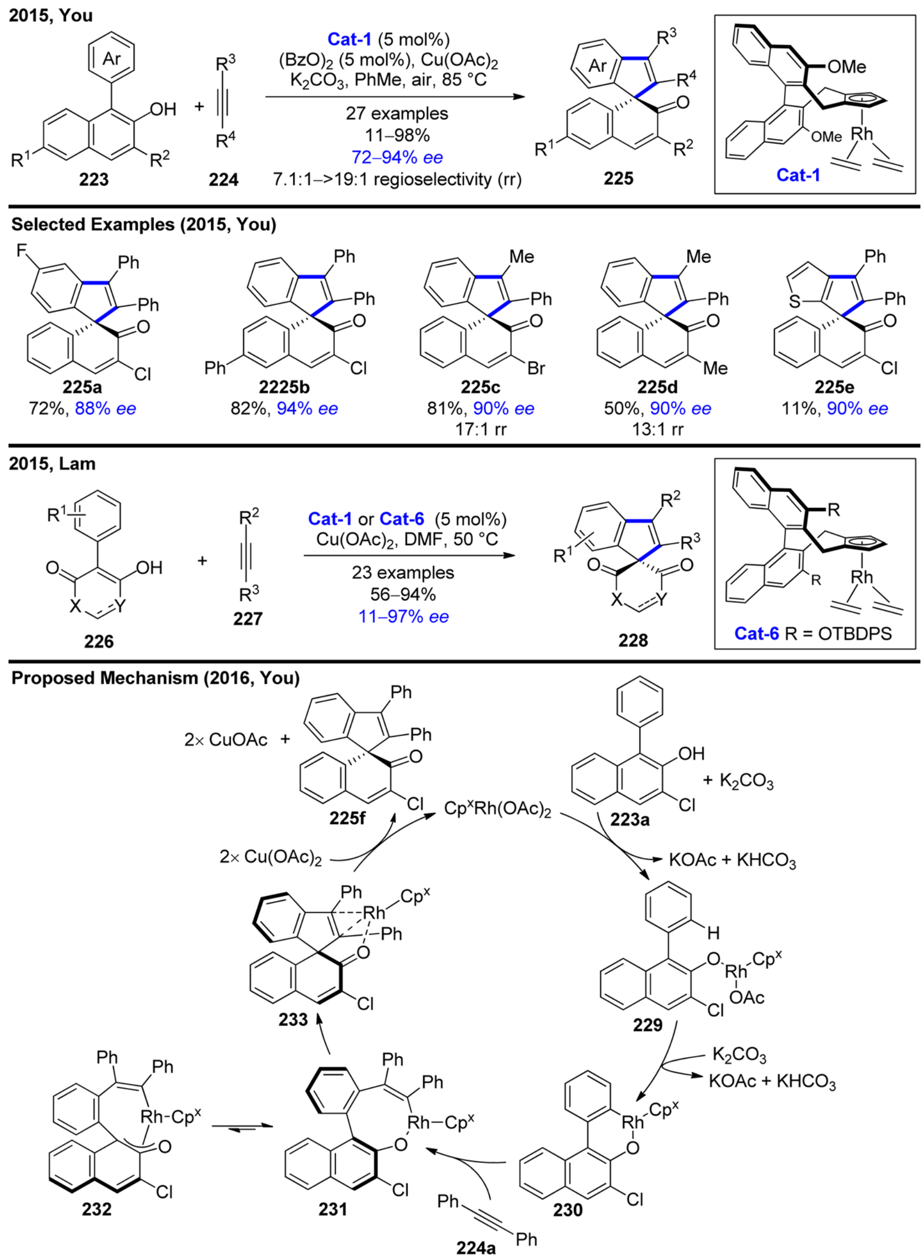
Scheme 58. Cp^X−Rh(III)-Catalyzed C−H Functionalization of Hydroxamic Acid Derivatives with Carbenoid and Tethered Aldehyde Coupling Partners



functionalization of hydroxamic acids **199** with substituted olefins **200** (Scheme 56). In the procedure disclosed by Ward and Rovis, the catalyst **Cat-2** is generated in situ upon mixing of a Rh(III) Cp* biotin derivative with an engineered streptavidin protein in buffered methanol. Under these conditions, a handful of pivaloyl-protected benzhydroxamic acids were coupled with acrylate or vinyl ketone derivatives **200** (where R^2 = H, R^3 = CO_2R, COR). All substrates reacted with excellent levels of regiocontrol, and representative examples include benzyl ester **201a** and electron-poor nitro derivative **201b**. Mechanistic studies indicate that the precise location of an engineered carboxylate residue is critical to facilitate the rate-limiting C−H bond cleavage and the chiral cavity is responsible for the observed selectivity. In contrast, Cramer et al. applied their new class of readily modifiable Cp^X−Rh(I) complexes in the same transformation, observing that diphenyl acetal derivative **Cat-3** provided an excellent level of enantiocontrol. The reaction could be carried out in ethanol at room temperature and initiates via generation of the active Rh(III) catalyst by oxidation with benzoyl peroxide. A wide variety of alkenes were successfully

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 59. Rh(III)-Catalyzed Enantioselective Spiroannulations



screened, yielding the functionalized products in 59−91% yield and 70−94% ee. Styrenes provided the highest levels of enantioselectivity (e.g., **201c** and **201d**), although 2,3-dihydrofuran (**201e**), ene-ynes (**201f**), and trimethylvinylsilane (**201g**), among others, were all tolerated. Notably, the catalyst developed by Ward and Rovis exhibits complementary behavior, in terms of olefin substrate scope, to that of Cramer et al. The electron-rich and sterically demanding nature of the Cp* unit in **Cat-2** appears to be best suited to electron-poor acrylates, whereas Cp^X derivatives allow for bulkier and more-electron-rich olefins. A subsequent combined experimental and computational study by Cramer, Corminboeuf, and their co-workers in an achiral setting demonstrated that the inherent substrate-controlled regioselectivity could be overcome by appropriate substitution on the Cp ring.[151]

The Cp^X ligands were initially designed on the basis of the assumption that a strong preference for one of the two possible tricoordinated species (**202** vs **203**), combined with control over the trajectory of the incoming third ligand L^3, would lead to one absolute configuration at the now stereogenic-at-metal complex **204** and, in turn, lead to the formation of a single product enantiomer. A sufficiently bulky group at the rear of the complex would dictate the approach of L^3, and the orientations of L^S and L^L would be controlled by adjustable substituents proximate to the metal (e.g., **205** and **206**). In addition, the ligands were designed as C_2-symmetric to circumvent the need for a diastereoselective metal complexation. Interestingly, Cp^X scaffolds adhering to these design principles appear to be quite generally applicable and have found success in various mechanistically disparate processes, including several C−H functionalization methodologies.[148]

Cp^X complexes have also been used for the functionalization of hydroxamic acid derivatives with allenes and tethered alkenes (Scheme 57). In 2013, the Cramer group disclosed a new

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

atropochiral BINOL-derived Cp^X scaffold and demonstrated that OTIPS derivative **Cat-4** exhibited superior enantiocontrol compared to their first-generation complex in the C−H allylation of *N*-methoxybenzamides **207** with achiral allenes **208**.[152] In this case, protodemetalation outcompetes reductive elimination, providing the corresponding allylated derivatives **209** in up to 98% ee. One year later, the Cramer group applied OMe derivative **Cat-1** to the intramolecular hydroarylation of 1,1-disubstituted alkenes **210**.[153] Although C−H activation is favored at the more sterically accessible *o*-C−H bond, this is an unproductive pathway and cyclization cannot occur. Instead, as a result of the reversibility of the CMD process, equilibration to the regioisomeric rhodacycle via activation of the more hindered *o*-C−H bond ultimately leads to functionalized dihydrofurans **211**. During the reaction development stages, using the achiral $[Cp^*Rh(OAc)_2]$ as catalyst, cyclization of benzyl ether **212** led to an almost 1:1 mixture of cyclized adducts **213** and **214**. Addition of PivOH favored protonolysis product **213**, as too did $AgSbF_6$. A mixture of both PivOH and $AgSbF_6$ provided the highest level of selectivity for **213**; however, when this mixture was employed with BINOL-derived Cp^X scaffolds, only racemic products were obtained. Interestingly, when used separately, PivOH and silver additives were able to provide highly enantioenriched products; however, superior yields were observed for PivOH.

In 2014 and 2015, the Cramer group expanded the scope of hydroxamic acid coupling partners to include both carbenes and aldehydes (Scheme 58). In the former case, arylhydroxamates **215** were coupled with alkyl donor/acceptor diazo derivatives **216**.[154] The reaction was conducted with OTIPS **Cat-4** and proceeds via an enantiodetermining carbenoid insertion. Despite the geometric and conformational requirements of this process differing from the examples of two-atom insertions described earlier, isoindolones **217** could be isolated in up to 93% ee, and representative examples include bromide, methoxy, and naphthyl derivatives **217a**, **217b**, and **217c**. Notably, benzylic and aryl donor/acceptor diazo derivatives also reacted smoothly (**217d** and **217e**); however, the latter provided products with the opposite absolute configuration and in only 56% ee. The authors propose that the origin of enantioselectivity may be rationalized by considering the two stereochemical models **218** and **219**. In both cases, the bulky pivalate moiety should direct the hydroxamate group away from the OTIPS substituent, leading to two possible carbenoid orientations. In structure **218**, the steric clash of the large ester substituent is minimized, leading to the observed *S*-configured products (*S*)-**217f**. In turn, the minor enantiomer might arise from the less favorable orientation depicted in **219** or from the opposite orientation of the cyclometalated hydroxamate (not shown). One year later, the same ligand scaffold, in this case as the OMOM derivative **Cat-5**, was employed for the intramolecular coupling of aldehydes **220**.[155] Under optimized conditions, hydroxychromanes **221** were isolated in 45−98% yield and up to 85% ee, demonstrating the nucleophilic character of the cyclometalated intermediates. At higher temperatures, a subsequent lactonization step produced the corresponding phthalides **222**, a common motif in many biologically active compounds.[156]

Cp^X−Rh complexes are not limited to hydroxamic acid-directed transformations, but they have also been applied in phenol-directed C−H functionalization methodologies (Scheme 59). In early 2015, the You group reported a dearomatization of *β*-naphthols **223** via annulation with disubstituted alkynes **224**, employing methoxy Cp^X derivative **Cat-1** as precatalyst.[157] Spirocyclic enones **225** were isolated in generally high yields and with excellent levels of enantio- and regiocontrol. Both symmetrical (**225a** and **225b**) and unsymmetrical (**225c** and **225d**) alkyne coupling partners were compatible, and even thiophene derivative **225e** could also be accessed in high enantiopurity (90% ee), albeit in low yield (11%). Later that same year, Lam and co-workers employed a similar strategy to realize an asymmetric spiroannulation of enols **226** with internal alkynes **227**.[158] In this case either **Cat-1** or **Cat-6** served as precatalyst and furnished spiroindenes **228** with high levels of enantiocontrol.

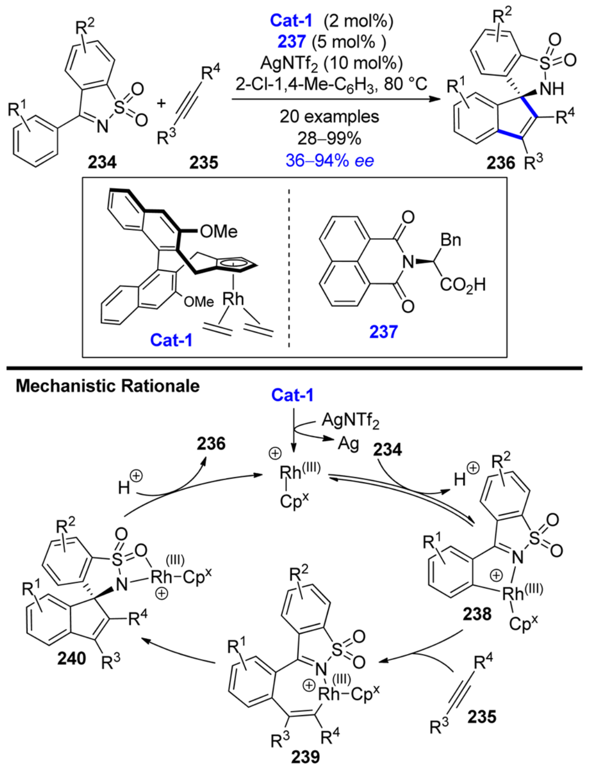
A subsequent computational study was disclosed by Zheng, You, and their co-worker the following year.[159] On the basis of these results, and several mechanistic experiments disclosed in their original report, the authors propose that the reaction begins with OH deprotonation of **223a** to deliver intermediate **229**, followed by a rate-limiting C−H activation to yield six-membered rhodacycle **230**. Coordination and migratory insertion of alkyne **224a** leads to the corresponding eight-membered axially chiral rhodacycle **231**. This step is believed to be both enantio- and regiodetermining (with unsymmetrical alkynes), with the former being catalyst-controlled and the latter substrate-controlled. Although this species may be in equilibrium with the high-energy *π*-oxaallyl−Rh intermediate **232**, only the η^1-O-bound enolate reacts further, via reductive elimination to dearomatized intermediate **233**. This is subsequently released to provide the product **225f**, and $Cu(OAc)_2$ serves to regenerate the active Rh(III) catalyst. A related mechanism was proposed by Lam et al.; however, in this case the working model is more speculative in nature. Deuteration experiments suggest that the migratory insertion is largely irreversible (i.e., forming the rhodacycle analogous to **231**), but without additional mechanistic investigations regarding the configurational stability of this compound, we are unable to comment further on which step can be considered stereochemistry-generating.

In 2016, the Cramer group reported[160] an enantioselective variant of Deng and co-workers'[161] rhodium(III)-catalyzed intermolecular [3 + 2] annulation of *N*-sulfonyl ketimines **234** with disubstituted alkynes **235** (Scheme 60). The reaction was conducted using **Cat-1**, L-phenylalanine derivative **237**, and $AgNTf_2$, in chlorinated solvent at 80 °C. Notably, the chirality of the carboxylic acid additive was irrelevant, and an identical result was obtained with the corresponding D-phenylalanine derivative. On the basis of several control experiments, the authors proposed that the reaction proceeds via oxidation of **Cat-1** to the corresponding cationic Rh(III) species, followed by an *N*-sulfonyl-imino-directed C−H activation to provide rhodacycle **238**. Migratory insertion of 1,2-diphenylethyne (**235**) into the Rh−carbon bond generates intermediate **239**, and a subsequent enantiodetermining addition across the C═N bond sets the spirocyclic center of **240**. Finally, protonation delivers **236** and closes the catalytic cycle.

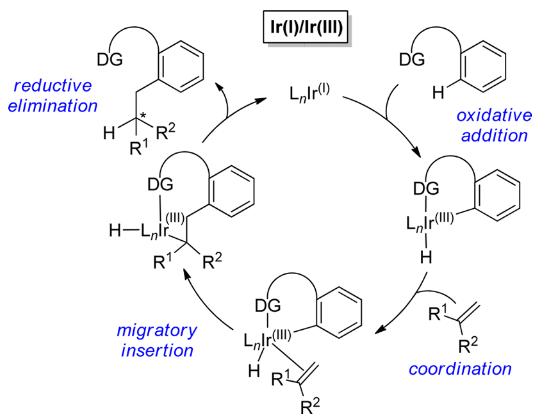
3.1.1.2. Iridium Catalysis. The majority of iridium-catalyzed methodologies proceeding through a stereochemistry-generating migratory insertion are believed to advance through an Ir(I)/Ir(III) cycle and involve the functionalization of aryl C−H bonds (Scheme 61). Although the products often closely resemble those of analogous Rh(I)/Rh(III)-catalyzed methodologies, the general mechanisms differ. In both cases, the reaction is believed to initiate via a directed oxidative addition into an aryl C−H bond, followed by coordination of a *π*-bond coupling partner. In contrast to Rh(I)/Rh(III) catalysis, which generally proceeds through a Chalk−Harrod-type mechanism[162] (migratory in-

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 60. Rh-Catalyzed [3 + 2]-Annulation of *N*-Sulfonyl Ketimines with Alkynes



Scheme 61. General Mechanism of Ir(I)/Ir(III)-Catalyzed C−H Functionalization Reactions Involving a Stereochemistry-Generating Migratory Insertion



sertion into the metal−hydride bond followed by a carbon−carbon-bond-forming reductive elimination; see Scheme 48), reductive elimination to form carbon−carbon bonds from an Ir center are rare or unknown.[163] Instead, iridium-catalyzed methodologies progress via migratory insertion into the Ir−aryl bond, followed by reductive elimination to forge the C−H bond and regenerate the active catalyst.

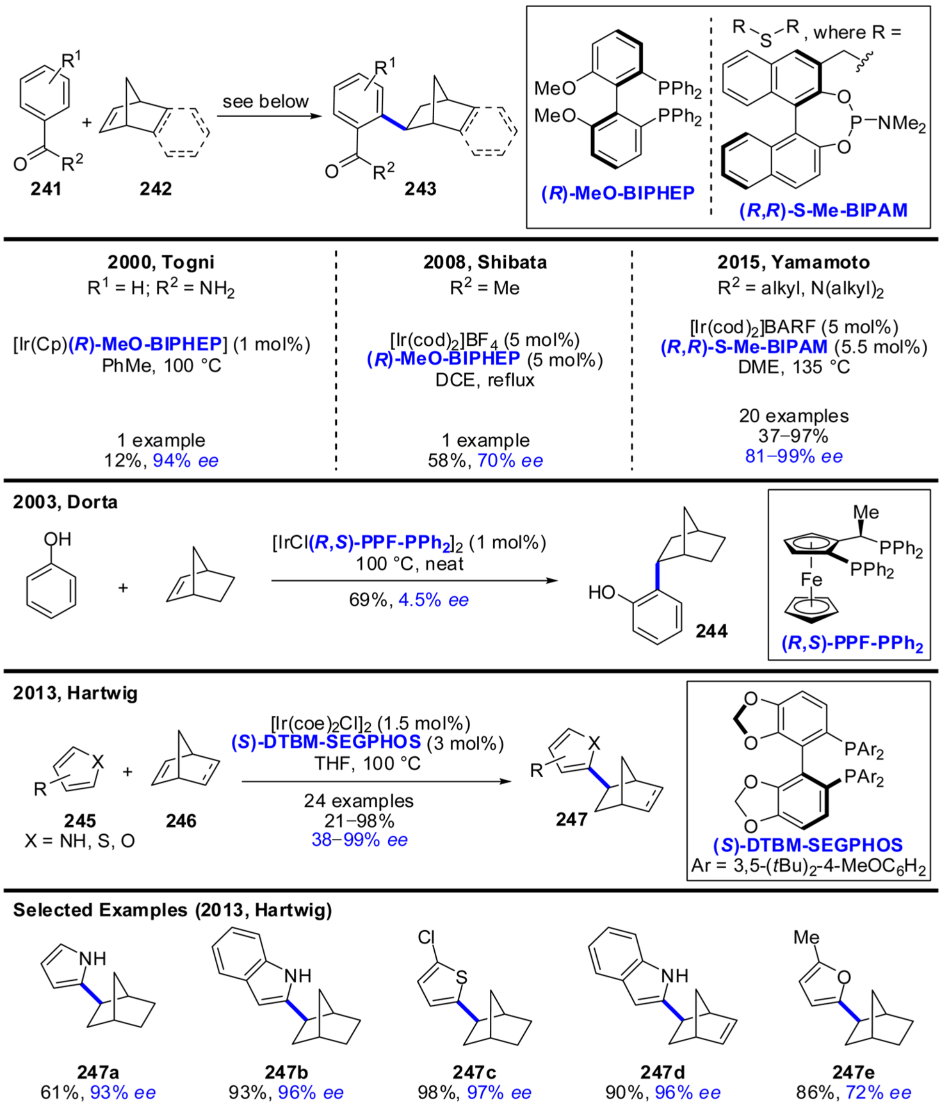
Strained norbornene derivatives are commonly employed coupling partners (Scheme 62). The earliest example was disclosed by the Togni group in 2000 and was discovered during studies directed toward the development of new asymmetric olefin hydroamination protocols.[164] Employing their newly developed 18-electron Cp−Ir(I)−(*R*)-MeO-BIPHEP complex, benzamide (**241**, where R^1 = H, R^2 = NH_2) was reacted with norbornene to give the corresponding *exo*-hydroarylated product **243** with high enantiocontrol (94% ee), albeit in low yield (12%). The authors speculate that likely a change of Cp hapticity, or perhaps phosphine chelate opening, is necessary for a catalytic activity. Eight years later, Shibata and co-workers demonstrated that cationic Ir(I) racemic bisphosphine complexes can catalyze the reaction of aryl ketones (**241**, where R^2 = Me) with norbornene. One enantioselective example was reported, also using (*R*)-MeO-BIPHEP as ligand, and in this case proceeded in 58% yield and 70% ee.[165] In 2015, the Yamamoto group reported a highly enantioselective arylation of norbornene derivatives **242** with aryl ketones and amides.[166] A cationic iridium(I) complex, used in conjunction with their newly prepared (*R*,*R*)-S-Me-BIPAM ligand, provided the functionalized products in up to 99% ee, with exclusive *exo*-diastereoselectivity. Bis-functionalization is believed to be inhibited for steric reasons, and deuterium-labeling experiments indicate that the C−H bond cleavage is irreversible and rate determining. Electron-rich aromatics can also be functionalized, as demonstrated by Dorta et al., who reported the Ir(I)-catalyzed hydroarylation of phenol, with norbornene.[167] Employing $[IrCl(R,S)\text{-PPFPPh}_2]_2$ as catalyst, the reaction proceeded with complete regio- and diastereocontrol; however, the alkylated product **244** was obtained in only 4.5% ee. Ten years later, the Hartwig group reported a highly enantioselective hydroheteroarylation of electron-rich heterocycles **245** with olefins **246**.[163] Building upon an earlier study concerning the hydroamination of aliphatic olefins,[168] addition of heteroaryl C−H bonds across the olefinic bond could be achieved via employment of $[Ir(coe)_2Cl]_2$ in combination with (*S*)-DTBM-SEGPHOS. The reaction proceeded with exclusive formation of *exo* products **247** in up to 98% yield and 99% ee. This protocol was applicable to a large range of substrates, including pyrroles (**247a**), indoles (**247b** and **247d**), thiophenes (**247c**), and norbornadiene (**247d**). Notably, for reasons that are unclear, the hydroarylation of furan substrates provided the products with lower enantioselectivities (**247e**). Mechanistic studies illustrated that the C−H activation event proceeds via oxidative addition into the C−H bond adjacent to the heteroatom in a nondirected fashion.

The hydroarylation of unstrained alkenes with *N*-heterocyclic compounds has also been demonstrated (Scheme 63). As part of a study focused on the C−H alkylation of indoles with terminal alkenes, the Shibata group discovered that by simply changing the nature of the *N*-directing group either achiral linear or chiral branched products could be favored.[169] One enantioselective example, catalyzed by an Ir(I)/(*R*)-SDP complex, was disclosed, involving alkylation of *N*-benzoyl indole with styrene to give **248** in 93% yield and 42% ee. Several years later, the same group reported an intramolecular variant, in this case applying *N*-alkenylindoles **249** as substrates.[170] The 4-methoxyphenyl ketone group served as directing group, resulting in exclusive alkylation at the C-2 position. For terminal olefin substrates, (*S*)-SEGPHOS delivered the 5-*exo*-cyclized products **250** in good to excellent enantioselectivities, whereas for internal olefins (*S*)-XylylBINAP proved superior. Notably, the alkylation of phenyl-substituted substrate **251** reversed the reaction regioselectivity, yielding 6-*endo*-type cyclized product **252** in 98% yield and 84% ee.

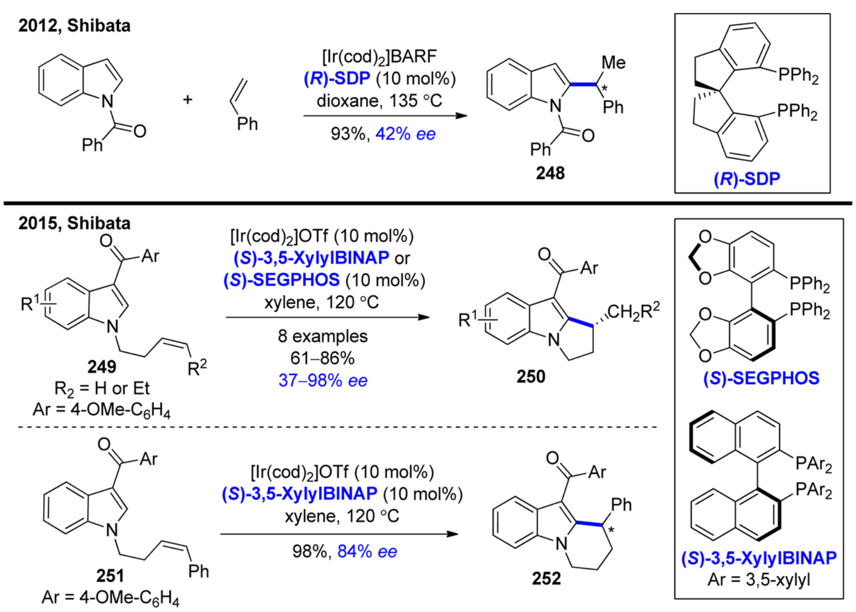
Several recent publications describe the alkylation of aromatics with unstrained alkenes (Scheme 64). In 2015, Ebe and Nishimura reported a cationic Ir-catalyzed intermolecular coupling of vinyl ethers, proceeding via nitrogen-directed C−H activation and a branch-selective migratory insertion.[171] Most

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 62. Ir(I)/Ir(III)-Catalyzed Enantioselective Intermolecular Hydroarylation of Strained Bicycloalkenes with Arenes



Scheme 63. Ir(I)/Ir(III)-Catalyzed Enantioselective Intermolecular Hydroarylation of Indole Derivatives



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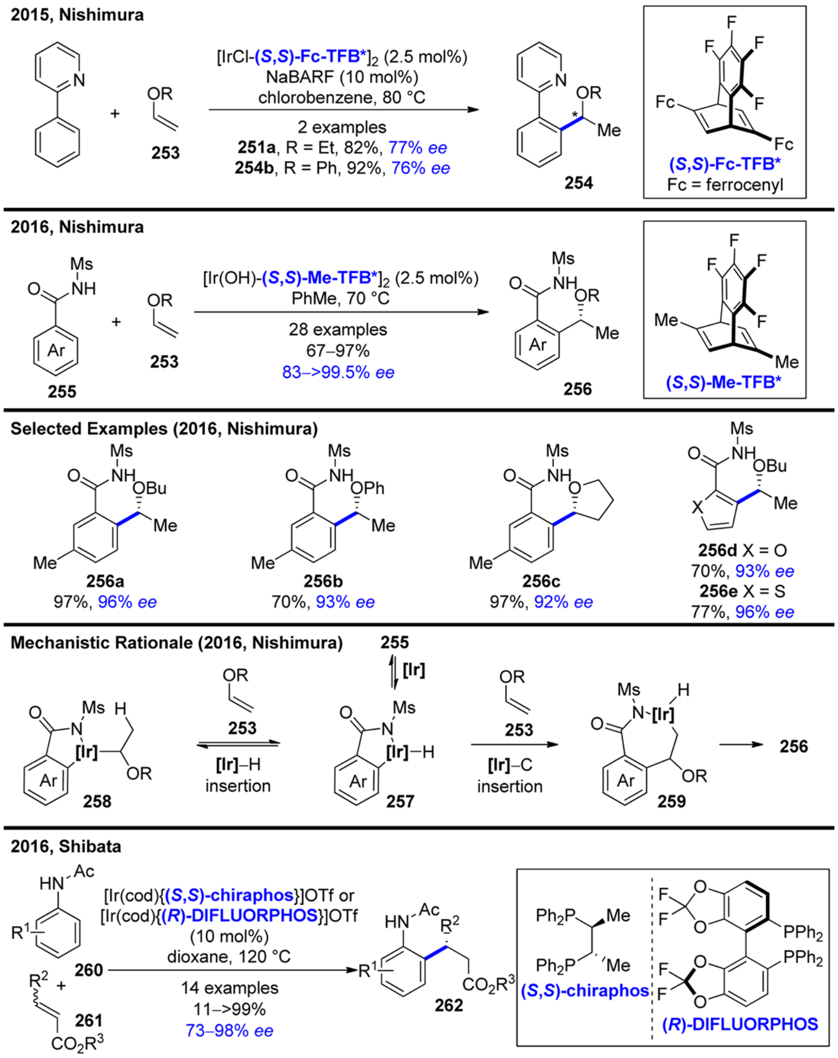
Chem. Rev. 2017, 117, 8908–8976

Scheme 64. Ir(I)/Ir(III)-Catalyzed Branch-Selective and Enantioselective Hydroarylation of Unstrained Alkenes

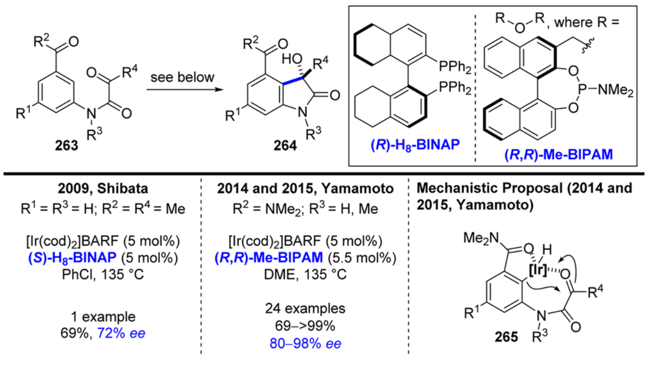


reactions were performed in a racemic manner with [IrCl(cod)]$_2$; however, a promising preliminary study using (*S*,*S*)-Fc-TFB* as ligand enabled the 2-pyridyl-directed functionalization of 2-phenylpyridine with vinyl ethers **253**. The alkylated products **254a** and **254b** were isolated in good yields and up to 77% ee. The authors hypothesized that the reaction proceeds via migratory insertion into an Ir−H bond (Chalk−Harrod-type mechanism); however, a subsequent computational study by the Huang group indicated that the reaction proceeds through via insertion into the Ir−aryl bond and that this process is both rate-limiting and enantiodetermining.[172] Huang et al. also proposed that both the electron-donating and steric effect of the alkoxy groups are responsible for the regioselectivity of the migratory insertion (e.g., branched versus linear-selectivity), consistent with related computational studies on the Heck reaction.[173−175] A second publication from the Nishimura group described an *N*-methanesulfonyl-directed enantioselective hydroarylation of benzamides **255** with vinyl ethers **253**.[176] Employing [IrCl((*S*,*S*)-Me-TFB*)]$_2$ as catalyst, the corresponding branched products **256** were synthesized in excellent enantiopurity. The transformation exhibits broad functional group tolerance for both coupling partners, and representative examples include the use of alkyl, aromatic, and cyclic ether derivatives (**256a**, **256b**, and **256c**, respectively), as well as heteroaromatics (**256d** and **256e**). In addition, the authors conducted a series of transformations on the enantioenriched products, including modification of both the amide and ether moieties, with no erosion in enantiopurity. In the reaction development stages, a strongly electron-withdrawing group on nitrogen was discovered to be critical, indicating that a highly acidic N−H proton is necessary for formation of Ir−aryl species **257** from the hydroxoiridium catalyst. Mechanistic investigations indicate that C−H activation and Ir−H insertion (to intermediate **258**) are both reversible, whereas an irreversible carbometalation to **259**, followed by reductive elimination, generates the corresponding branched products **256** (consistent with Zhang and Huang's earlier described computational study[172]). The following year Shibata and co-workers disclosed a catalytic asymmetric C−H alkylation of acetanilides **260** with *β*-substituted acrylates **261**, employing either [Ir(cod){(*S*,*S*)-chiraphos}]OTf or [Ir(cod){(*S*)-DIFLUORPHOS}]OTf as catalyst.[177] In this methodology, the branched alkylated products could be accessed with complete regioselectivity in up to >99% yield and in 73−99% ee.

Iridium catalysis has also been used for the intramolecular asymmetric hydroarylation of ketones (Scheme 65). In 2009, the Shibata group reported the synthesis of achiral functionalized benzofurans via a C−H functionalization of *α*-aryloxy ketones.[178] A preliminary attempt at an enantioselective variant by the

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

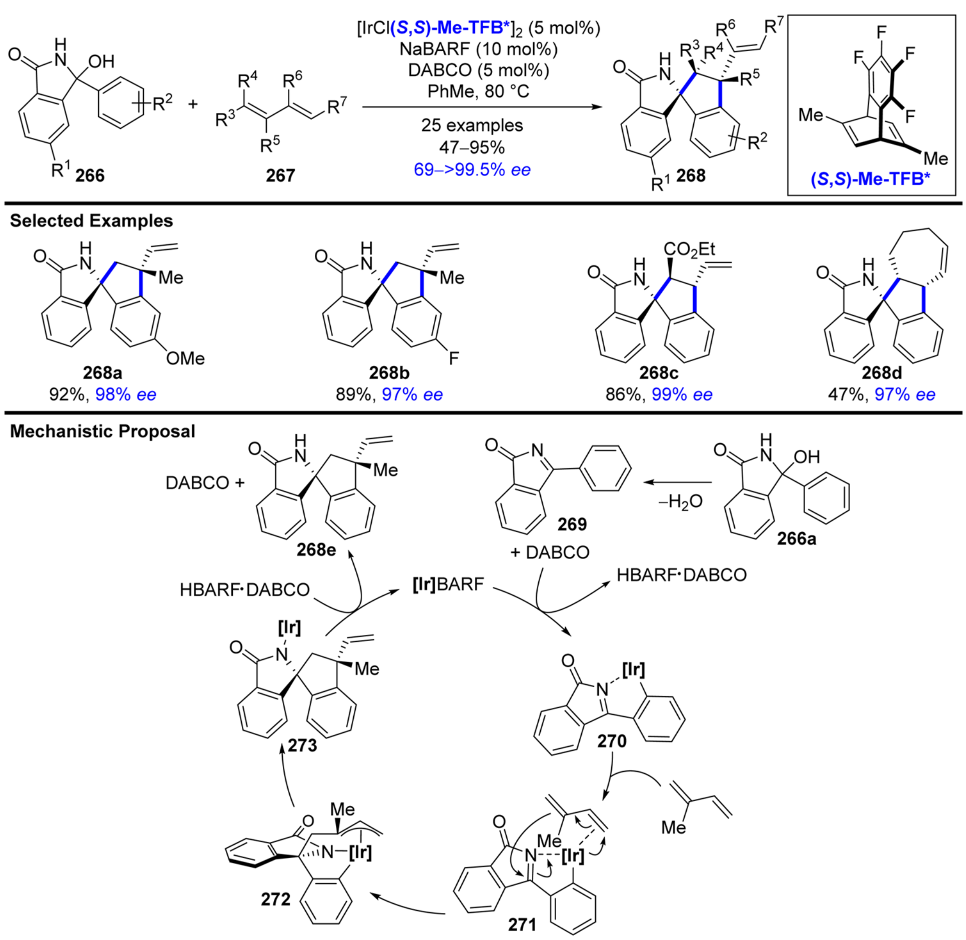
Scheme 65. Ir(I)/Ir(III)-Catalyzed Enantioselective Intramolecular Hydroarylation of Ketones



cyclization of pyruvamide derivative **263** (where $R_1 = R_3 = H$; $R_2 = R_4 = Me$) to yield oxindole **264** was also reported. Among the chiral ligands screened, (*S*)-H_8-BINAP gave the best result, yielding the product in 69% yield and 72% ee. Building upon Shibata's work, the Yamamoto group reported a highly enantioselective directed hydroarylation of α-ketoamides **263** (where $R_2 = NMe_2$; R_3 = H, Me) to construct 3-hydroxy-2-oxindoles **264**.[179] In this case, bidentate phosphoramidite (*R*,*R*)-Me-BIPAM was employed as the chiral ligand, and the *N*,*N*-dimethyl carbamoyl group served as the directing group. The authors proposed that C−H cleavage occurs at the more hindered ortho position to generate the key intermediate **265**, which is coordinated by two carbonyl groups and subsequently undergoes a stereochemistry-generating addition to the ketone carbonyl moiety. A broad scope of aromatic and aliphatic α-ketoamides were successfully screened, providing the functionalized products in 69 to >99% yield and 80−98% ee. In some cases, preforming the [Ir(cod)-(*R*,*R*)-Me-BIPAM]BARF complex provided slightly higher enantioselectivities compared to in situ catalyst generation. The following year, the same group published a follow-up study investigating the reaction mechanism and expanding the scope of the transformation.[180] Isotope-labeling experiments, ^{1}H NMR investigations, and a Hammett study were conducted, indicating that the reaction proceeds through a reversible C−H bond cleavage event and that the migratory insertion processes is both rate-limiting and enantiodetermining.

In 2013, Nishimura and co-workers published an enantioselective version[181] of their previously disclosed Ir-catalyzed C−H activation/[3 + 2]-annulation of *N*-sulfonyl ketimines with 1,3-dienes (Scheme 66).[182] In the present study, 3-aryl-3-hydroxyisoindolin-1-ones **266** were successfully coupled with 1,3-dienes **267** in the presence of preformed [IrCl(*S*,*S*)-Me-TFB*]$_2$, generating spiroaminoindane derivatives **268** in 47−95% yield and 69 to >99.5% ee, with complete diastereocontrol and in most cases proceeding with high levels of regiocontrol. A library of 25 compounds was prepared, and representative examples include electron-rich methoxy-substituted derivative **268a**, halogenated analogue **268b**, and the incorporation of both ester-substituted and cyclic 1,3-dienes (**268c** and **268d**). The

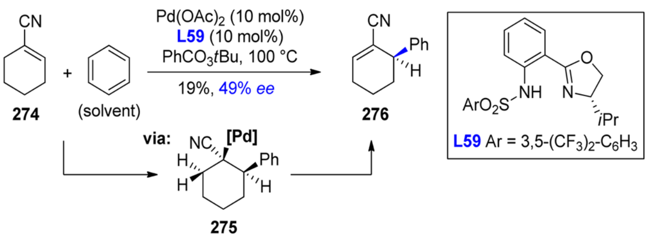
Scheme 66. Ir-Catalyzed Asymmetric C−H Activation/[3 + 2]-Annulation of Ketimines with 1,3-Dienes



DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

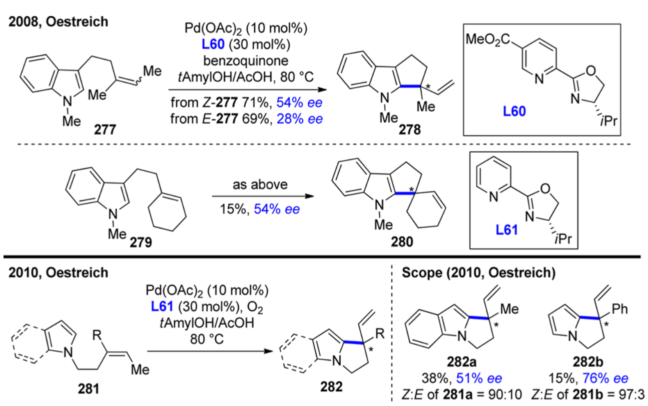
authors proposed that the reaction begins with in situ dehydration of hemiaminal **266a** to generate ketimine **269**. This then partakes in a directed *o*-C−H activation, followed by a DABCO-promoted deprotonation to form aryliridium(I) species **270**. Coordination of 1,3-diene at the less substituted olefin generates **271**, which subsequently undergoes oxidative cyclization to deliver π-allyliridium(III) intermediate **272**. Finally, reductive elimination and subsequent protonolysis provides the annulation product **268e**.

Scheme 67. First Catalytic Enantioselective Dehydrogenative Heck Reaction



3.1.1.3. Palladium Catalysis. The first catalytic enantioselective dehydrogenative Heck reaction (also referred to the Fujiwara−Moritani reaction[73]) was reported by Mikami and co-workers in 1999 (Scheme 67).[183] Employing chiral sulfonylamino-oxazoline **L59** and a Pd(II) source, activated alkene **274** was successfully coupled with benzene, providing the arylated product **276** in 19% yield and 49% ee. The reaction proceeds via a palladium-mediated C−H activation of benzene, followed by a stereochemistry-generating migratory insertion of **274** into the Pd−carbon bond to generate intermediate **275**. Reductive elimination of the *syn*-β-hydrogen and reoxidation of the catalyst with *tert*-butyl peroxybenzoate closes the cycle. Attempts to change the electron-withdrawing group, ligand structure, or catalyst:ligand stoichiometry all proved detrimental to the enantioselectivity of the reaction.

Scheme 68. Intramolecular Dehydrogenative Heck Reactions of *N*-Heterocycles



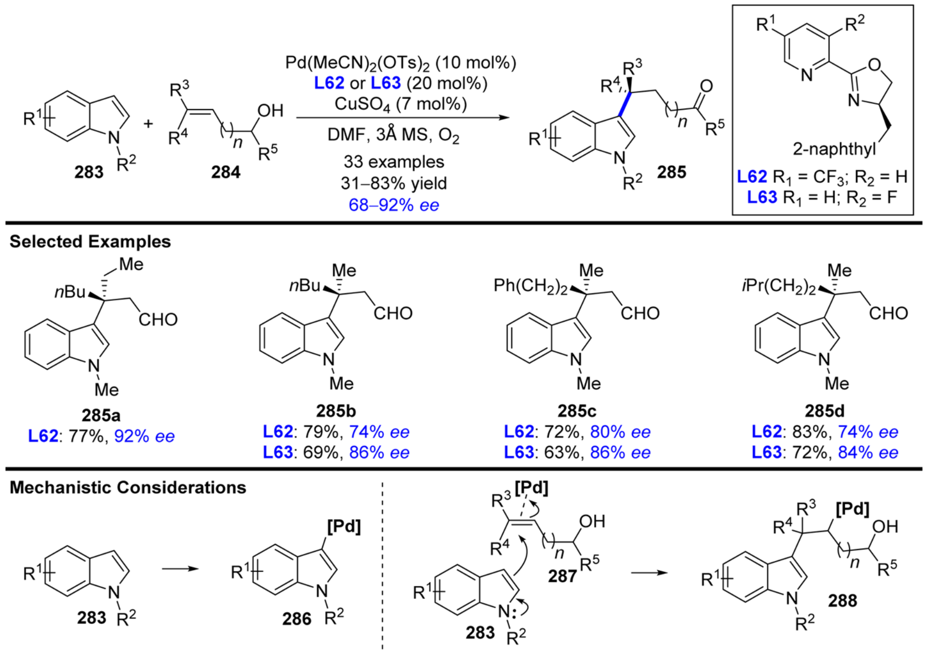
The Oestreich group have since published two studies concerning the development of intramolecular variants (Scheme 68). The first example, from 2008, explored the alkylation of 3-substituted indoles **277** with a novel class of NicOx ligands[184] (originally reported in a racemic sense by Ferreira and Stoltz in 2003[185]) Optimization identified methyl ester derivative **L60** as the ligand providing the highest level of enantiocontrol, when used in conjunction with benzoquinone as the stoichiometric oxidant. Both the *Z* and *E* isomers of **277** provided cyclized product **278** with the same absolute configuration and in similar yields; however, the enantioselectivities varied significantly (54% vs 28% ee). The authors also disclosed the cyclization of cyclohexene derivative **279** with PyOX **L61** as ligand, in this case generating spirocyclic indole **280** in 15% yield and 54% ee. Two years later, Oestreich and co-workers reported the cyclization of *N*-tethered olefins **281** under closely related conditions.[186] Using isomerically enriched substrates, indole derivative **282a** could be isolated in 38% yield and 51% ee, and the corresponding pyrrole derivative **282b** in 15% yield and 76% ee. Attempts to construct six-membered ring analogues via the same methodology resulted in either no conversion or no stereoinduction, prompting the authors to speculate that a change in mechanism from an electrophilic palladation to a Friedel−Crafts-type pathway may be responsible.

In 2015, Sigman and co-workers applied their earlier disclosed enantioselective redox relay Heck reaction methodology[187,188] to the intermolecular dehydrogenative Heck coupling of indoles **283** with trisubstituted alkenes **284** (Scheme 69).[189] During ligand optimization studies, trifluoromethyl PyrOx derivative **L62** was identified as a competent ligand for the synthesis of various chiral indoles **285**; however, the enantioselectivity proved highly sensitive toward the nature of both substrates. These conditions worked best for ethyl-substituted alkene coupling partners, but a significant decrease in enantiocontrol was observed when analogous methyl-substituted derivatives were employed (e.g., **285a** versus **285b**). The authors elected to conduct a second ligand optimization study, in this case guided by computational analysis. Various steric and electronic parameters of the ligands were calculated, and a simple correlation between the reaction enantioselectivity and the natural bond orbital charge on the oxazoline nitrogen was revealed. Specifically, a more electronegative charge correlated with improved stereocontrol, and several new ligands were synthesized according to this trend. Fluoro derivative **L63** provided the best results, and when benchmarked against trifluoromethyl derivative **L62**, superior enantioselectivities were observed (e.g., **285b**−**285d**). Two mechanistic pathways were proposed for the addition of the indole moiety to the alkene, either a Heck-type process proceeding via an electrophilic aromatic substitution to yield organometallic intermediate **286** or, alternatively, a Wacker-type nucleophilic addition to generate **288**. The authors speculate that if the Heck-type mechanism is in operation, then similar levels of enantiocontrol should be obtained with the same catalyst system under standard Heck and dehydrogenative Heck conditions, and indeed this was the case.

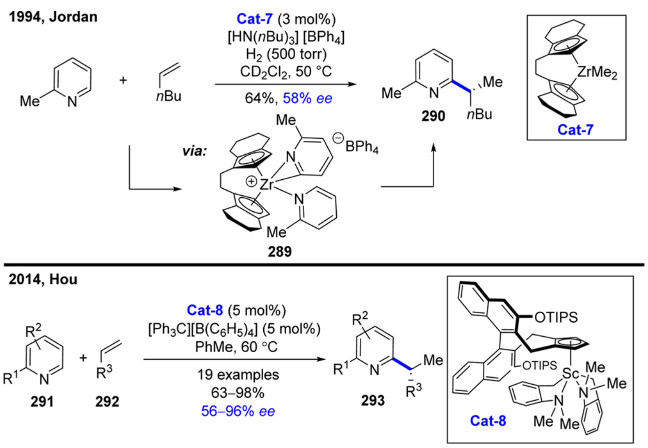
3.1.1.4. Other Transition Metals as Catalysts. Zirconium, scandium, nickel, and cobalt catalysts have each been employed in C−H functionalization methodologies that incorporate a stereochemistry-generating migratory insertion. In 1994, the Jordan group described the first catalytic enantioselective arene C−H bond functionalization reaction.[190] Coupling of 2-picoline and hex-1-ene was accomplished using Brintzinger's C_2-symmetric *ansa* zirconocene complex **Cat-7** at 50 °C in the presence of H_2, providing alkylated derivative **290** in 56% yield and 58% ee (Scheme 70). Stoichiometric studies enabled the isolation of intermediate **289**, which was demonstrated to readily undergo alkene insertion at room temperature. In 2014, Hou and co-workers reported a general approach for the functionalization

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 69. Intermolecular Dehydrogenative Heck Reaction of Indoles with Trisubstituted Olefins



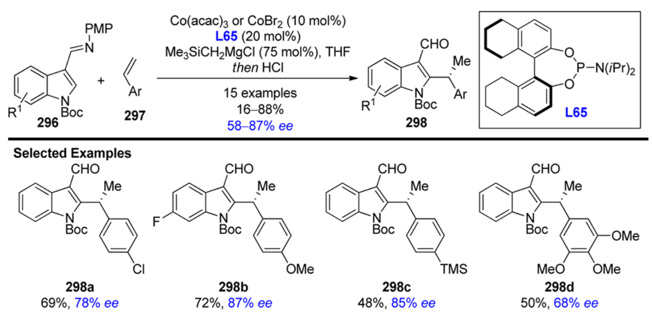
Scheme 70. Zr- and Sc-Catalyzed C−H Functionalization of Substituted Pyridines



of substituted pyridines **291** with terminal alkenes **292**, employing Sc−Cp^X complex **Cat-8** as catalyst.[191] The strong affinity between **Cat-8** and the pyridine substrates was diminished by increasing the steric bulk proximate to nitrogen via the introduction of alkyl or halogen substituents. The functionalized products **293** were isolated in moderate to excellent yields (65−98%) and enantioselectivities (56−96% ee).

As part of a larger study focused on a nickel-catalyzed regiodivergent synthesis of racemic annulated pyridones, Donets and Cramer reported preliminary investigations into an enantioselective variant (Scheme 71).[192] Using the bulky NHC ligand **L64** to favor *endo*- over *exo*-cyclization, an intramolecular C−H alkylation of 2-pyridones **294** enabled the synthesis of cyclized derivatives **295**. Both acyclic (**295a**) and cyclic olefins

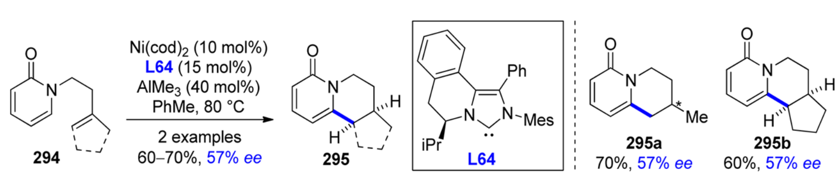
Scheme 72. Co-Catalyzed Intermolecular C−H Functionalization of Indoles



(**295b**) gave comparable results, proceeding in 70% and 60% yield, respectively, and both in 57% ee.

A cobalt-catalyzed, imine-directed C−H alkylation of indoles **296** with styrenes **297** was accomplished by the Yoshikai group in 2015 (Scheme 72).[193] By utilizing Co(acac)$_3$ or CoBr$_2$ as precatalyst and chiral phosphoramidite **L65** as ligand, enantioenriched branched hydroarylation products **298** were synthesized with moderate to good enantioselectivities. Aryl halides were well-tolerated (e.g., **298a** and **298b**) and so too were arylsilanes (**298c**) and electron-rich styrenes (**298b** and **298d**). On the basis of kinetic isotope experiments, as well as earlier

Scheme 71. Ni-Catalyzed Intramolecular Hydroarylation of *N*-Homoallyl Pyridones

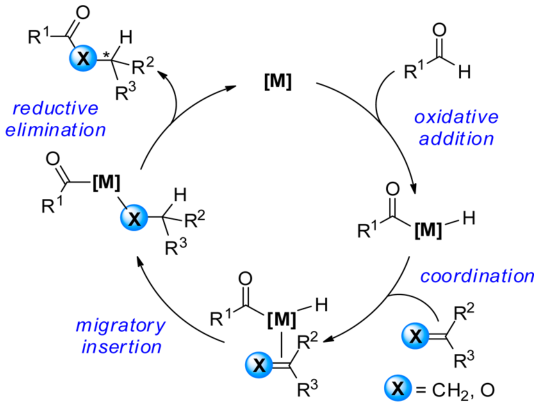


DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

achiral studies,[194−196] the authors propose that the reaction proceeds via a C−H oxidative addition/migratory insertion/reductive elimination pathway and that the first two processes are reversible.

3.1.2. Aldehyde C−H Functionalization. *3.1.2.1. Hydroacylation.* The hydroacylation reaction was one of the first C−H functionalization processes to be conducted in a catalytic

Scheme 73. General Mechanism for the Transition-Metal-Catalyzed Enantioselective Hydroacylation Reaction

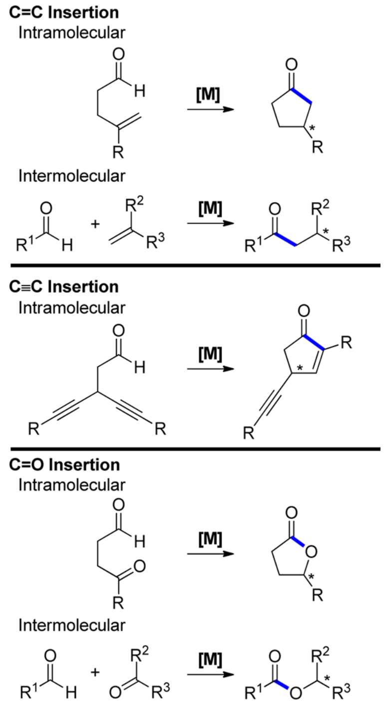


enantioselective manner.[197−200] Notably, the overall transformation is completely atom economic[10,11] and thus represents a particularly attractive route to chiral ketones and esters. The generally accepted mechanism is presented in Scheme 73 and begins with oxidative addition of a transition metal into an aldehyde C(sp^2)−H bond to yield an acyl−metal complex. Coordination of a π-bond coupling partner, shown as either an olefin or ketone, is followed by a stereochemistry-generating migratory insertion into the metal−hydride bond. Finally, reductive elimination serves to release the product and restore the active catalyst. Mechanistic studies indicate that the relative rates and reversibility of each step varies between methodologies,[201−203] making it difficult to generalize about which event is enantiodetermining.

To date, five enantioselective reaction modes have been realized (Scheme 74). Olefins are the most frequently employed coupling partner and have been utilized in both an intra- and intermolecular manner. Conversely, only one example of an enantioselective alkyne insertion has been reported, and it proceeds through an intramolecular desymmetrization of an achiral diyne. More recently, the insertion of ketones has emerged as a viable transformation, allowing access to enantioenriched esters and lactones. In each reaction class the intramolecular variant is most common, which is unsurprising given the potential regiocontrol offered by tethering the π-bond coupling partner. Cationic rhodium complexes are the most widely employed catalysts, usually used in conjunction with a chiral bisphosphine ligand; however, recent reports of cobalt- and iridium-catalyzed methodologies have been disclosed.

3.1.2.1.1. C=C Insertion. Several enantioselective hydroacylation approaches to 3-substituted cyclopentanones have been published (Scheme 75). The first example was reported by Sakai and co-workers, in 1989,[204] and represents the first catalytic enantioselective hydroacylation reaction that does not proceed by means of kinetic resolution (discussed later in section 7). 4-*n*-Butylpenten-1-al (**299a**, where R = *n*Bu) was treated with the neutral chlorobis(cyclooctene)Rh(I) dimer and chiral bi-

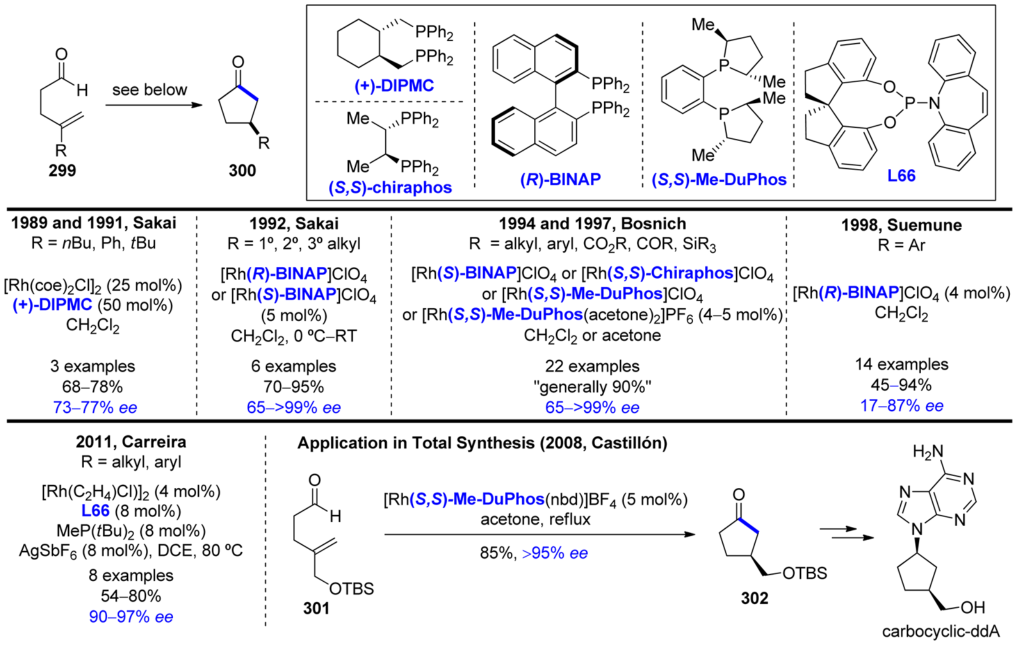
Scheme 74. Classification of Enantioselective Hydroacylation Reactions



sphosphine ligand (+)-DIPMC, resulting in an intramolecular cyclization to provide the corresponding cyclopentanone derivative **300a** in 78% yield and 73% ee. In 1991, Sakai and co-workers demonstrated that these same conditions were suitable for the analogous phenyl- and *tert*-butyl-substituted derivatives, with similar selectivities observed for all three substrates.[205] Despite the near-stoichiometric catalyst loading (50 mol % of Rh), this landmark study demonstrated that the hydroacylation reaction of achiral aldehydes could be rendered enantioselective. In the late 1980s, the Bosnich research group observed that cationic Rh(I) complexes disfavor aldehyde decarbonylation, an unproductive pathway commonly observed in hydroacylation chemistry. This was ascribed to the availability of an additional coordination site, enabling better accommodation of the π-bond coupling partner, and ultimately enabled the application of lower catalyst loadings.[201,202] This concept was first applied in an enantioselective context by Sakai and co-workers in 1992 via employment of cationic BINAP−Rh(I) perchlorate complexes (5 mol %) for the cyclization of primary, secondary, and tertiary alkyl-substituted derivatives of **299**, yielding chiral cyclopentanones **300** in enantiomeric excesses ranging from 65 to >99%.[206] Two years later, Bosnich demonstrated that the same catalyst system, with either (*S*)-BINAP or (*S*,*S*)-chiraphos as ligand, was highly general, tolerating ketones, esters, silanes, and aryl substituents on **299**.[207] In two subsequent studies from the same group, application of (*S*,*S*)-Me-DuPhos as chiral ligand provided much improved enantioselectivities for primary and secondary alkyl substituents, functionality that had generally been the least selective in their earlier work.[208,209] In 1998, Suemune and co-workers disclosed a detailed study exploring the effect of electron-rich and -poor aryl substituents, using a cationic (*R*)-BINAP complex.[210] In general, electron-rich aromatics provided lower selectivities (17−29% ee) versus the corresponding electron-poor derivatives (44−87% ee). The most recently

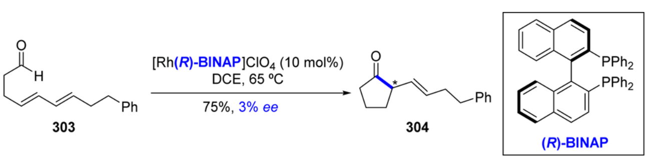
DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 75. Enantioselective Synthesis of 3- and 3,4-Substituted Cyclopentanones



developed method comes from the lab of Carreira and constitutes the first time phosphoramidite−alkene ligands have been employed in this reaction.[211] During prior independent studies from the Miller and the Larock groups in an achiral setting, it was observed that introduction of ethylene to the reaction mixture improved yields, proposing that coordinatively saturating the cationic Rh species limits catalyst decomposition.[212−215] This observation prompted the Carreira group to investigate chiral ligands incorporating a potentially coordinating alkene, and following screening studies, SPINOL-derived **L66** was shown to provide high levels of enantioinduction in the conversion of **299** to **300**. Unexpectedly, the addition of an achiral phosphine (1:1 with respect to chiral ligand **L66**) was necessary for reaction. Bosnich's reaction conditions have since been applied in the total synthesis of a carbocyclic nucleoside by Castillón and co-workers.[216] In their key step, silyl ether **301** was reacted with a cationic Rh(I)−(*S*,*S*)-Me-DuPhos complex in refluxing acetone, leading to chiral cyclopentanone **302** in 85% yield and >95% ee.

Scheme 76. Hydroacylation of 4,6-Dienal

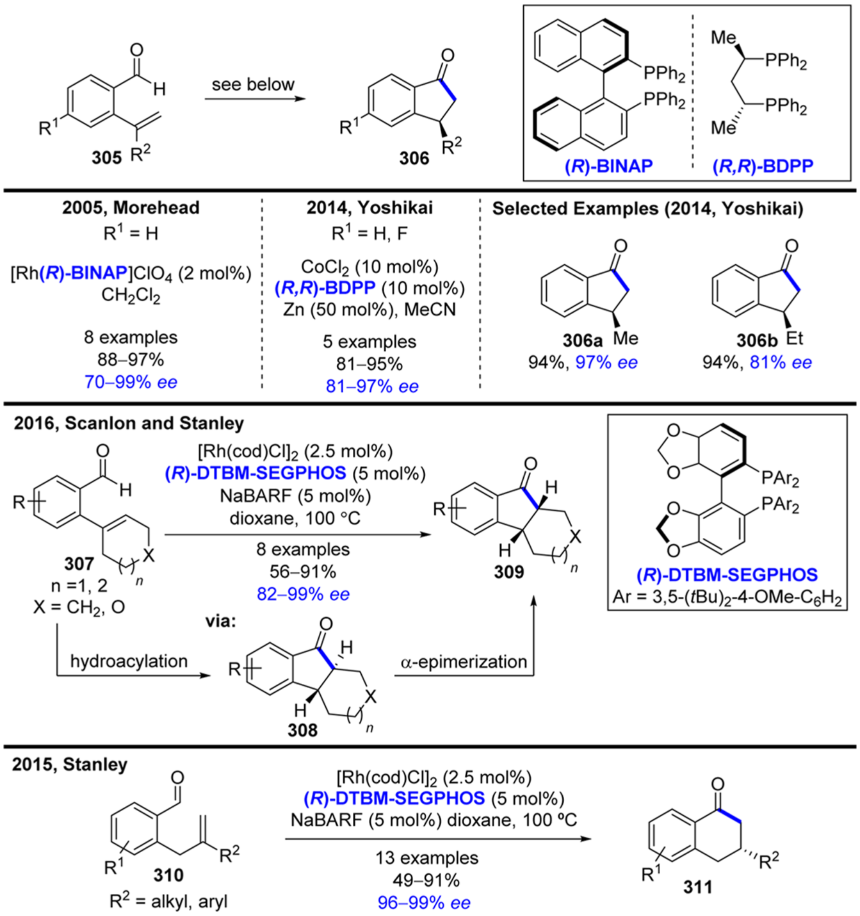


As part of a study focused on the racemic synthesis of cycloheptenones through an intramolecular hydroacylation reaction, Mori and co-workers reported one attempt at an enantioselective variant (Scheme 76).[217] Utilizing conditions that closely resemble those developed by Sakai and Bosnich, detailed above, 4,6-dienal **303** was treated with [Rh(*R*)-BINAP]ClO_4 at elevated temperatures. Although the cyclized product **304** was obtained in only 3% ee, this result corresponds to a complete shift in selectivity compared to reaction with 1,2-bis(diphenylphosphino)ethane as ligand, which was selective for seven-membered ring formation. Notably, this is only one of many hydroacylation methodologies where a switch of ligand scaffold completely changed the product distribution (vide infra).

The enantioselective intramolecular hydroacylation of substituted *o*-vinyl- and *o*-allylbenzaldehydes enables efficient access to benzo-fused cyclic ketones (Scheme 77). The first example of this nature came from the lab of Morehead, in 2005, and involved the [Rh(*R*)-BINAP)]ClO_4-catalyzed reaction of substituted styrenes **305** to yield chiral indanones **306**.[218] All examples were high yielding (88−97%) and proceeded with moderate to excellent levels of enantiocontrol (70−99% ee). Almost 10 years later, Yang and Yoshikai developed alternative reaction conditions for the same transformation, in this case via Co(I) catalysis.[219] Zinc was employed to reduce the $CoCl_2$ precatalyst, and (*R*,*R*)-BDPP served as chiral ligand. The enantioselectivity of the reaction proved highly sensitive toward the olefinic substituents; for example, methyl-substituted derivative **306a** was isolated in 97% ee, whereas the corresponding ethyl analogue **306b** was isolated in a reduced 81% ee. In the same publication, Yang and Yoshikai demonstrated that the intramolecular hydroacylation of ketones could be conducted under closely related conditions, and mechanistic investigations into this reaction mode were also reported (Scheme 86). Currently, this remains the only cobalt-catalyzed enantioselective hydroacylation study, although related reactions in racemic and achiral settings are known.[220−223] Notably, in late 2016, the Coltart research group published a complementary approach to chiral indanones, via the same retrosynthetic disconnection, however, in this case via C(sp^2)−H functionalization of the corresponding aldiminium (see Scheme 92).[224] In 2016, Scanlon, Stanley, and their co-workers reported a Rh-catalyzed asymmetric intramolecular hydroacylation of 1,1,2-trisubstituted cycloalkenes **307** to construct *cis*-tetracyclic hexahydro-9*H*-fluoren-9-one scaffolds **309**.[225] The reaction is believed to proceed through intermediate **308** via an intramolecular hydroacylation/α-epimerization sequence, and on the basis of control experiments and DFT calculations, the authors proposed that a cationic Rh

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 77. Synthesis of Chiral Benzo-Fused Ketones via an Enantioselective Intramolecular Hydroacylation Reaction



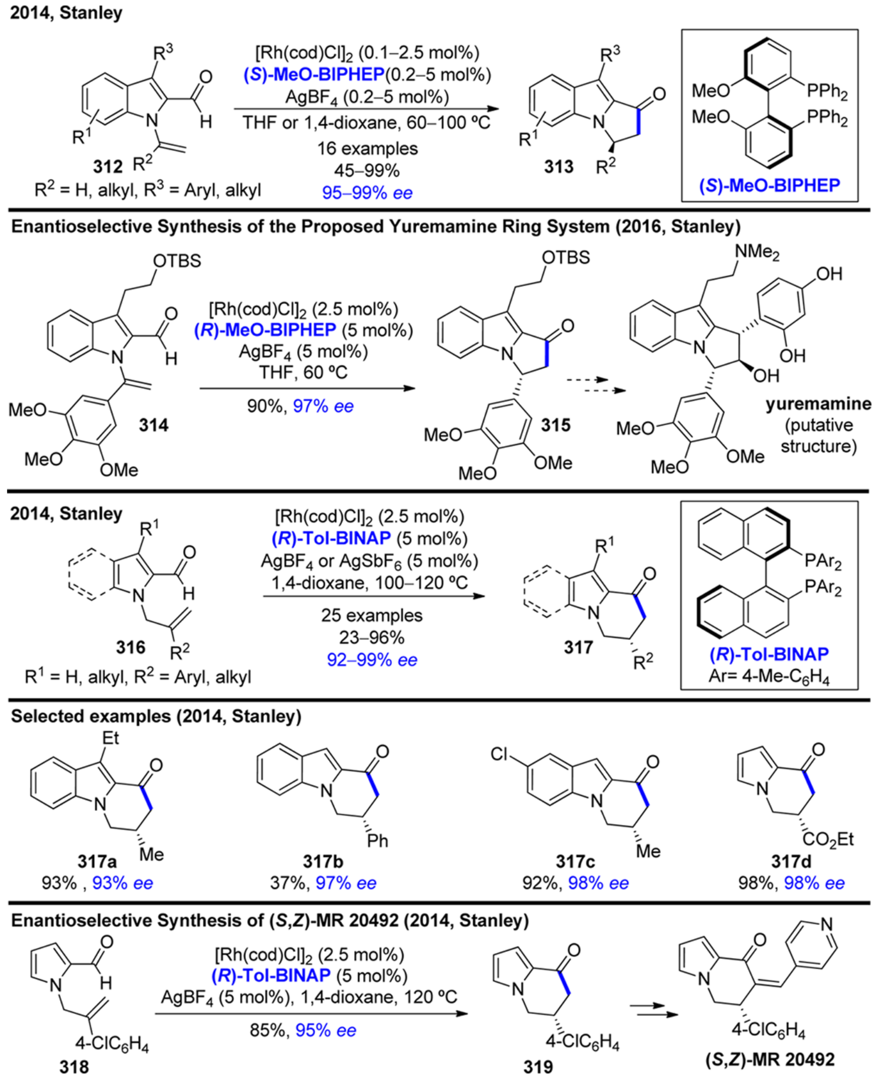
species catalyzes both processes. A Rh(I)-catalyzed hydroacylation of *o*-allylbenzaldehydes **310** with (*R*)-DTBM-SEGPHOS was also reported by Stanley and co-workers.[226] In all cases, only six-membered ring formation was observed, providing 3,4-dihydronaphthalen-1(2*H*)-ones **311** in excellent enantiopurity (see Scheme 79 for a related mechanistic evaluation concerning the effects of alkene substitution on the regioselectivity of migratory insertion).

The Stanley group have also disclosed the synthesis of several pyrrole- and indole-fused cyclic ketones (Scheme 78). Their first report documented a Rh(I)-catalyzed intramolecular hydroacylation of *N*-vinylindole-2-carboxaldehydes **312**, generating 2,3-dihydro-1*H*-pyrrolo[1,2-*a*]indol-1-ones **313** in yields ranging from 45 to 99% and up to 99% ee.[227] Neutral complexes were unreactive, but a move to cationic analogues successfully addressed this problem. The researchers demonstrated that the catalyst loading could be decreased to as low as 0.2 mol % while the same level of enantioinduction was maintained, albeit with a slight decrease in yield. Recently, the Stanley group applied their methodology toward the synthesis of the putative structure of the natural product yuremamine.[228] Functionalized indole **314** was cyclized using their previously described conditions, forming dihyropyrroloindolone **315** in 90% yield and 97% ee. Unfortunately, the structure of the natural product was recently revised,[229] and accordingly, synthetic studies were not continued. To the best of our knowledge, the first enantioselective synthesis of six-membered rings via a hydroacylation reaction was also reported by Stanley and co-workers.[230] Substituted *N*-allyl derivatives **316** were cyclized using a cationic Rh(I) complex and (*R*)-Tol-BINAP as chiral ligand. Both alkyl- and aryl-substituted *N*-allylindoles reacted with excellent levels of enantiocontrol (**317a** and **317b**); however, competitive decarbonylation made purification of some substrates challenging; thus, isolated yields were not always representative. Aryl chlorides, as well as pyrroles, were well-tolerated (**317c** and **317d**), enabling an efficient enantioselective synthesis of the nonsteroidal aromatase inhibitor MR 20492 (**318** to **319**). Notably, in all cases no competitive five-membered ring formation was observed.

In 2009, Dong and co-workers reported an intramolecular approach to seven and eight-membered rings (Scheme 79).[203] As the length of the alkene tether increases, any bias for the migratory insertion process becomes less pronounced, introducing potential difficulties in the synthesis of medium-sized rings. At the time of publication, only the enantioselective synthesis of five-membered cyclic ketones was known; however, inspired by the related reports,[231−233] coordination of a heteroatom in the alkene tether was expected to promote hydroacylation over competitive isomerization, decarbonylation, or catalyst decomposition pathways. Using terminal or 1,2-disubstitued alkenes **320**, the corresponding seven-membered cyclic ketones **321** were isolated in 80−91% yield and 89−98% ee. Alkene geometry was determined to be mostly inconsequential, and an almost identical result was obtained from either the *E*- or the *Z*-isomer. 1,1-Disubstituted thioether tethered alkenes **322** were also screened, resulting in a reversal of regioselectivity, leading to the corresponding seven- and eight-membered ring analogues **323**. Preliminary mechanistic studies show that the heteroatom is crucial for reaction, and in contrast to many other hydroacylation

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 78. Enantioselective Intramolecular Hydroacylation of Substituted *N*-Vinyl- and *N*-Allylindoles and -pyrroles



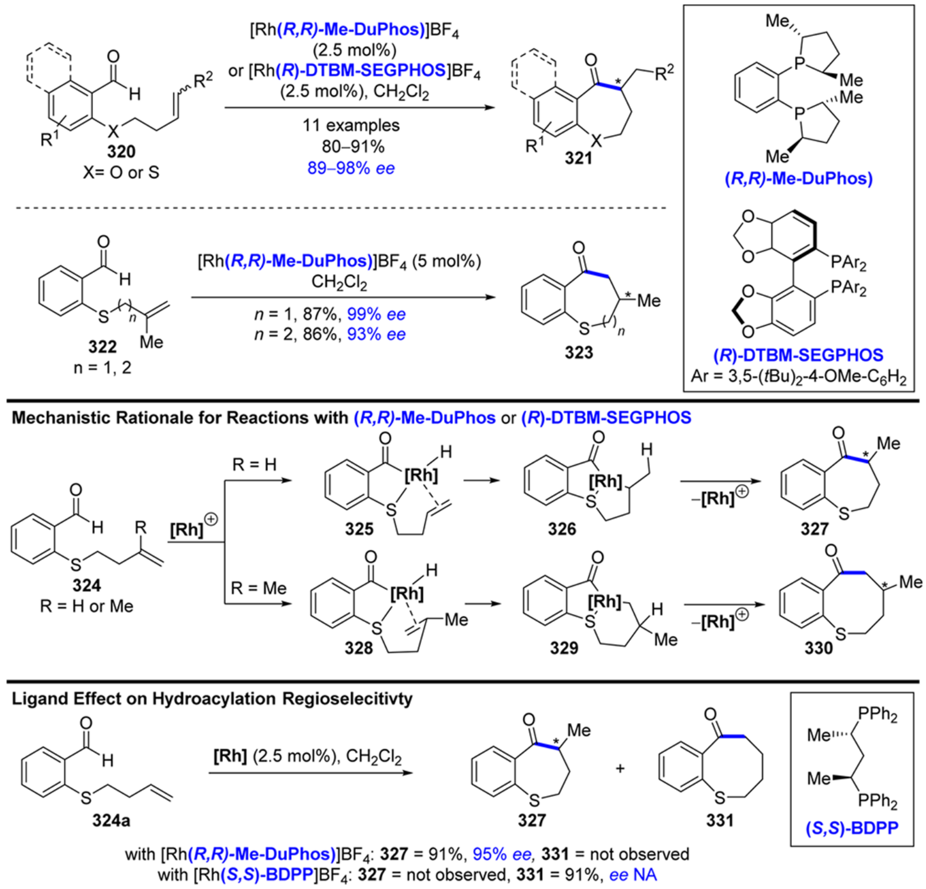
methodologies,[202,213,234] the reductive elimination does not appear to be rate-determining. The regioselectivity of hydroacylation with (*R,R*)-Me-DuPhos or (*R*)-DTBM-SEGPHOS can be rationalized by considering the oxidative addition intermediates of thioethers **324**. When R = H, preferential coordination of the alkene should favor the less-strained orientation depicted in **325**. Migratory insertion into the metal hydride bond delivers the five-membered rhodacycle **326**, which reductively eliminates to yield the seven-membered ring analogue **327**. In comparison, the introduction of α-branching may lead to the more strained conformation **328** to reduce steric interactions resulting from the Me substituent. Subsequent migratory insertion generates **329**, and finally, reductive elimination delivers the eight-membered ring analogue **330**. However, it should be emphasized that the regioselectivity was shown to be dependent on both the chiral ligand and the alkene substitution pattern. For example, reaction of thioether **324a** with (*R,R*)-Me-DuPhos gave the corresponding branched cycloheptenone **327** in 91% yield and 95% ee; however, when (*S,S*)-BDPP was employed as ligand, exclusive formation of achiral eight-membered ring derivative **331** was observed.

The enantioselective desymmetrization of prochiral dienes has also been demonstrated (Scheme 80). In 1993, Sakai and co-workers reported that BINAP could effectively promote a highly diastereo- and enantioselective hydroacylation of 3,4-disusbtituted 4-pentenal **332a** (where R^1 = Me, R^2 = H), generating the *trans*-diastereoisomer **333a** in >99% ee.[235] Several years later, Tanaka, Suemune, and their co-workers revealed that the same conditions were also suitable for isopropyl- and phenyl-substituted derivatives of **332**.[236−238] In addition, substrates bearing a quaternary stereocenter (where $R^2 \neq$ H) were screened, and in all cases, the *trans*-diastereoisomer was preferentially formed in excellent enantiopurity. Both groups also reported that *cis*-diastereoisomers **333** were favored with stoichiometric loadings of neutral Rh(I)−BINAP complexes (not shown).[235,236] Related desymmetrization methodologies have since been disclosed by Dong and co-workers (Scheme 91).

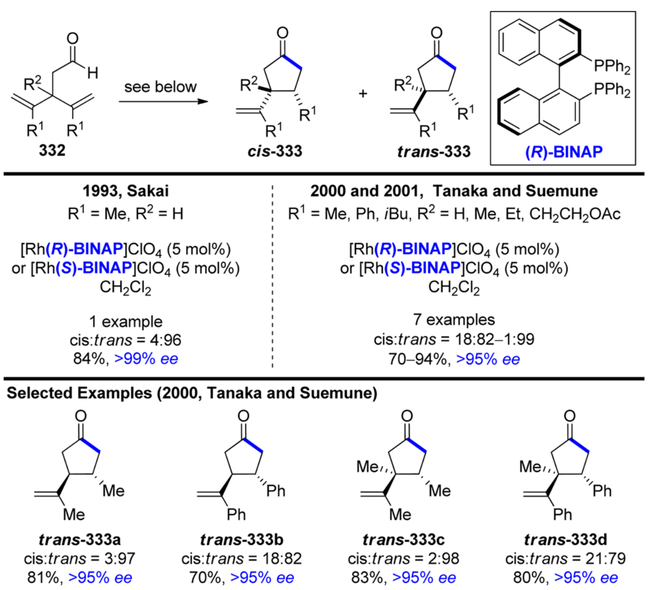
Two research groups have described strain-driven intermolecular enantioselective hydroacylation reactions of norbornene and/or norbornadiene (Scheme 81). The first report was disclosed by Stemmler and Bolm, in 2007, and represents the first intermolecular enantioselective hydroacylation reaction.[233] Drawing upon earlier racemic studies by Suemune, Tanaka, and their co-worker,[239] the hydroacylation of salicylaldehydes **334** with norbornadiene was explored using various chiral ligands. The importance of a coordinating phenolic oxygen on the aryl aldehyde coupling partner had previously been demonstrated by Miura and co-workers, who proposed it suppresses decarbon-

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 79. Heteroatom-Directed Enantioselective Intramolecular Hydroacylation



Scheme 80. BINAP Promoted Highly Enantioselective Desymmetrizations



ylation.[240] Extensive reaction optimization by Bolm determined that monodentate phosphoramidites (*S*)-MonoPhos or **L67** provided the best levels of enantioinduction, and although only modest enantiomeric excesses were obtained (11−54%), the reactions all proceeded in excellent yield and diastereoselectivity. Further ligand screening revealed a switch in diastereoselectivity when Walphos-type bidentate phosphine ligands **L68** or **L69** were employed, enabling the synthesis of *exo*-products **335** in similarly high yields and diastereoselectivities, and with improved levels of enantiocontrol (55−82% ee). Finally, the reaction of norbornene with (*S*)-MonoPhos was found to be *exo*-selective, but only very low levels of enantioinduction were observed. Rationalization of the diastereoselectivity in these three reactions draws upon deuterium-labeling studies conducted by Suemune, Tanaka, and their co-worker.[239] With monodentate phosphoramidite ligands, norbornadiene can behave as a chelating ligand (e.g., **337**); thus, addition occurs preferentially to the *endo* face. This selectivity is reversed with bidentate phosphine ligands or when norbornene is used in place of norbornadiene. As chelation is no longer possible, coordination of only one alkene, preferably on the less hindered *exo*-face (e.g., **338**), leads to the corresponding *exo*-products. In 2015, Nagamoto and Nishimura reported the first iridium-catalyzed hydroacylation reaction.[241] Development of a racemic reaction utilizing $[Ir(OH)(cod)]_2$ as catalyst prompted the authors to screen chiral diene ligands for the development of an enantioselective version. Employing (*S,S*)-Me-TFB*, salicylaldehydes **334** were successfully converted to *exo*-adducts **336** with reasonable levels of enantioselectivity (82−88% ee), and representative examples include arylmethoxy and aryl-fluorine derivatives **336a** and **336b**.

The Dong group has also reported an intermolecular hydroacylation of symmetrical cyclic alkenes (Scheme 82).[242] A strain-releasing hydroacylation of salicylaldehyde derivatives **334** with achiral cyclopropenes **339**, using Josiphos-type ligand **L70**, delivered *trans*-cyclopropylketones **340** bearing a quaternary stereocenter in up to >20:1 dr and up to >99% ee. The addition of base enhanced the rate of reaction, possibly via

DOI: 10.1021/acs.chemrev.6b00692
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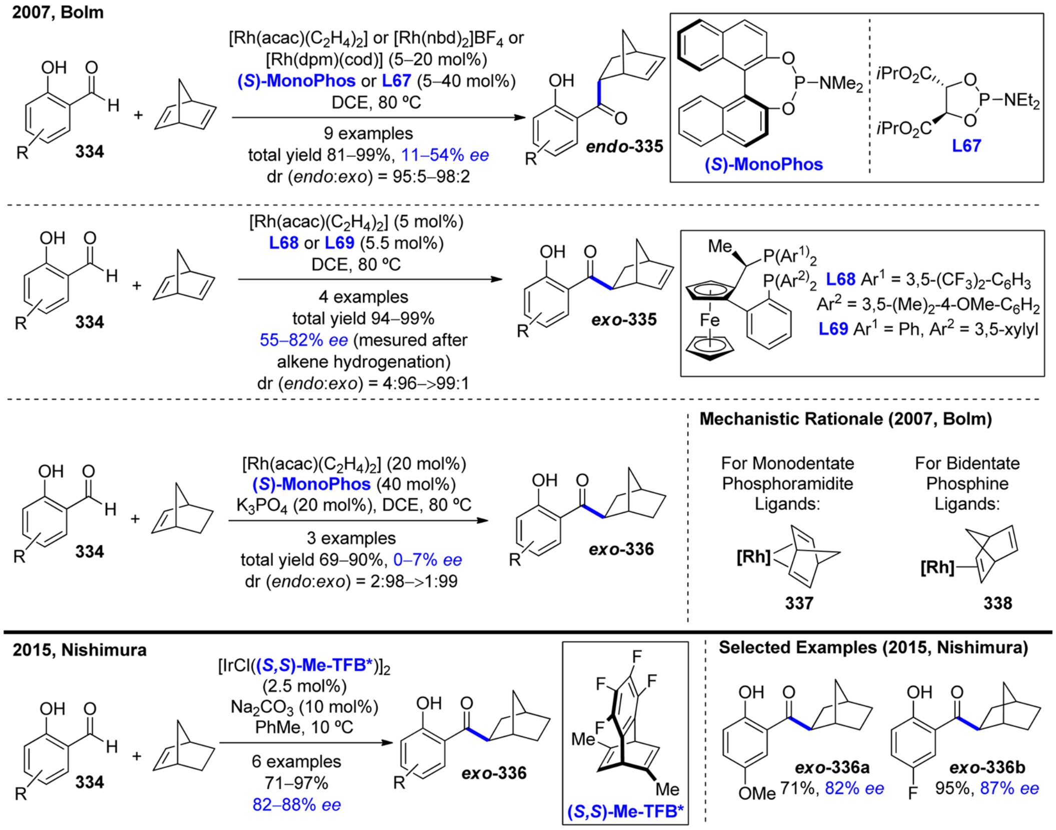
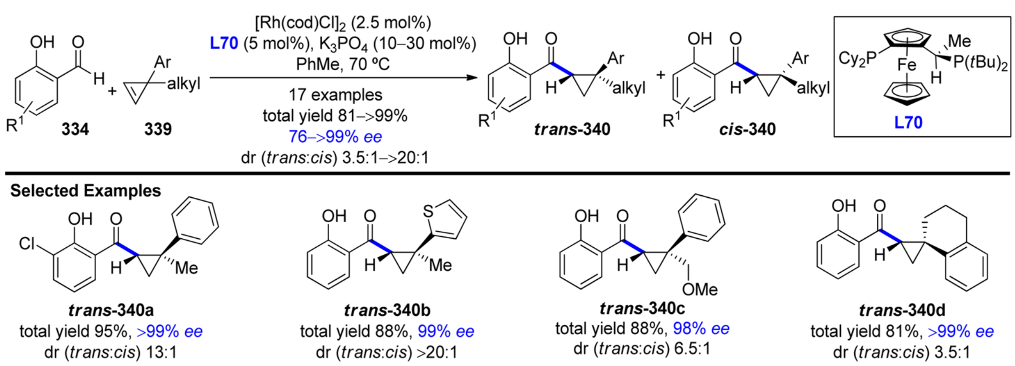
Scheme 81. Intermolecular Enantioselective Hydroacylation of Norbornene and Norbornadiene



Scheme 82. Enantioselective Hydroacylation of Cyclopropenes



formation of a stronger-coordinating phenolate,[240] and the diastereoselectivity appears to be controlled by the larger aryl substituent directing migratory insertion to the opposite face. The reaction exhibits a wide functional group tolerance, including aryl chlorides (**340a**) and cyclopropanes bearing heteroaromatic (**340b**), Lewis basic (**340c**), and spirocyclic (**340d**) functionality.

The intermolecular hydroacylation reaction of unsymmetrical π-bond coupling partners introduces the added complexity of regiocontrol during the migratory insertion process. Several research groups have reported strategies to address this challenge, most commonly via the incorporation of neighboring coordinating functionality (Scheme 83). The first reported enantioselective variant proceeds via the dynamic kinetic resolution of racemic allenes[232] and as such is discussed in section 7.2. In contrast, the first reaction incorporating an achiral coupling partner was disclosed by Tanaka, Suemune, and their co-workers, in 2009, and involved cross-coupling of salicylaldehyde and 1,5-hexadiene.[243] (*S*)-BINAP was employed as chiral ligand, in combination with a neutral Rh(I) source and a catalytic quantity of $ZnBr_2$. The authors proposed that the zinc salt may behave as a Lewis acid, activating the aldehyde toward reaction. Under optimized conditions, a 1:1 mixture of the chiral branched (**341**) and achiral linear (**342**) hydroacylation products were isolated in a combined yield of 86%, both as a mixture of constitutional alkene isomers. The ee of **341** was measured after alkene hydrogenation and determined to be 84%. That same year, Shibata and Tanaka reported the first intermolecular hydroacylation reaction that does not require functionalized aldehydes to stabilize the intermediate acylmetal species, but rather, a chelating π-bond coupling partner is believed to facilitate reaction.[244] In this example, alkyl- and aryl-substituted aldehydes **343** were coupled with acrylamides **344**, using a cationic Rh(I) complex in conjunction with bisphosphine (*R*,*R*)-

DOI: 10.1021/acs.chemrev.6b00692
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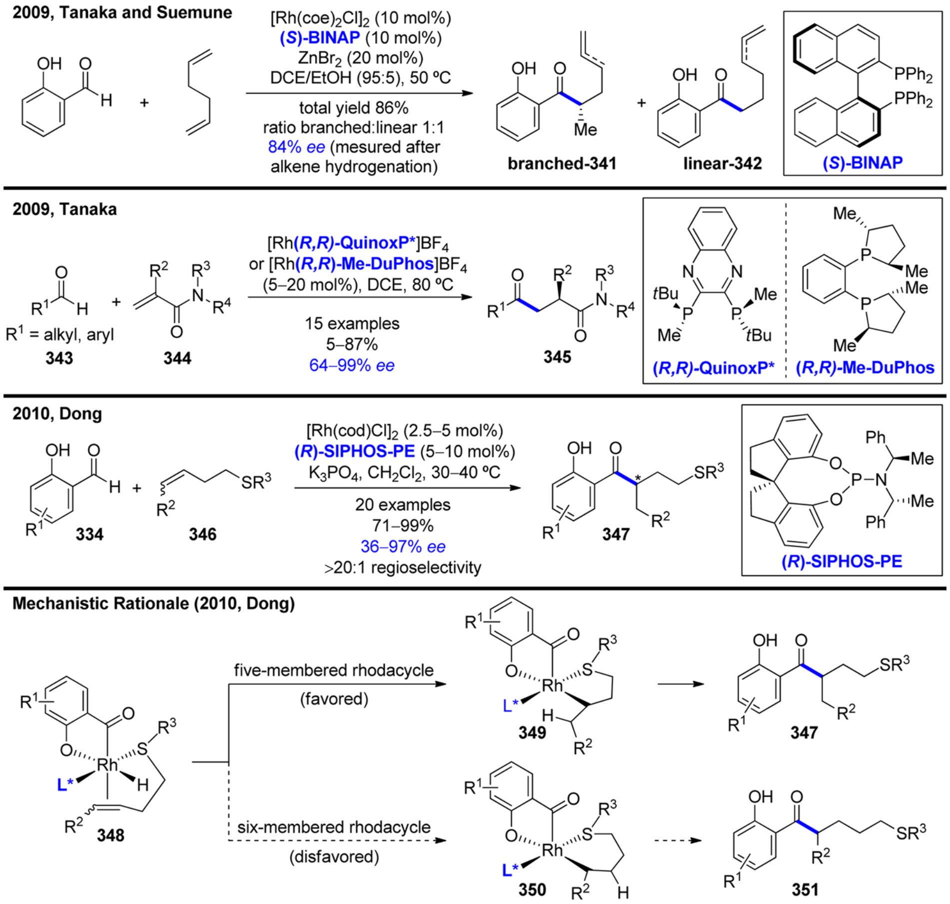
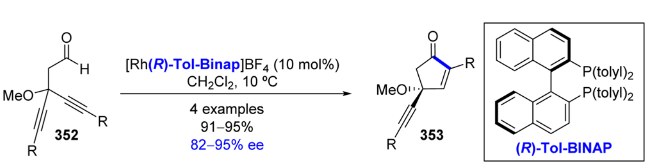
Scheme 83. Intermolecular Enantioselective Hydroacylation of Achiral Acyclic Olefins



QuinoxP* or (*R*,*R*)-Me-DuPhos. In all cases only one regioisomer was observed, and except for reaction with benzaldehyde, excellent enantioselectivities were obtained (≥97% ee). In 2010, Dong and co-workers reported the directed regio- and enantioselective hydroacylation of salicylaldehyde derivatives **334** with homoallylic sulfides **346**, employing the monodentate phosphoramidite (*R*)-SIPHOS-PE as ligand.[245] Structurally diverse α-substituted ketones **347** were obtained in up to 99% yield and up to 97% ee. Aryl-substituted sulfides performed best, and the geometry of internal alkenes was largely inconsequential. The authors rationalize the regioselectivity of the reaction by considering the preferred geometry of the migratory insertion process. After oxidative addition of the Rh complex into the aldehyde C(sp^2)−H bond, the Rh(III) hydride species **348** has two free coordination sites available for the alkene coupling partner. Hydroacylation preferentially occurs via the five-membered rhodacycle **349**, as opposed to the corresponding six-membered analogue **350**. Reductive elimination then provides the enantioenriched **347**, and the minor regioisomer **351** is only observed in trace amounts (>20:1 regioselectivity).

Scheme 84. Enantioselective Hydroacylation of Diynals



3.1.2.1.2. C≡C Insertion. Only one report concerning the enantioselective hydroacylation of alkynes has been disclosed (Scheme 84). In 2002, Tanaka and Fu demonstrated that prochiral diynes **352** could be effectively desymmetrized in the presence of a cationic Rh(I) source and (*R*)-Tol-BINAP, enabling access to chiral cyclopentenones **353** in excellent yield and up to 95% ee.[246] The authors propose the high level of enantiocontrol may be attributable to coordination of the methoxy group to rhodium, as multipoint complexation of a substrate often provides more organized intermediates.[247] In the same study, the kinetic resolution of several related racemic alkynals was also achieved (Scheme 110).

3.1.2.1.3. C═O Insertion. In 2008, Dong and co-workers published the first transition-metal-catalyzed enantioselective hydroacylation of ketones (Scheme 85).[248] Interestingly, although this represents a change from nucleophilic to electrophilic π-bond coupling partners, essentially identical reaction conditions appear to be suitable for both systems. In this study, ether- and thioether-tethered ketones **354** were hydroacylated in an intramolecular manner with [Rh(*R*)-DTBM-SEGPHOS]BF_4, to form seven-membered ring analogues **355** in up to 99% ee. During optimization studies it was observed that the aryl substituents on the phosphine ligand need to be suitably electron rich to avoid decarbonylation; however, alkyl-substituted derivatives appeared to be too basic and inhibit the reaction. The following year, the scope of the reaction was expanded to include a thioether analogue, as well as several additional aryl-substituted ethers. In every case but one (where X = O and R = 4-MeO-C_6H_4), excellent enantioselectivities were

DOI: 10.1021/acs.chemrev.6b00692
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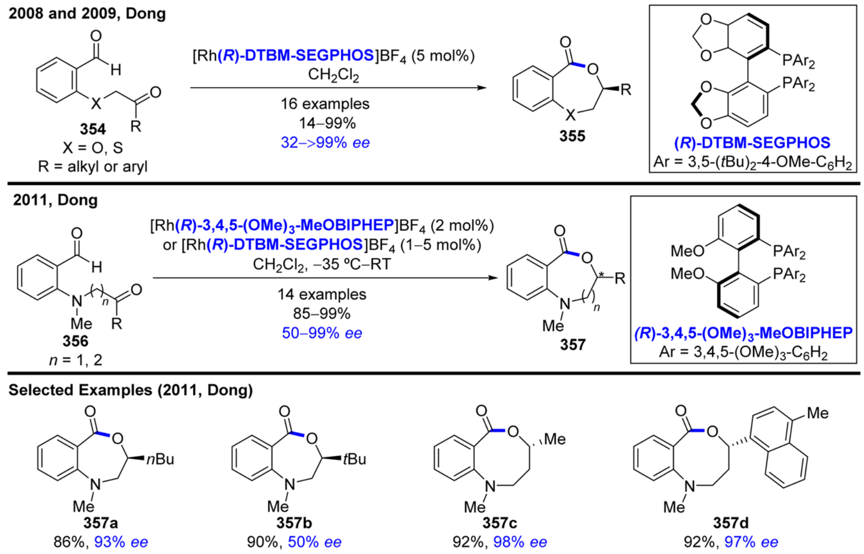
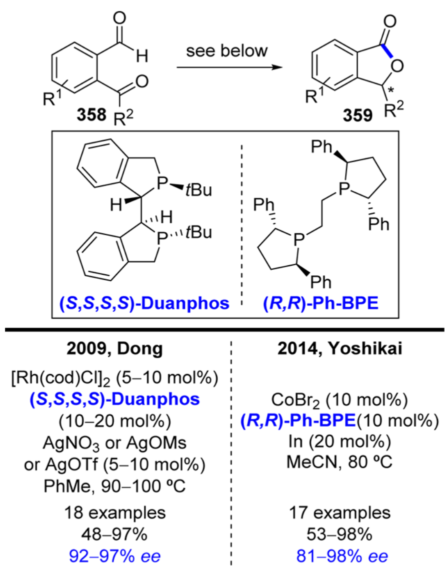
Scheme 85. Heteroatom-Directed Enantioselective Intramolecular Hydroacylation of Ketones



observed.[231] Combined experimental and computational mechanistic studies indicate that the reaction proceeds via the same elementary steps as for alkene coupling partners (Scheme 73) and that ketone insertion is rate-limiting. Replacement of the heteroatom linker with a methylene group completely shut down the reaction, demonstrating the importance of a chelating oxygen or sulfur atom. The Dong group have since demonstrated that amines are also competent directing groups via the reaction of substituted anilines **356** with axially chiral bisphosphine ligands.[249] (*R*)-3,4,5-$(OMe)_3$-MeOBIPHEP was best suited to the synthesis of benzo[*e*][1,4]oxazepinones (where n = 1), whereas (*R*)-DTBM-SEGPHOS provided benzo[*c*][1,5]-oxazecinones (where n = 2) with excellent levels of enantiocontrol. In the former case, several alkyl substituted derivatives were successfully reacted at −35 °C, providing the correspond products in up to 93% ee (e.g., **357a** and **357b**). The formation of eight-membered rings required higher temperatures, however in this case, both alkyl and aryl substituted derivatives were reported, and consistently high levels of enantioselectivity were achieved (e.g., **357c** and **357d**). Notably, the opposite absolute stereochemistry was favored for seven- and eight-membered ring formation, despite employing ligands of the same configuration. Further experiments exploring the scope of the transformation determined that the precise location of the chelating heteroatom is crucial for reactivity, as too is the length of the ketone tether.

Two studies describing the intramolecular hydroacylation of ketones that do not incorporate an additional coordinating heteroatom have been disclosed (Scheme 86). In 2009, Dong demonstrated the cyclization of 2-ketobenzaldehydes **358** with (*S*,*S*,*S*,*S*)-Duanphos, yielding the biologically relevant phthalide motif **359**.[250] The nature of the counterion impacted both the reactivity and enantioselectivity: stronger coordinating counterions gave better selectivity for hydroacylation over decarbonylation and higher levels of enantioinduction; however, this tended to come at the expense of reaction rate. Eventually, $AgNO_3$ was discovered to provide an excellent balance between all parameters and was employed for all methyl ketone derivatives. For alternate ketone substitution patterns (where $R^2 \neq$ Me), highly substrate specific counterion effects were observed, necessitating an individual counterion screen in each

Scheme 86. Nondirected Enantioselective Intramolecular Hydroacylation of Ketones

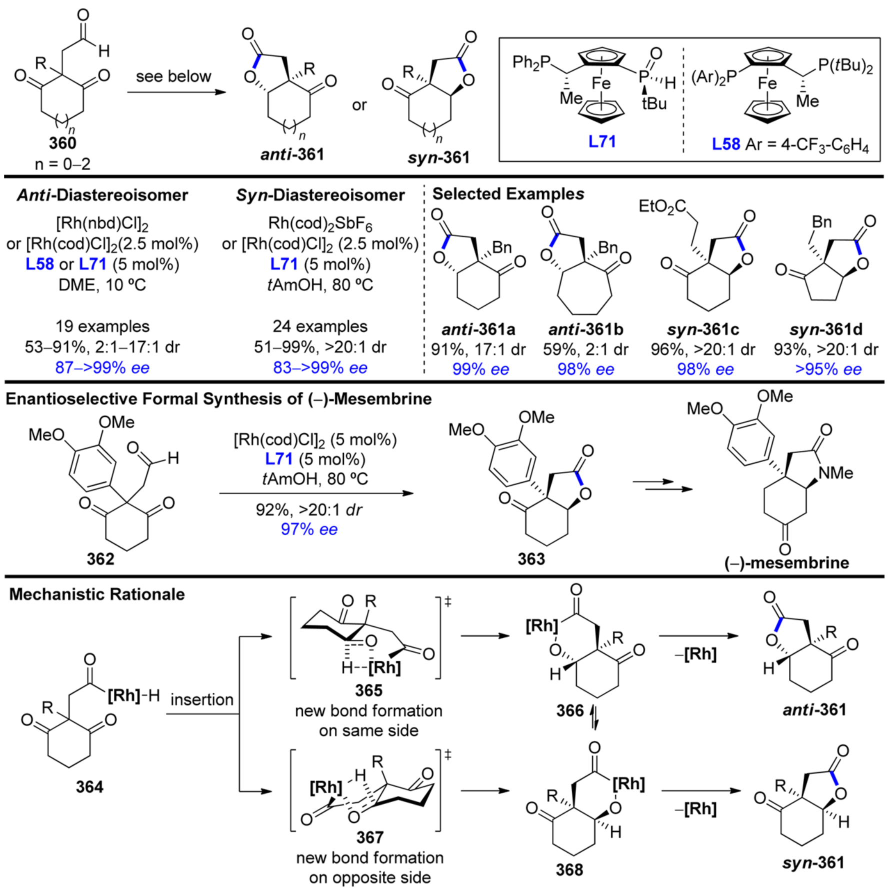


case. In 2014, as part of their earlier described synthesis of chiral indanones (Scheme 77), Yang and Yoshikai reported the same transformation as Dong, however, in this case employing a Co(I) catalyst.[219] Although comprehensive mechanistic studies have not been conducted, deuterium-labeling experiments confirm that the aldehyde C(sp^2)−H bond is intramolecularly incorporated into the product, excluding the possibility of a Tishchenko-type mechanism via hydride delivery from a free cobalt species.[251,252] In addition, the authors propose that the reductive elimination is rate determining, as a significant KIE effect was not observed.

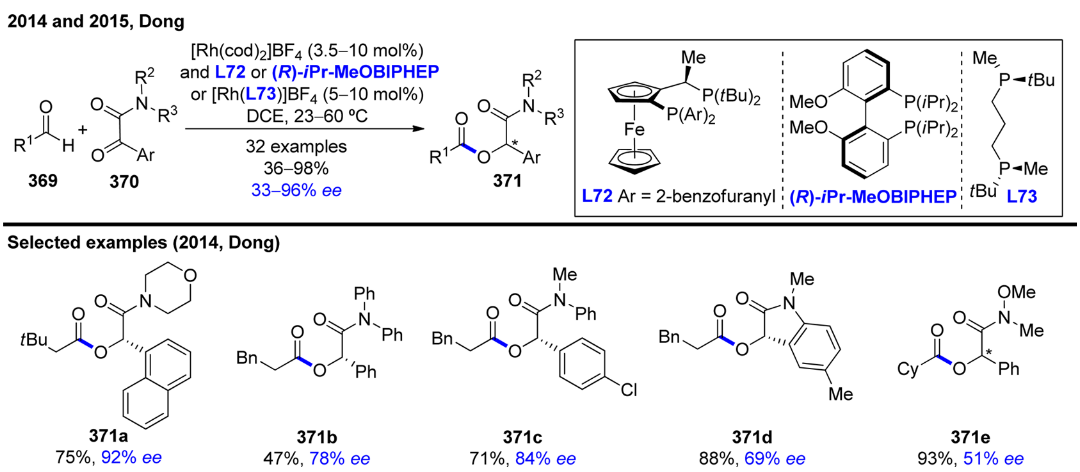
In 2016, the Dong group published an enantioselective diastereodivergent desymmetrization of 4,4′-diketo aldehydes **360** (Scheme 87).[253] Either *anti*- or *syn*-bicyclic γ-lactones **361** could be accessed, depending on the nature of the reaction conditions. Generally speaking, polar aprotic solvents, lower temperatures, and neutral rhodium chloride complexes favored the *anti*-products, whereas polar protic solvents, cationic complexes, and higher temperatures lead to the *syn*-diaster-

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 87. Diastereodivergent Intramolecular Hydroacylation of Ketones

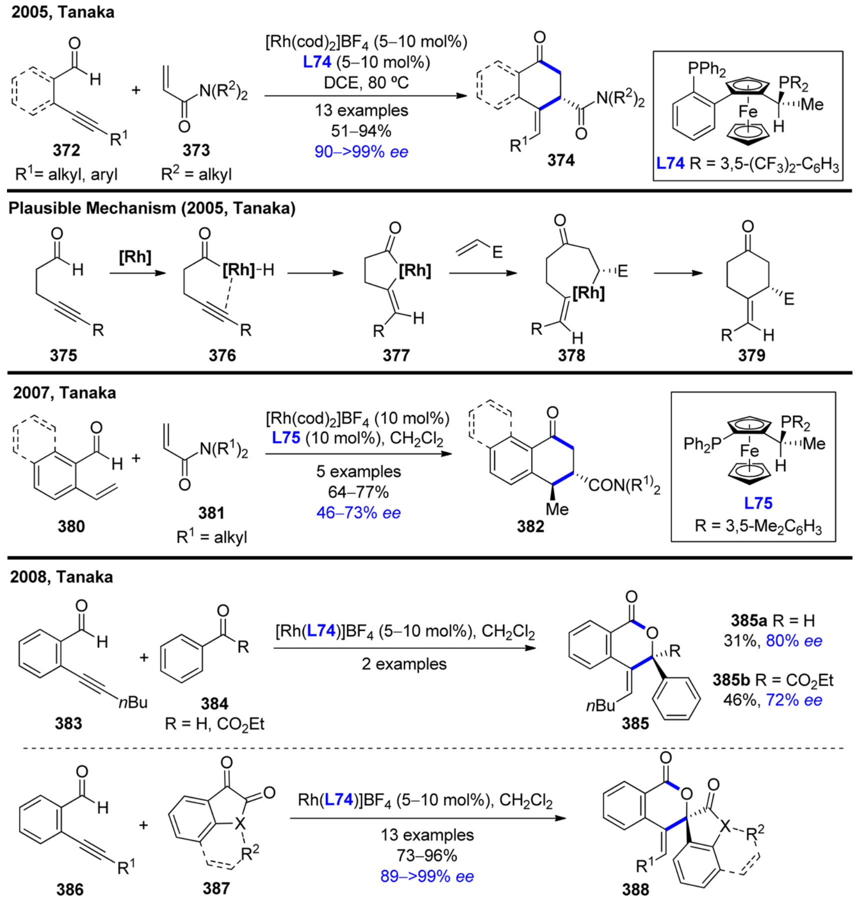


Scheme 88. Intermolecular Enantioselective Hydroacylation of α-Ketoamides



eoisomers. More specifically, when $[Rh(nbd)Cl]_2$ or $[Rh(cod)Cl]_2$ were employed with either JoSPOphos ligand **L58** or JoSPOphos ligand **L71** in DME at 10 °C, *anti*-configured lactones were synthesized in up to >99% ee and up to 91% yield. In contrast, *syn*-cyclization was typically conducted with $Rh(cod)_2SBF_6$ and JoSPOphos ligand **L71**, in *t*AmOH at 100 °C. Under these conditions, extremely high levels of diastereocontrol were achieved (>20:1 dr), and in all but one example, >90% ee was observed. Representative examples from this study include six- and seven-membered ring analogues *anti*-**361a** and *anti*-**361b**, ester-bearing substrate *syn*-**361c**, and five-membered ring analogue *syn*-**361d**. The authors also applied this methodology in a formal synthesis of (−)-mesembrine via the *syn*-selective cyclization of dimethyl aryl derivative **362**. Lactone **363** was synthesized in 92% yield, >20:1 dr, and 97% ee and was subsequently converted into an intermediate from Kulkarni et al.'s 2002 synthesis of the natural product.[254] On the basis of literature precedent, as well as their own computational and experimental studies, the authors propose that following oxidative addition of the rhodium catalyst into the aldehyde $C(sp^2)$−H bond to yield acyl−metal complex **364**, a diastereodivergent migratory insertion can occur. This process proceeds with bond formation occurring on either the same or the opposite side of the carbocycle (via **365** or **367**), and the

Scheme 89. Cationic Rh(I)-Catalyzed Intermolecular [4 + 2]-Annulation of Aldehydes



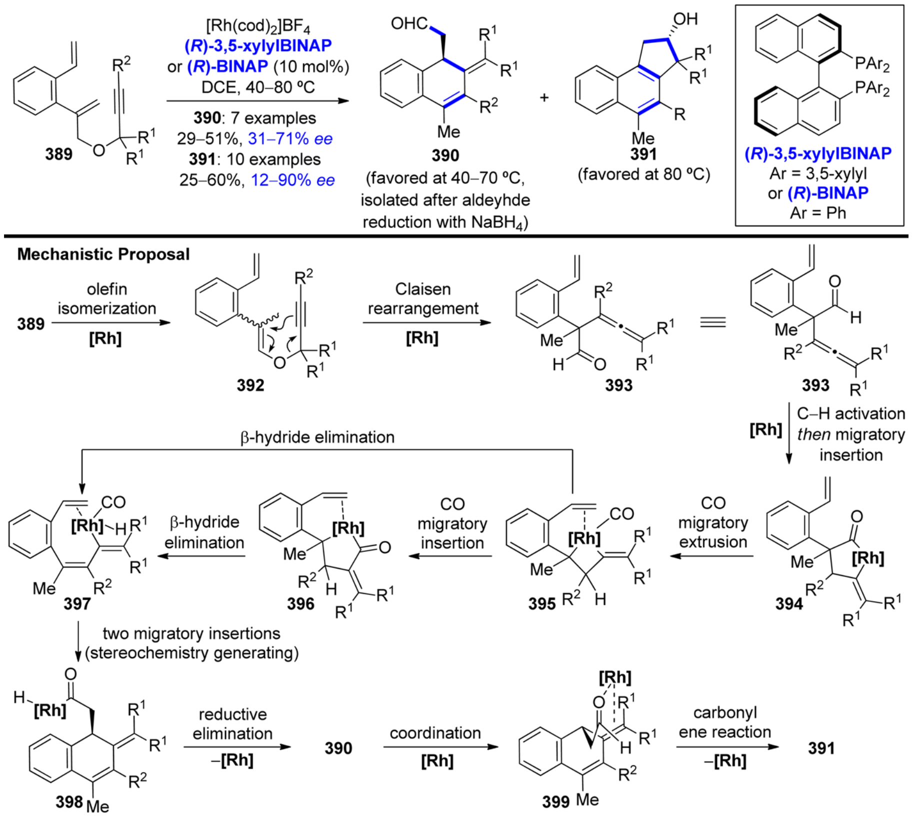
relative transition state energies and geometries are impacted by the solvent and the ability of the counterion to coordinate. As this process is reversible, the resultant rhodacycles **366** and **368** are in equilibrium, and an irreversible reductive elimination yields the corresponding products *anti*-**361** or *syn*-**361**.

The enantioselective intermolecular hydroacylation of ketones remains comparatively unexplored. To date, only one reaction mode has been developed, by the Dong research group, and involves the cross-coupling of nonchelating aldehydes **369** with α-ketoamides **370** (Scheme 88).[255] Following a screening of Rh-bis(phosphine) catalysts, novel Josiphos-type ligand **L72** was identified as an effective stereochemistry-controlling element, enabling the synthesis of a diverse array of functionalized esters **371** in up to 96% ee. Sterically demanding aldehydes were well-tolerated (**371a**), and products derived from both symmetrically and unsymmetrically substituted amides, including cyclic isatin derivatives, were readily accessed (**371b**−**371d**). The hydroacylation of α-keto-Weinreb amides required an alternative catalyst, in this case derived from (*R*)-*i*Pr-MeOBIPHEP, allowing the synthesis of **371e** in excellent yield (93%) but with only a modest level of enantiocontrol (51% ee). A follow-up publication documented the development and application of new 1,3-bis(dicyclohexylphosphino)propane-inspired chiral ligands in the same reaction.[255,256] *P*-Stereogenic derivative **L73** provided the best reactivity, and promising preliminary enantioselectivities were also obtained. Deuterium-labeling studies indicated that the C−H activation event was rate-limiting.[255] This result, coupled with an observed second-order dependence of the reaction rate on catalyst concentration, prompted the authors to propose that a second cationic Rh species activates the aldehyde as a Lewis acid during C−H activation.

3.1.2.2. Other Reactions. Several methodologies related to the hydroacylation reaction have been reported, each involving the functionalization of an aldehyde C(sp^2)−H bond and each proceeding through a stereochemistry-generating migratory insertion. In a series of papers from 2005 to 2008, the Tanaka group developed an enantioselective Rh-catalyzed intermolecular [4 + 2]-annulation reaction (Scheme 89). The earliest report described the coupling of 4-alkynals **372** with *N,N*-dialkylacrylamides **373** to yield chiral cyclohexanone derivatives **374**.[257] By employing a cationic Rh(I) complex with Walphos ligand **L74**, high levels of enantioinduction (90 to >99% ee) and complete control over reaction regioselectivity and alkene geometry were achieved. The authors propose that the reaction may proceed via oxidative addition of Rh into the aldehyde C(sp^2)−H bond of **375** to generate Rh−acyl species **376**, followed by *cis*-selective addition of the Rh−H species to give five-membered rhodacycle **377**. Complexation of the alkene coupling partner, followed by a stereochemistry-generating migratory insertion provides intermediate **378**, which reductively eliminates to yield ketone **379**. This same reactivity profile has since been applied to the diastereo- and enantioselective coupling of vinylarylaldehydes **380** with amides **381**.[258] In this case, Walphos ligand **L75** proved optimal, providing the substituted tetralones **382** in up to 77% yield and 73% ee. The most recent application involves the employment of carbonyl coupling partners.[259] Initial studies were conducted with *n*Bu-substituted alkynal **383**, employing either benzaldehyde or ethyl oxophenylacetate (**384**, where R = H or CO_2Et, respectively) as coupling partner. Under optimized

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 90. Enantioselective Rh(I)-Catalyzed Cascade Reactions of Dienynes



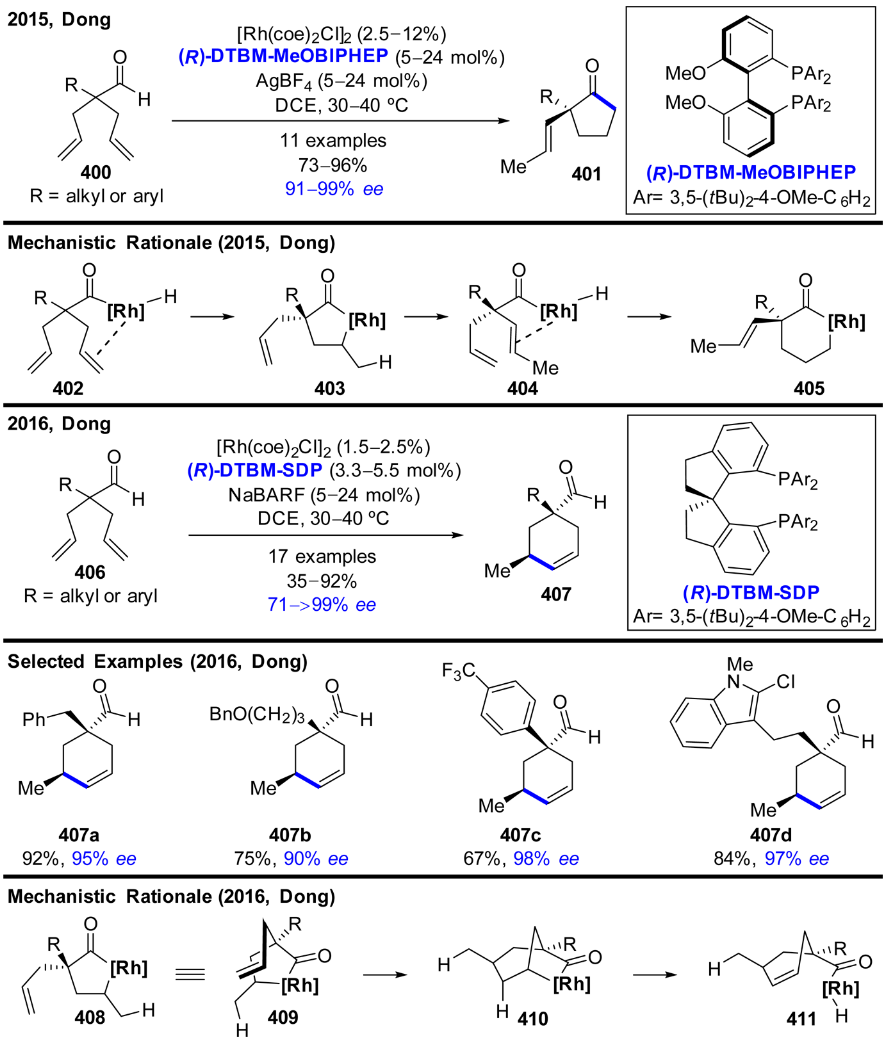
conditions, also using Walphos ligand **L74**, only modest results were obtained (31−46% yield, 72−80% ee). A change to cyclic 1,2-diketones **387** significantly improved the reaction, enabling the synthesis of spirocyclic benzopyranones **388** in excellent yield and enantioselectivity.

In 2012, the Tanaka group reported a rhodium-catalyzed enantioselective cascade reaction of dienynes **389**, favoring the selective formation of bicyclic aldehydes **390** or tricyclic alcohols **391** depending on the temperature of the reaction (Scheme 90).[260] The transformation was conducted using either a cationic rhodium (*R*)-3,5-xylylBINAP or (*R*)-BINAP complex, in DCE at 40−80 °C, and both aryl- and alkyl-substituted alkynes were well-tolerated. Drawing upon their earlier disclosed studies,[261] the authors propose that the reaction begins with olefin isomerization to enol ether **392**, which consequently participates in a Claisen rearrangement to yield allenic aldehyde **393**. Oxidative addition of Rh into the aldehyde C(sp^2)−H bond, followed by an intramolecular migratory insertion, provides rhodacycle **394**. Migratory extrusion of CO to **395** is followed by either a CO migratory insertion/*β*-hydride elimination sequence to yield **396** and then **397** or, alternatively, a direct *β*-hydride elimination from **395** to provide the same intermediate. As a result of rhodium coordination, the *Z*-configured olefin isomer is presumed to be favored (as drawn), which subsequently undergoes an enantioselective carboformylation sequence. Although not detailed, this step presumably proceeds via a series of two migratory insertions to generate acyl−rhodium complex **398**, followed by a reductive elimination to yield the aldehyde products **390**. Finally, at higher temperatures a subsequent stereoselective carbonyl ene reaction via intermediate **399** yields alcohols **391**.

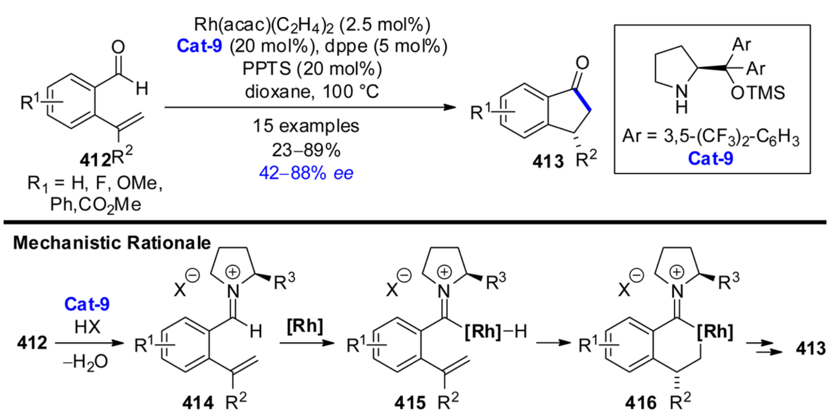
Two recent publications from the Dong group described Rh-catalyzed intramolecular desymmetrization reactions of prochiral *α*,*α*-bisallyl aldehydes **400** (Scheme 91).[262,263] Both methodologies are believed to proceed via mechanisms closely related to the standard hydroacylation reaction, and depending on the nature of the phosphine ligand employed, divergent cyclization pathways operate. When the reaction was conducted with a cationic Rh(I)/(*R*)-DTBM-MeOBIPHEP complex, exclusive formation of cyclopentanones **401** bearing an *α*-quaternary stereocenters was observed.[262] Both aryl and alkyl substitution was well-tolerated, and yields and enantioselectivities ranged from 73 to 96% and 91 to 99% ee, respectively. On the basis of related literature reports[264,265] and their own mechanistic studies, Dong and co-workers proposed that the reaction proceeds via an isomerization/hydroacylation sequence. Specifically, oxidative addition intermediate **402** undergoes an intramolecular migratory insertion of an alkene into the Rh−hydride bond, leading to the five-membered rhodacycle **403**. An endocyclic *β*-hydride elimination produces isomerized acyl−Rh intermediate **404**, which subsequently undergoes an olefin-directed hydrometalation to **405**. Finally, reductive elimination delivers the cyclopentanone products **401** and regenerates the active catalyst. In contrast, when SPINOL-derived bisphosphine (*R*)-DTBM-SDP was employed, under similar conditions, chiral cyclohexenes **407** were isolated in up to 92% yield and up to >99% ee.[263] Several functionalized derivatives could be prepared, including-phenyl substituted derivative **407a**, benzyl ether **407b**, electron-poor aromatic **407c**, and chloroindole **407d**. The mechanism of this transformation is believed to proceed through the same five-membered rhodacycle proposed in their earlier study; however, in this case carboacylation of the pendant olefin predominates, leading to intermediate **410**. The bite angle of the

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 91. Divergent Rh-Catalyzed Desymmetrization of α,α-Bisallyl Aldehydes



Scheme 92. Synthesis of Chiral Indanones by Cooperative Organocatalysis and Transition-Metal Catalysis



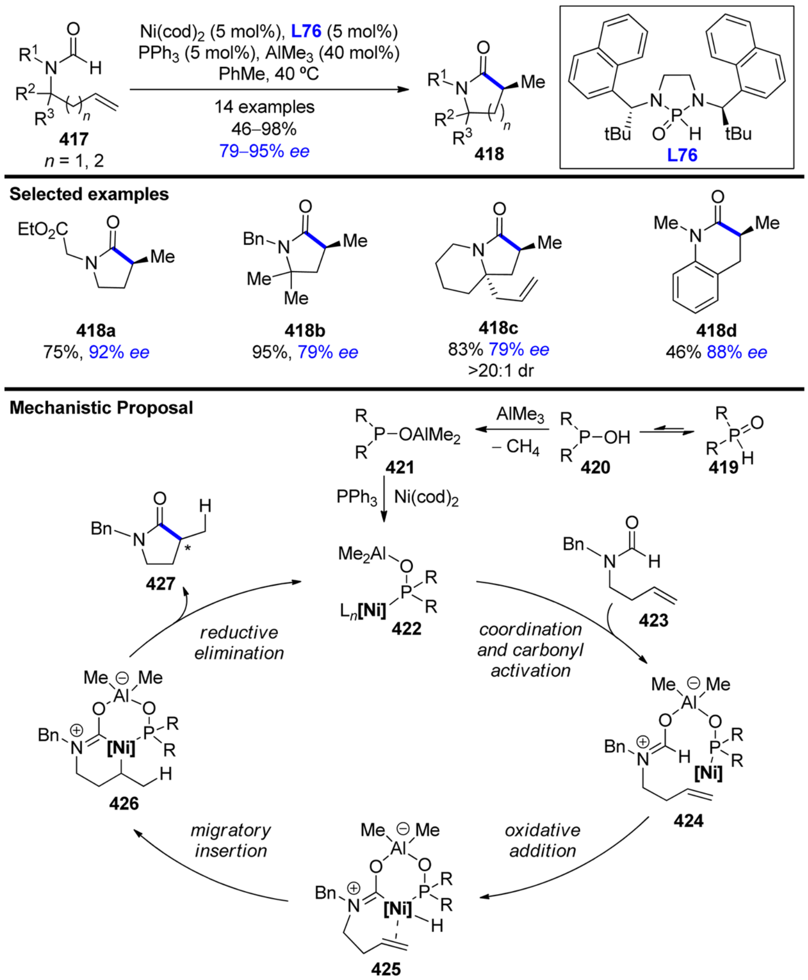
ligand is critical for promoting carboacylation versus isomerization/hydroacylation, with the former being favored by bisphosphine ligands with a larger value. β-Elimination then generates acyl–Rh(III) hydride **411**, which reductively eliminates to provide the chiral cyclohexenes **407**. The synthetic utility of this methodology was further demonstrated by the authors through elaboration of the products into various highly functionalized derivatives.

3.1.3. Aldiminium C–H Functionalization.

Recently, Coltart and co-workers disclosed a procedure for the enantioselective functionalization of aldiminium $C(sp^2)$–H bonds via the merger of organocatalysis and transition-metal catalysis, allowing a one-pot conversion of benzaldehydes **412** to indanones **413** in up to 89% yield and 88% ee (Scheme 92).[224] Asymmetric induction is achieved through employment of pyrrolidine derivative **Cat-9**, which is believed to condense with the aldehyde substrates to generate aldiminium species **414**. The

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908–8976

Scheme 93. Enantioselective Ni-Catalyzed Hydrocarbamoylation Approach to Pyrrolidones



authors propose that oxidative insertion of an achiral Rh species into the aldiminium C–H bond should be faster than the background reaction with the corresponding aldehyde, thus preferably generating metal complex **415**. Migratory insertion of the alkene moiety into the Rh–H bond delivers six-membered cyclo-rhodium intermediate **416**, and finally, reductive elimination and hydrolysis provide chiral indanones **413** and regenerate both the organic and transition-metal catalysts. Overall this transformation represents the same retrosynthetic disconnection as the enantioselective hydroacylation reaction (see Scheme 77 for closely related examples); however, this complementary approach replaces the more commonly employed chiral phosphine ligands with a chiral amine catalyst.

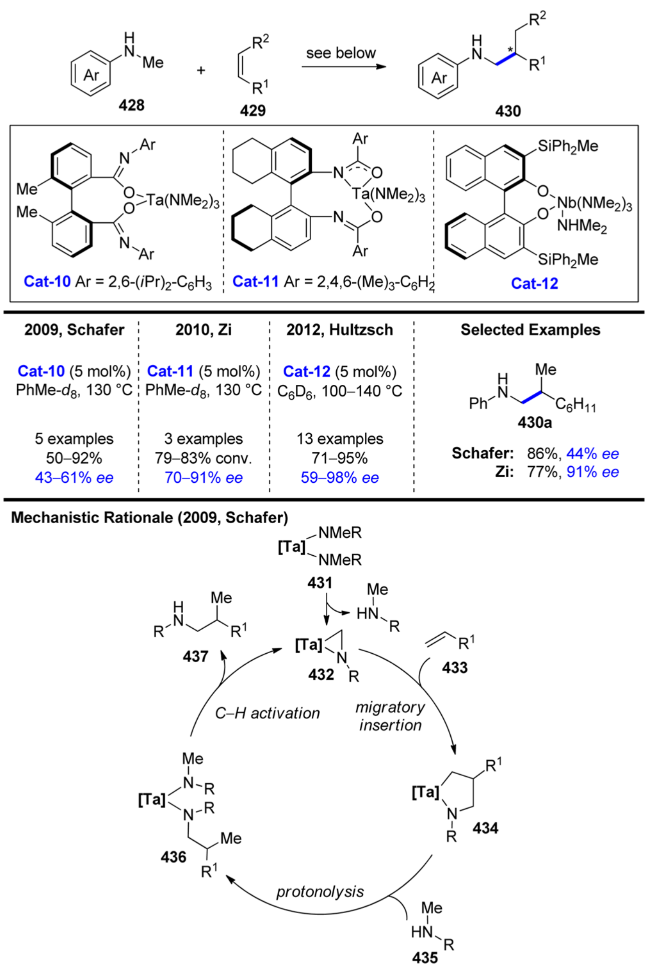
3.1.4. Formamide C–H Functionalization. Formamides are significantly less reactive than aldehydes toward transition-metal C–H insertion.[266] To date, only one enantioselective hydrocarbamoylation methodology has been reported, by Donets and Cramer in 2013, and it involves a nickel(0)/Lewis acid-catalyzed intramolecular functionalization of homoallylic formamides **417** (Scheme 93).[267] During the reaction development stage, an extensive screening of chiral phosphine ligands was undertaken. Only one entry provided the target material, a result that was eventually attributed to a phosphine oxide impurity acting as ligand, leading the authors to the development of a new class of air- and moisture-stable diaminophosphine oxide ligands **L76**. Under optimized conditions, the chiral pyrrolidones **418** could be accessed in up to 98% yield and 95% ee. Catalytic triphenylphosphine was necessary to assist with displacement of cod from the nickel center, and $AlMe_3$ serves as a Lewis acid to activate the formamide. A wide range of functionalized products could be accessed, including ester **418a**, *gem*-dimethyl derivative **418b**, *N*-fused bicycle **418c**, and six-membered ring analogue **418d**, although in this case competing *endo*-cyclization lowers the yield. Following various mechanistic experiments, Cramer et al. proposed that the reaction begins with complexation of the phosphine oxide **420** with $AlMe_3$ via the alcohol of its tautomeric phosphinous acid form **419**. Complexation of phosphorus to Ni provides intermediate **422**, which then coordinates formamide **423**, while concurrently activating the carbonyl functionality. Oxidative addition of nickel into the C–H bond provides Ni(III)–hydride species **425**, followed by a stereochemistry-generating migratory insertion to metallacycle **426**. Finally, reductive elimination releases the hydrocarbamoylated product **427** and regenerates the Ni(0) catalyst.

3.2. C(sp^3)–H Functionalization

3.2.1. Hydroaminoalkylation. Enantioselective methodologies that involve the functionalization of C(sp^3)–H bonds via a stereochemistry-generating migratory insertion are rare. To the best of our knowledge, all reported examples involve a group 5 metal catalyzed α-alkylation of secondary amines **428** with olefinic coupling partners **429** to provide enantioenriched amines of general structure **430** (Scheme 94). Building upon

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908–8976

Scheme 94. Catalytic Enantioselective α-Alkylation of Secondary Amines with Group 5 Transition Metals



earlier achiral hydroaminoalkylation studies disclosed by Herzon and Hartwig,[268,269] Schafer and co-workers established that amidate−tantalum complexes were competent catalysts for the same transformation.[270] Extension to an asymmetric variant was made possible by preparation of biaryl derivative **Cat-10**, which was demonstrated to provide promising levels of enantioselectivity in preliminary investigations. The following year, Zi et al. reported that related tantalum−amidate **Cat-11** provided improved levels of enantiocontrol for several identical substrates (i.e., **430a**, 44% versus 91% ee).[271,272] More recently, the Hultzsch group discovered that niobium catalyst **Cat-12** was more reactive than its corresponding tantalum derivative, while comparable levels of enantiocontrol were maintained in most cases, enabling a library of chiral amines to be prepared in up to 98% ee.[273] Mechanistically, the hydroaminoalkylation is believed to proceed via a C−H activation of bis(amide) **431** to form metallaaziridine **432**. Migratory insertion of olefin **433** into the tantalum−carbon bond of **434**, followed by protonolysis with amine reagent **435**, yields intermediate **436**. Finally, C−H activation enables release of the product **437**, while regenerating metallaaziridine **432**.

4. OTHER STEREOCHEMISTRY-GENERATING STEPS

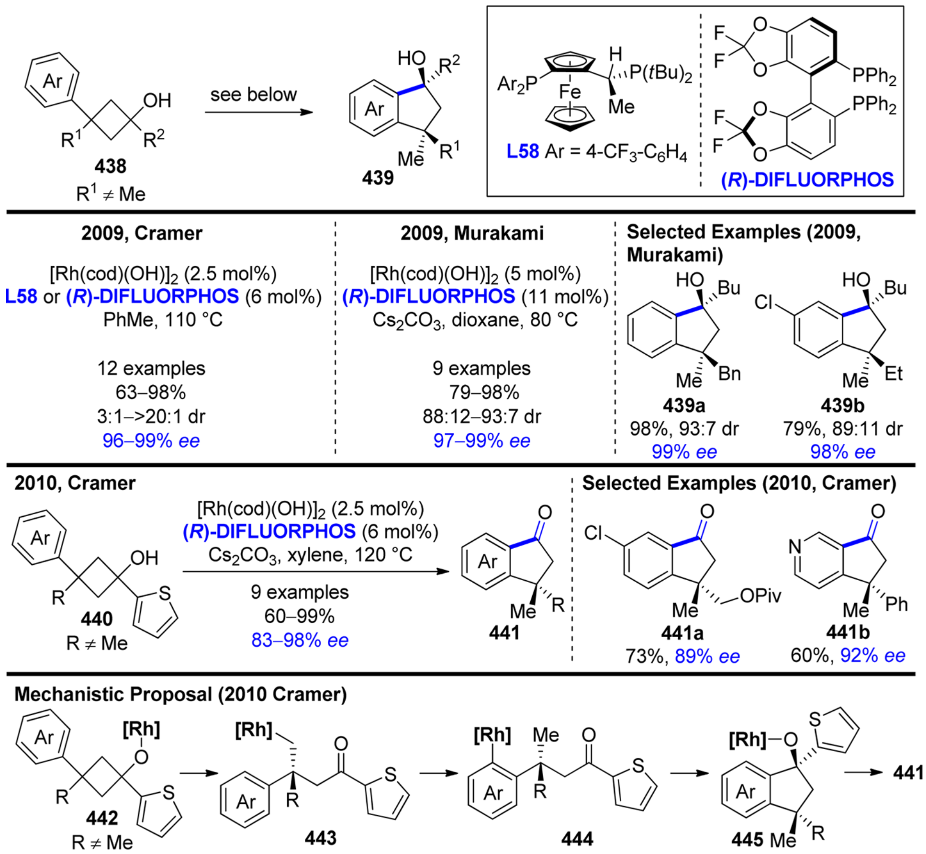
A small number of enantioselective C−H functionalization methodologies proceed via a stereochemistry-generating step that is neither a C−H activation nor migratory insertion. To the best of our knowledge, the first reported examples were disclosed as part of a Rh-catalyzed C−C/C−H bond activation sequence of *meso*-cyclobutanols **438**, published independently by the Cramer[143] and Murakami[144] groups in 2009 (Scheme 95). In this methodology, the selection of substituents dictates whether the migratory insertion or C−C activation is stereochemistry-generating. Specifically, when R^1 = Me, the former is stereochemistry-generating (discussed earlier in Scheme 54); however, this switches to the C−C activation for all other substituents. With regard to this second case (i.e., where $R^1 \neq$ Me), both research groups employed similar reaction conditions, namely, Josiphos-type ligand **L58** or (*R*)-DIFLUORPHOS, used in conjunction with $[Rh(cod)(OH)]_2$. The majority of examples proceeded in a highly diastereo- and enantioselective manner to yield indanols **439** bearing two quaternary stereocenters. Notably, the same catalyst system was found to provide high levels of enantiocontrol in cases where the migratory insertion was stereochemistry-generating. Representative examples from Murakami's work include benzyl-substituted derivative **439a** (accessed in 98% yield, 93:7 dr, and 99% ee) and aryl chloride **439b** (accessed in 79% yield, 89:11 dr, and 98% ee). The following year, Cramer et al. extended the reaction, enabling the conversion of 2-thiophenyl-substituted cyclobutanols **440** into functionalized indanones **441**,[274] again employing (*R*)-DIFLUORPHOS as the source of enantiocontrol. A variety of functional groups were tolerated under the reaction conditions, including pivalate-protected alcohol **441a** and pyridine derivative **441b**. The authors propose that the reaction proceeds in a manner similar to that of their earlier studies, beginning with a stereochemistry-generating *β*-carbon elimination of rhodium alkoxide **442** to generate alkyl−Rh species **443**. Following a 1,4-Rh shift to **444**, 1,2-addition to the carbonyl provides rhodium alkoxide **445**. However, rather than undergoing protonolysis, a second *β*-carbon elimination occurs to provide indanones **441**.

In 2014, the Tanaka group reported an enantioselective cycloisomerization of 1,6-enynes **446** as a route to enantiomerically enriched bicyclo[3.1.0]hexane derivatives **447** in 33−93% yield and 54−96% ee via employment of a cationic Rh(I)/(*S*)-SEGPHOS or (*S*)-DTBM-SEGPHOS complex with benzoic acid (Scheme 96).[275] Mechanistic studies, including the observation that the carbonyl groups on the enyne linkage are necessary for reactivity, led the authors to propose that the reaction proceeds via enantioselective oxidative coupling to generate rhodacyclopentene intermediate **448**, followed by protonation with benzoic acid to afford rhodium benzoate intermediate **449**. A carbonyl group at the linkage operates as a chelating group, facilitating C−H functionalization at the *γ*-C−H on the methylene group rather than on the R^2 group.

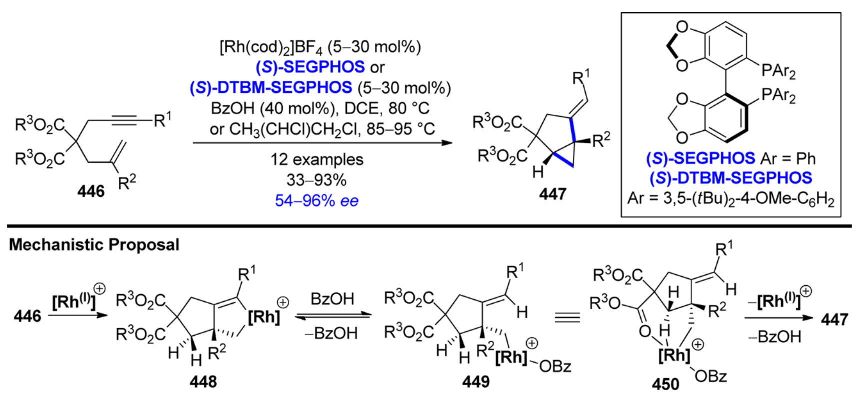
In 2016, the Cramer group reported the first, and currently only, example of an enantioselective Ni-catalyzed aryl C−H functionalization reaction (Scheme 97).[276] Novel C_2-symmetric NHC **L77** was found to provide modest-to-high levels of enantiocontrol (69−91% ee) and complete diastereocontrol for the three-component coupling of aromatic aldehydes **451**, norbornenes **452**, and silanes **453** (originally reported in a racemic fashion by Ogata, Fukuzawa, and their co-workers[277]). During reaction optimization studies, a variety of established NHC ligands were initially screened in the coupling of benzaldehyde, norbornene, and triisopropylsilane, including Kündig ligand **L78**,[278] Glorius's IBiox **L79**,[279] and Cramer's C_1-symmetric **L80**;[280] however, all furnished the target in only low yields and with poor selectivities. Promisingly, Grubbs's C_2-symmetric imidazolidin-2-ylidene **L81**[281] provided the corre-

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 95. Stereochemistry-Generating C−C Activations of Cyclobutanols To Yield Chiral Indanols or Indanones



Scheme 96. Rhodium-Catalyzed Enantioselective Cycloisomerization of 1,6-Enynes to Bicyclo[3.1.0]hexanes



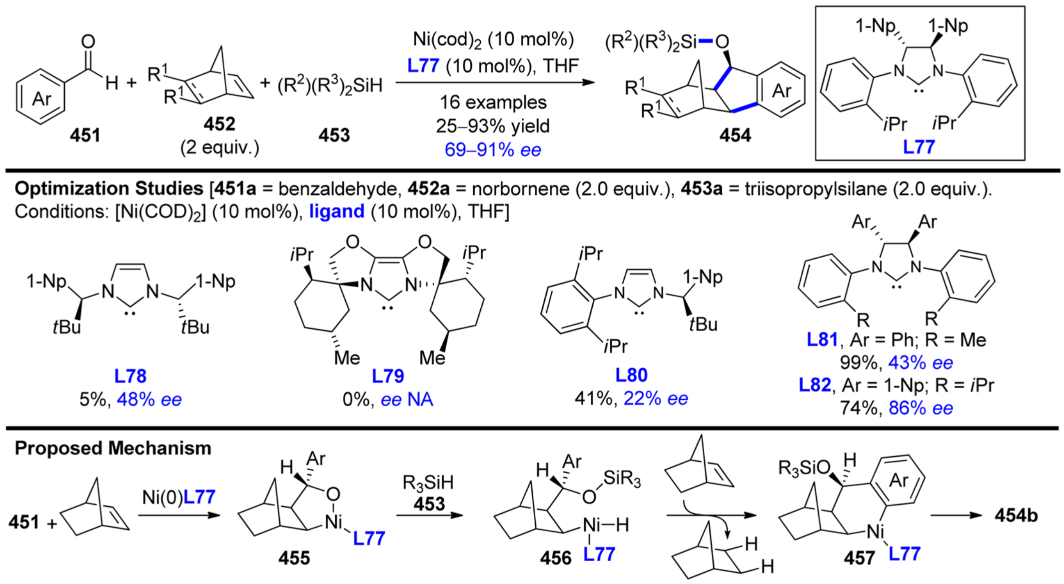
sponding silylated indanol **454a** in 99% yield and 43% ee. Further modification of this structure eventually identified iPr/1-naphthyl derivative **L82** as optimal, enabling isolation of the target in 74% yield and 86% ee. On the basis of the racemic report by Ogata, Fukuzawa, and their co-workers,[277] the authors propose that the reaction proceeds via a stereochemistry-generating and enantiodetermining oxidative cyclization of aromatic aldehydes **451** with norbornene to form oxanickelacycle species **455**, followed by σ-bond metathesis with silane **453** to generate nickel−hydride **456**. Hydrometalation of a second equivalent of norbornene, intramolecular aryl C−H activation, and release of norbornane form cyclometalated intermediate **457**, and finally, reductive elimination provides the product **454b** and regenerates the active Ni(0) catalyst.

5. AMBIGUOUS OR UNKNOWN STEREOCHEMISTRY-GENERATING STEPS

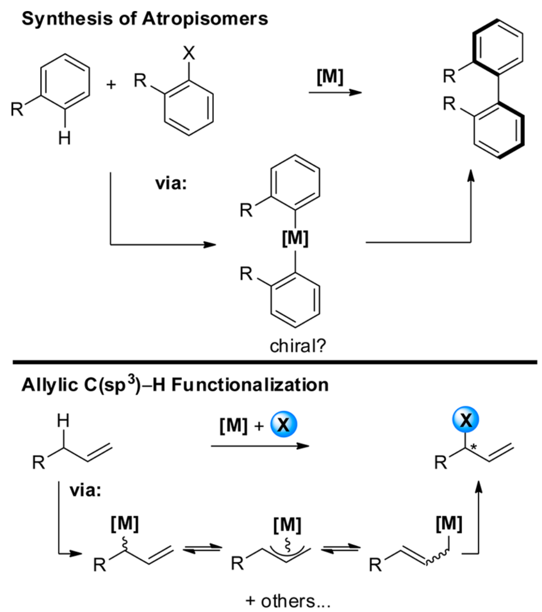
In the case of methodologies where the stereochemical nature of reaction intermediates is ambiguous or unknown, it can become difficult to identify which mechanistic step is stereochemistry-generating without detailed experimental and/or computational investigations. Within the context of this review, two classes of transformation fall into this category: the synthesis of atropisomers, and allylic C(sp^3)−H functionalization reactions (Scheme 98). In the former case, the configurational stability of any intermediates must be considered. If they interconvert quickly, then they may best be considered as achiral. With regard to the latter class of transformation, the stereochemical nature of π-allyl species is highly dependent on the metal, ligand, substrate, and specific reaction conditions; thus, it is difficult to generalize

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 97. Nickel-Catalyzed Enantioselective Three-Component Coupling



Scheme 98. Classes of Transformations with an Ambiguous or Unknown Stereochemistry-Generating Step



about what stereochemical information may be imparted during the C−H activation event.[282−284]

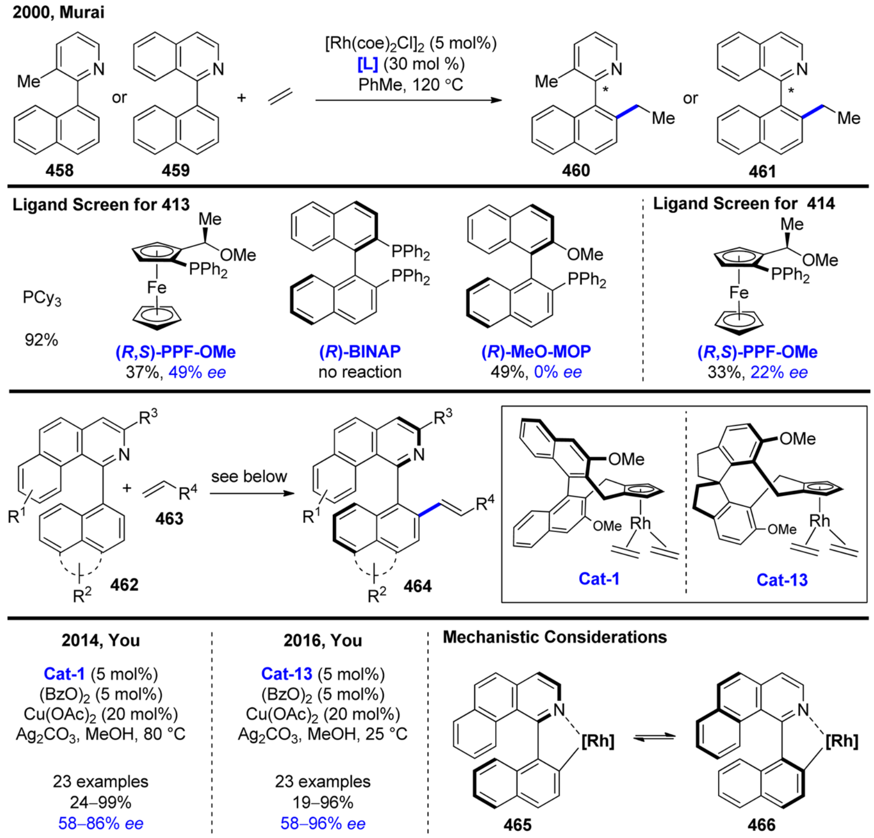
5.1. Synthesis of Atropisomers

Several *N*-heteroaromatic-directed C−H functionalization approaches to biaryl atropisomers have been reported (Scheme 99). The first example, disclosed by Murai and co-workers in 2000, involved a Rh(I)-catalyzed atropo-enantioselective alkylation of naphthalenes **458**, yielding the axially chiral products **460**, and proceeds via oxidative addition to generate a Rh−hydride intermediate, followed by a migratory insertion/reductive elimination sequence.[285] Although the reaction proceeded well with tricyclohexylphosphine, only a low yield and moderate ee was observed with Josiphos-type ligand (*R*,*S*)-PPF-OME. Moreover, (*R*)-BINAP failed to react, and monophosphine (*R*)-MeO-MOP provided racemic products. Shifting to quinoline derivative **459** proved detrimental, and a lower yield and enantioselectivity was observed for the product **461**. In 2014, Zheng and You demonstrated that this class of reaction could be rendered highly enantioselective by employing chiral cyclopentadienyl complexes Cp^X. Substituted benzo[*h*]isoquinolines **462** were alkenylated with various terminal alkenes **463**, employing BINOL-derived Rh complex **Cat-1** and a mixture of $Cu(OAc)_2$ and Ag_2CO_3 as oxidants. In contrast to the procedure developed by Murai, this reaction proceeds via a Rh(III)-catalyzed oxidative alkenylation. The atropisomeric products **464** were accessed in good yields and enantioselectivities (up to 99% yield and up to 86% ee).[286] Two years later, You and co-workers disclosed the development of a new SPINOL-derived Rh complex **Cat-13**. This was benchmarked in the same reaction and provided slightly increased enantioselectivities under the same conditions. After additional optimization, the reaction was conducted at lower temperature, providing the alkylated products **464** in up to 96% ee. Notably, for all three of these methodologies, the configurational stability of the starting materials was not disclosed; thus, whether these reactions can be considered as dynamic kinetic resolutions is unclear (kinetic resolutions covered later in section 7). If the configurational stability of the starting materials is sufficiently low so that the two enantiomeric forms interconvert quickly at room temperature, then perhaps they are best described as achiral molecules. Despite this, their enantioselective functionalization may still involve the selective recognition of one enantiomeric conformation by a chiral catalyst, conceptually emulating a dynamic kinetic resolution. Alternatively, the reaction may be better described as a dynamic kinetic asymmetric transformation (DYKAT),[287,288] in which interconversion of diastereomeric intermediates occurs (e.g., **465** to **466**); however, as yet no mechanistic studies have been published.

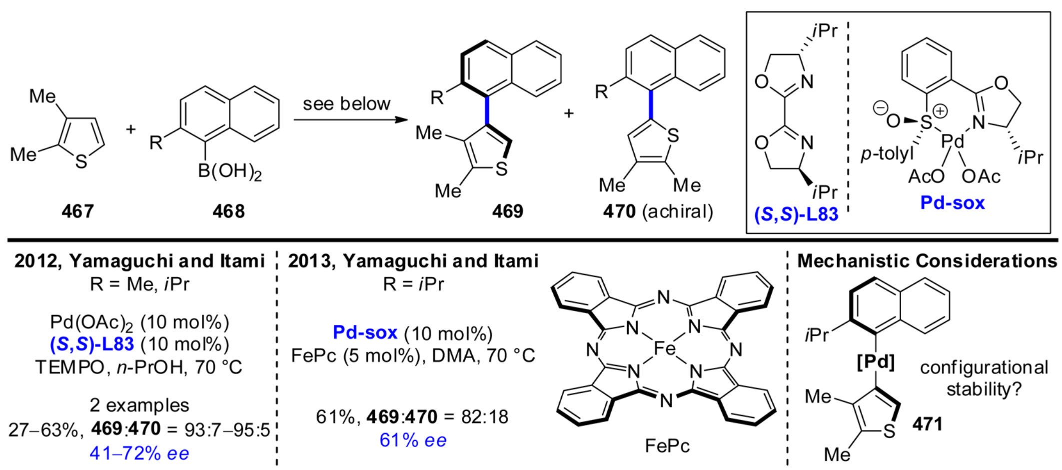
In 2012 and 2013, Yamaguchi, Itami, and their co-workers disclosed Pd-catalyzed procedures for the synthesis of hindered biaryls (Scheme 100). Both sets of conditions were applied to the atropo-enantioselective C−H arylation of thiophene derivative **467** with arylboronic acids **468**, providing a mixture of regioisomeric biaryls **469** and **470**. In their earlier disclosed paper, bisoxazoline **L83** was employed as chiral ligand with a Pd(II) source, and TEMPO served as a stoichiometric

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 99. Rh-Catalyzed Enantioselective C−H Functionalization of Biaryl *N*-Heterocycles



Scheme 100. Pd-Catalyzed Atropo-Enantioselective Biaryl Coupling via C−H Functionalization



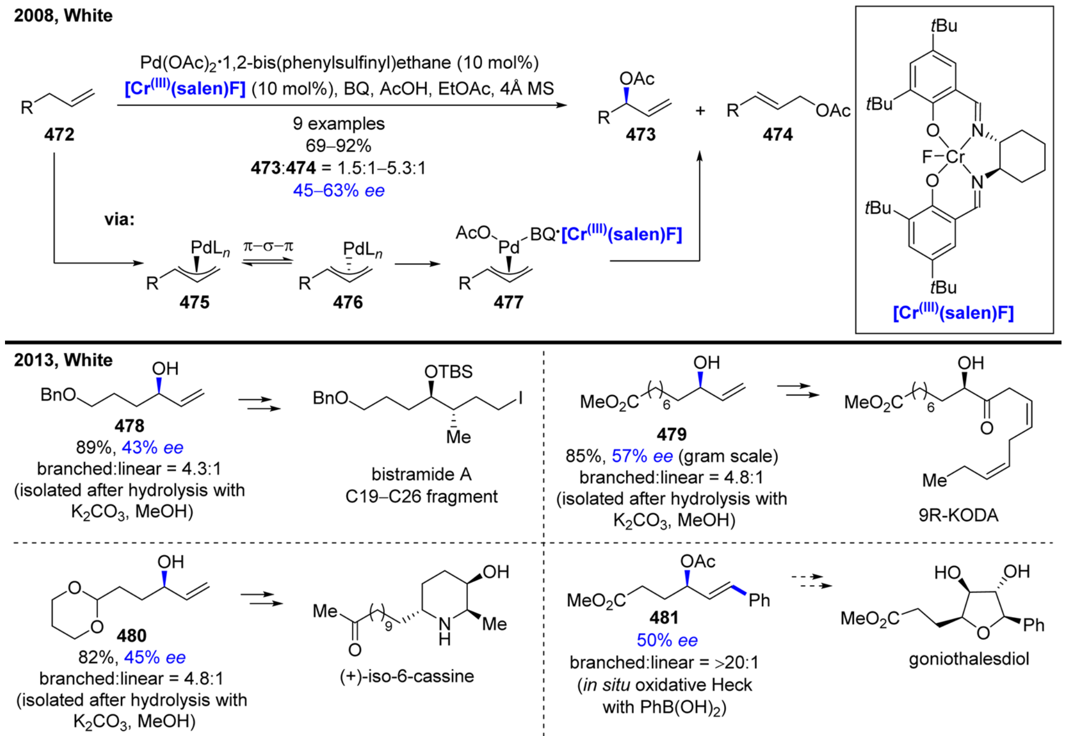
oxidant.[289] When (2-methylnaphthalen-1-yl)boronic acid (**468a**, where R = Me) was used as coupling partner, the reaction proceeded in 63% yield (**469a**:**470a** = 95:5) and in 41% ee. Changing to (2-isopropylnaphthalen-1-yl)boronic acid (**468b**, where R = *i*Pr) resulted in a reduced 27% yield (**469b**:**470b** = 93:7) but an improved 72% ee. The following year, Yamaguchi, Itami, and their co-workers demonstrated that under aerobic oxidative conditions, in this case using Pd−sox and iron−phthalocyanine (FePc), the corresponding *i*Pr derivative could be accessed in 61% yield (**469b**:**470b** = 82:18) and 61% ee.[290] Without additional mechanistic studies, we are unable to comment on which step of the catalytic cycle is stereochemistry-generating, as the configurational stability of reaction intermediates, such as organopalladium species **471**, has not been reported.

5.2. Allylic C(sp^3)−H Functionalization

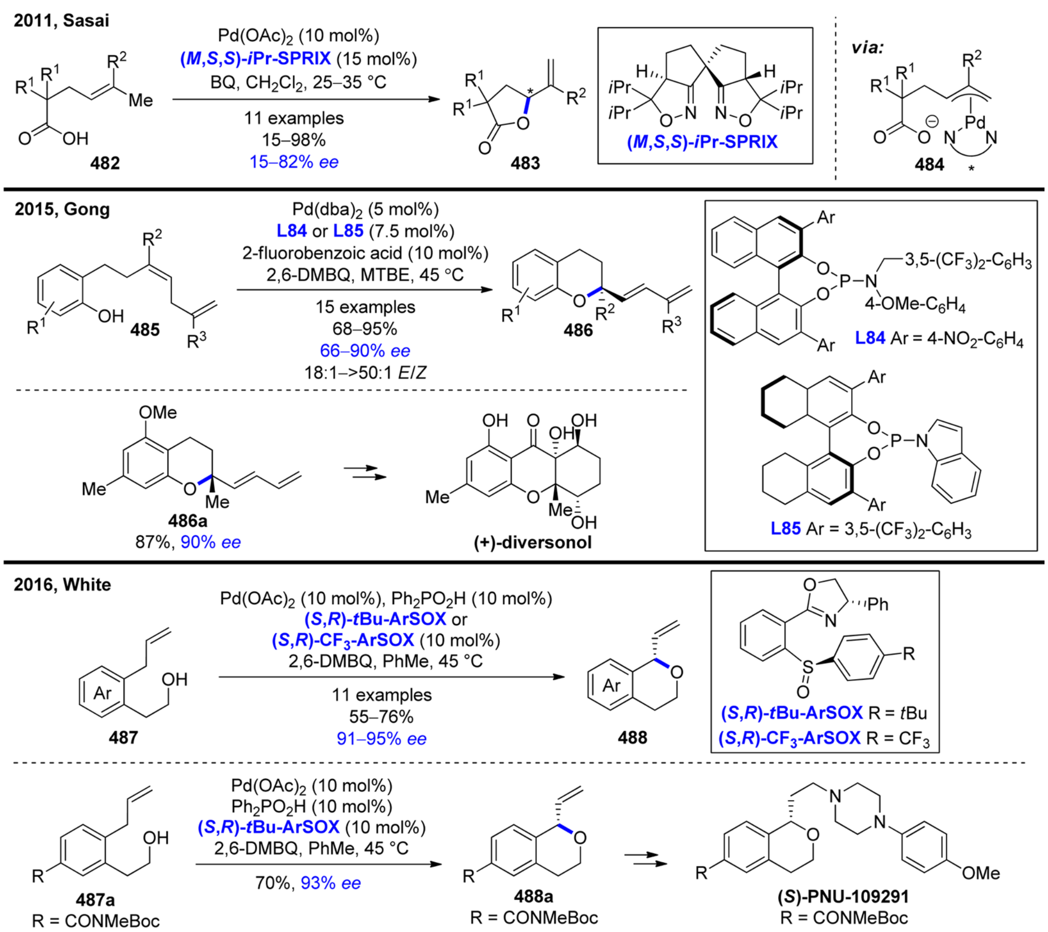
The copper-catalyzed oxidation of allylic C(sp^3)−H bonds with peresters (the Kharasch−Sosnovsky reaction) was the first allylic C(sp^3)−H functionalization reaction to be conducted in an asymmetric fashion. Although this methodology has been covered in detail elsewhere[16,20,21] and is thus beyond the scope of this review, for comparative purposes we feel it worthwhile to mentioned that good levels of enantiocontrol have only been achieved using an excess of symmetrical cyclic olefins,[291] and as such, much attention has been devoted to the development of alternative protocols.

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 101. First Pd-Catalyzed Enantioselective Allylic C(sp^3)−H Functionalization Reaction and Its Applications in Synthesis



Scheme 102. C−O Bond Formation *via* Pd-Catalyzed Enantioselective Allylic C(sp^3)−H Functionalization



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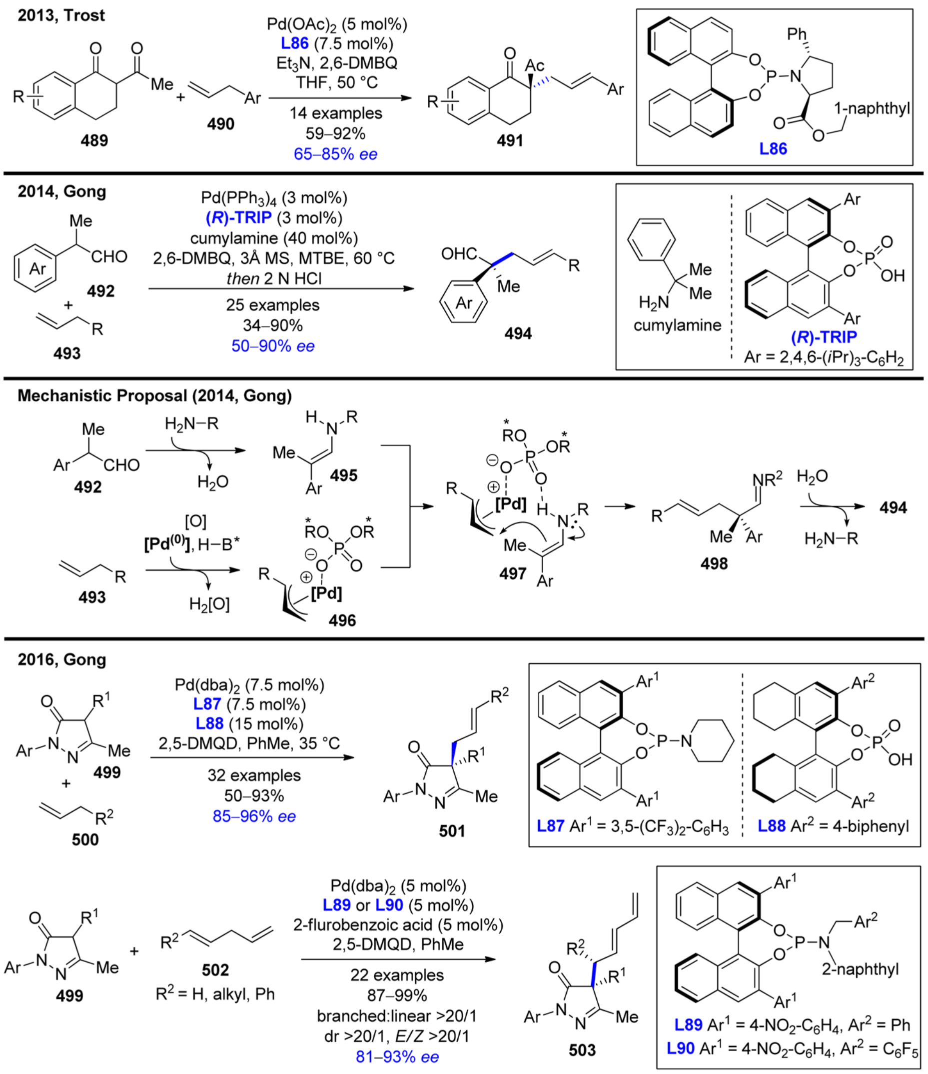
Chem. Rev. 2017, 117, 8908−8976

Scheme 103. C−C Bond Formation via Pd-Catalyzed Enantioselective Allylic C(sp^3)−H Functionalization



5.2.1. Palladium Catalysis.

In 2008, the White group disclosed the first Pd-catalyzed enantioselective allylic C(sp^3)−H activation of terminal alkenes (Scheme 101).[292] Initial attempts to conduct an acetoxylation of olefins **472** with chiral sulfoxide ligands, under palladium catalysis, proved to be ineffective due to the rapid $\pi-\sigma-\pi$ equilibrium between the π-allyl−Pd intermediates **475** and **476**, thus scrambling any chiral information that may be imparted during C−H cleavage. The authors postulated that a chiral Lewis acid cocatalyst may influence the stereochemical outcome of the reaction, while simultaneously accelerating bond formation.[293−296] Following a screening of established chiral Lewis acids and subsequent optimization studies, the addition of [Cr(III)(salen)F] as cocatalyst enabled the synthesis of allylic esters **473** in good yields (69−92%), and although only moderate enantioselectivities were obtained (45−63% ee), subsequent enantioenrichment could be achieved through enzymatic kinetic resolution. Control experiments demonstrated that functionalization does not occur in the absence of benzoquinone (BQ), and further mechanistic investigations suggest that the reaction proceeds via reductive elimination of acetate in activated intermediate **477**. Notably, this report represents the first example of asymmetric induction by a chiral Lewis cocatalyst with an organometallic intermediate, as well as one of the earliest Pd-catalyzed enantioselective C−H functionalization reactions. Several years later, the White group demonstrated the value of this methodology via its application in the synthesis of oxygenated chiral building blocks.[297] Benzyl ether **478**, methyl ester **479**, and cyclic ketal **480** were all synthesized in good yield and moderate ee (measured following acetate hydrolysis). The enantiopurity of each could be enhanced to 99% ee through enzymatic resolution, thus providing known intermediates from previously disclosed total syntheses of bistramide A,[298] 9R-KODA,[299] and (+)-iso-6-cassine.[300] In the case of phenyl-substituted derivative **481**, the White group demonstrated that a one-pot allylic oxidation/oxidative Heck process was feasible via the successive addition of reagents. In this case, enantiopurity was enhanced through a Sharpless asymmetric dihydroxylation protocol, ultimately leading to a proposed precursor to goniothalesdiol.

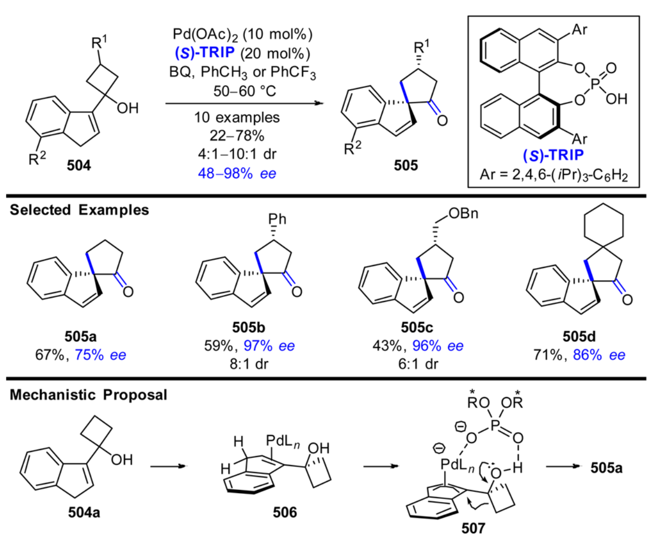
Several allylic C(sp^3)−H functionalization methodologies that proceed via intramolecular trapping of a π-allyl−Pd species with an oxygen-based nucleophile have been reported (Scheme 102). The first example was disclosed by the Sasai group in 2011 and involved the cyclization of 4-alkenyl acids **482**, facilitated by (M,S,S)-iPr-SPRIX and a Pd(II) source, leading to enantioenriched γ-lactones **483** in up to 82% ee.[301] A Thorpe−Ingold effect was necessary for good levels of enantiocontrol, and the reaction was observed to be highly sensitive toward the steric

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

environment of the olefin moiety. On the basis of preliminary mechanistic experiments, including the discovery of a kinetic isotope effect comparable in value to other reactions involving π-allyl−Pd intermediates,[302,303] the authors propose that the reaction proceeds via allylic C−H bond activation to generate π-allyl−Pd complex **484**, as opposed to a more traditional Wacker-type process. In 2015, Gong and co-workers accomplished the C−H activation/cyclization of phenols **485**, enabled by cooperative catalysis of a chiral palladium complex and an achiral Brønsted acid.[304] Chiral chromans **486**, a common motif in biologically active natural products, were synthesized in 68−95% yield and 66−90% ee, with excellent levels of *E*/*Z*-selectivity. Axially chiral phosphoramidites **L84** and **L85** provided the best levels of enantiocontrol, when used in conjunction with 2-fluorobenzoic acid as cocatalyst. Interestingly, omission of 2-fluorobenzoic acid still resulted in high yields, but a significant reduction in enantioselectivity was observed. A small library of functionalized products was prepared, including electron-rich chroman **486a**, which was subsequently converted into an intermediate from Nicolaou and Li's 2008 synthesis of (+)-diversonol.[305] As with the earlier described study by Sasai and co-workers, mechanistic experiments suggest an allylic C−H activation pathway rather than a Wacker-type mechanism. Most recently, the White group reported a highly enantioselective synthesis of isochromans **488** (91−95% ee) via a Pd(II)-catalyzed intramolecular allylic C−H functionalization reaction.[306] Drawing inspiration from their earlier disclosed racemic studies,[307] as well as their enantioselective allylic C(sp^3)−H acetoxylation protocol (demonstrated earlier in Scheme 101),[292] the authors speculated that ligands incorporating a coordinating sulfoxide to promote C−H bond cleavage,[307] as well the π-acidic/σ-donor properties of an oxazoline to mimic the role of BQ,[292] may provide a new approach to control the enantioselectivity of allylic C(sp^3)−H functionalization reactions. After extensive ligand optimization studies, diarylated sulfoxide-oxazolines (*S*,*R*)-*t*Bu-ArSOX and (*S*,*R*)-CF_3-ArSOX were observed to provide excellent levels of enantiocontrol. Interestingly, in contrast to Gong and co-workers' 2015 study,[304] the Brønsted acid additive (in this case Ph_2PO_2H) was found to significantly improve the yield of the reaction, but it had little influence on the enantioselectivity of the process. The reaction exhibited a broad functional group tolerance with regard to aryl substituents. For example, amide **487a** could be cyclized in 70% yield and 93% ee, despite the potential for palladium chelation. The resultant vinylisochroman **488a** was subsequently converted, in short order, to $5HT_{1D}$ agonist (*S*)-PNU-109291. Mechanistic studies indicated that the reaction proceeds through an allylic C−H activation process and that the functionalization step is enantiodetermining. Notably, earlier attempts by Liu, Itami, and their co-workers to induce asymmetry in an allylic C(sp^3)−H intermolecular carboxylation of terminal alkenes, under similar conditions with diarylated sulfoxide-oxazoline ligands, proved unsuccessful (<5% ee).[308]

Palladium-catalyzed allylic C(sp^3)−H functionalization reactions have also been employed to generate C−C bonds (Scheme 103). In 2013, Trost et al. reported the coupling of 2-acetyltetralones **489** with allylarenes **490**, furnishing the corresponding alkylated products **491**, bearing a quaternary stereocenter, in moderate to good yields and enantioselectivities.[309] Initial screenings of known chiral mono- and bidentate phosphorus ligands that have found success in analogous enantioselective transformations were met with failure, prompting the authors to explore the development of novel phosphoramidite derivatives. Ultimately, BINOL/pyroglutamic acid-derived ligand **L86**, when used in combination with $Pd(OAc)_2$, Et_3N, and 2,6-dimethoxybenzoquinone (2,6-DMBQ), provided the enantioenriched alkylated products in 65−85% ee. Notably, the Trost group has since demonstrated that their newly developed non-C_2-symmetric ligands are also suitable for application in other transition-metal-catalyzed processes.[310] Drawing inspiration from the work of List et al.,[311,312] Gong and co-workers successfully combined asymmetric counterion catalysis with palladium-catalyzed allylic C(sp^3)−H functionalization, enabling α-allylation of aldehydes **492** with terminal olefins **493**.[313] Employing DMBQ as a stoichiometric oxidant, in the presence of catalytic quantities of $Pd(PPh_3)_4$, (*R*)-TRIP, and cumylamine, enantioenriched aldehydes **494** were accessed in 34−90% yield and 50−90% ee. The reaction was proposed to proceed via Schiff base condensation of cumylamine with aromatic aldehydes **492** to yield enamines **495**. Concurrent oxidation of terminal alkenes **493**, in the presence of a Pd(0) source and a chiral phosphoric acid, generates cationic π-allylpalladium species **496**. Nucleophilic addition of the enamine onto the π-allyl species within the coordination sphere of chiral phosphate anion (via **497**) constructs the all-carbon quaternary stereocenter of **498**, which subsequently undergoes hydrolysis to release the target aldehydes **494**. Notably, this methodology is complementary to List's earlier disclosed aldehyde α-allylation procedures in which the cationic π-allylpalladium species were generated via either C−N[311] or C−O[312] bond activation. More recently, Gong and co-workers successfully realized an asymmetric allylic C−H alkylation of pyrazol-5-ones **499** with terminal olefins **500** under the cooperative catalysis of a palladium−phosphoramidite **L87** complex and Brønsted acid **L88**.[314] The chiral catalysts were demonstrated to exhibit a significant synergistic effect on the stereochemical outcome of the transformation, providing linear pyrazol-5-ones **501**, bearing an all-carbon quaternary stereogenic center, in moderate to excellent yields and in up to 96% ee. In addition, the authors demonstrated that chiral BINOL-derived phosphoramidite ligands **L89** or **L90** allowed 1,4-pentadienes **502** as coupling partners, leading in this case to branched products **503** with excellent *E*/*Z*-selectivity and diastereo- and enantioselectivities.

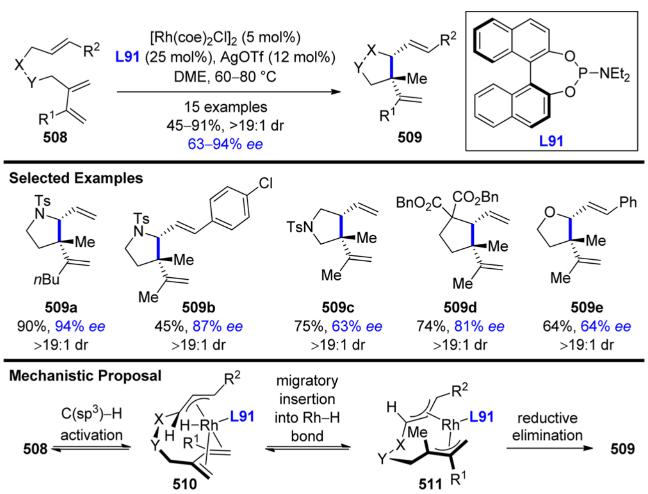
Scheme 104. Pd(II)/Brønsted Acid-Catalyzed Allylic C(sp^3)−H Activation/Semipinacol Rearrangement of Cyclobutanols



DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

In 2012, Chai and Rainey described a Pd(II)/Brønsted acid-catalyzed allylic C−H activation route to compounds containing a stereogenic spirocyclic carbon center (Scheme 104).[315] Under optimized conditions, cyclobutanols **504** could be transformed into spirocyclic indenes **505** in 22−78% yield and in moderate to good diastereo- and enantioselectivity. During the reaction development stages, several neutral and cationic Pd(II) complexes were screened in combination with chiral oxazoline ligands; however, only low yields and selectivities were obtained. In attempts to generate more reactive complexes, the authors screened a variety of chiral Brønsted acid cocatalysts, ultimately identifying (*S*)-TRIP as a competent means of controlling the enantioselectivity of the reaction. BQ was employed as a stoichiometric oxidant, and noncoordinating solvents proved critical for achieving high levels of enantiocontrol. Selected examples from their study include parent substrate **504a**, phenyl- and OBn-substituted derivatives **505b** and **505c**, and tetracycle **505d** that bears two spirocyclic carbons. On the basis of mechanistic studies, the authors propose a tentative mechanism whereby cyclobutanol **504a** complexes with palladium to form **506**, which subsequently undergoes a rate-limiting C−H activation to π-allyl−Pd complex **507**. In this intermediate, the chiral phosphoric acid may behave as a counteranion, as proposed by Mukherjee and List in their aldehyde α-allylation

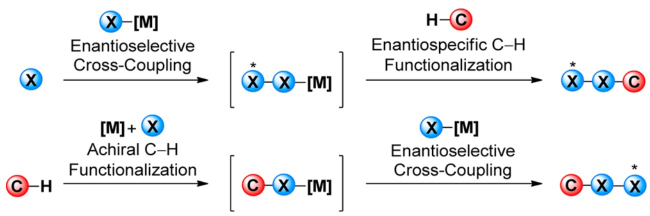
Scheme 105. Rh(I)-Catalyzed Enantioselective Allylic C(sp^3)−H Activations/Cyclization



studies.[311] A semipinacol ring expansion yields product **505a** and generates a Pd(0) species, which is reoxidized to Pd(II) by BQ.

5.2.2. Rhodium Catalysis. In 2011, Li and Yu successfully developed an enantioselective variant[316] of their earlier disclosed[317] racemic Rh(I)-catalyzed allylic C(sp^3)−H activation/intramolecular cyclization of trienes **508** (Scheme 105). Initial ligand screening studies observed that chelating BINAP diphosphines inhibited the reaction, but a change to monodentate phosphoramidites gave promising yields and selectivities. Diethylamine derivative **L91** was found to provide the highest level of enantiocontrol, and following further reaction optimization, cyclized derivatives of general structure **509**, bearing a quaternary all-carbon stereocenter, could be isolated in up to 91% yield, >19:1 dr, and up to 94% ee. Several different functionalized frameworks could be accessed with this methodology, including pyrrolidines **509a**−**509c**, cyclopentane **509d**, and tetrahydrofuran **509e**. The following year, Li and Yu published a detailed computational study exploring the mechanism of the transformation.[318] DFT calculations indicated that the reaction proceeds via a reversible diene-directed allylic C(sp^3)−H activation to yield intermediate **510**, followed by migratory insertion into the Rh−H bond to generate bis-π-allylic Rh complex **511**. An irreversible *cis*-selective reductive elimination forges the C−C bond and releases the cyclized products. Notably, the value of these newly accessible frameworks has been demonstrated in part by Yu and co-workers through the application of tetrahydropyrrole **509a** as a chiral ligand in a highly enantioselective Rh(I)-catalyzed conjugate addition methodology.[319]

Scheme 106. Scope of One-Pot Sequential Transformations Covered in this Review



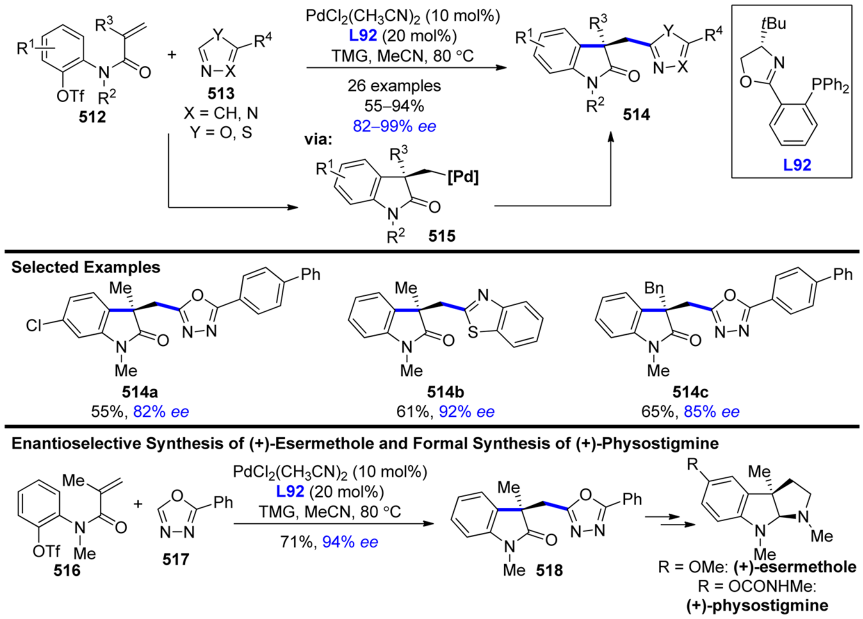
6. OTHER REACTIONS AS STEREOCHEMISTRY-GENERATING

One-pot sequential transformations have the potential to rapidly generate structural complexity in a remarkably efficient manner. Several reports combining an achiral or enantiospecific C−H functionalization reaction with a separate enantioselective transformation have been disclosed (Scheme 106). Conceptually, there are several ways to realize such a transformation; however, to best align this section with the rest of the review, we limit our study to only those examples where the same catalyst system is facilitating both the C−H functionalization and the enantioselective step. In addition, we have elected to exclude those examples where a discrete nonorganometallic intermediate is generated between steps. To the best of our knowledge, the majority of examples fall under this second classification and, as such, are beyond the scope of this review.[320,321]

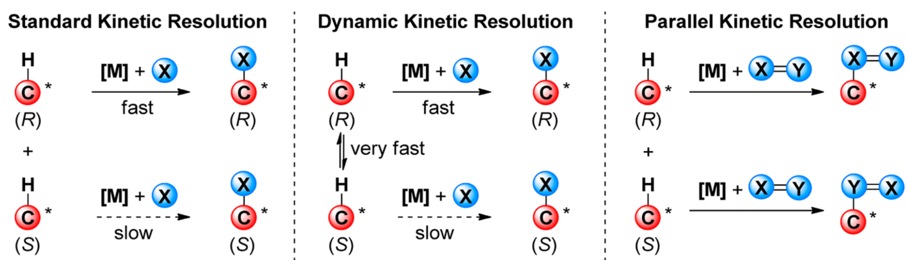
As far as we are aware, the only example that meets these conditions was published by Zhu and co-workers, in 2015, and proceeds via a palladium-catalyzed domino Heck/C−H functionalization pathway (Scheme 107).[322] *N*-Aryl acrylamides **512** could be efficiently cyclized and coupled with heteroarenes **513** to deliver oxindoles **514** in up to 94% yield and up to 99% ee, overall generating two carbon−carbon bonds and an all-carbon quaternary stereocenter. The reaction is believed to occur via an intramolecular enantioselective carbopalladation to generate σ-C(sp^3)−Pd complex **515**, followed by intermolecular trapping with the azole coupling partner. PHOX-type ligand **L92** proved optimal and was used in conjunction with TMG as base and $PdCl_2(CH_3CN)_2$ as palladium source. Various functional groups were well-tolerated, including aryl chlorides (**514a**), 2-aryloxadiazole (**514a** and **514c**), and benzothiazole (**514b**), and notably, benzyl-substituted derivative **514c** could be accessed without competing intramolecular C−H functionalization. The value of the enantioenriched oxindoles was demonstrated by their application in natural product synthesis. Aryl triflate **516** was successfully coupled with 2-phenyl-1,3,4-

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 107. Pd-Catalyzed Enantioselective Domino Heck/Intermolecular C−H Functionalization



Scheme 108. Classification of Kinetic Resolutions Incorporating a Transition-Metal-Catalyzed Enantioselective C−H Functionalization



oxadiazole (**517**) to generate enantioenriched indolin-2-one **518** in 71% yield and 94% ee. This was subsequently converted into (+)-esermethole, which in turn is an intermediate in an earlier reported synthesis of (+)-physostigmine, also conducted by the Zhu group.[323]

7. KINETIC RESOLUTIONS

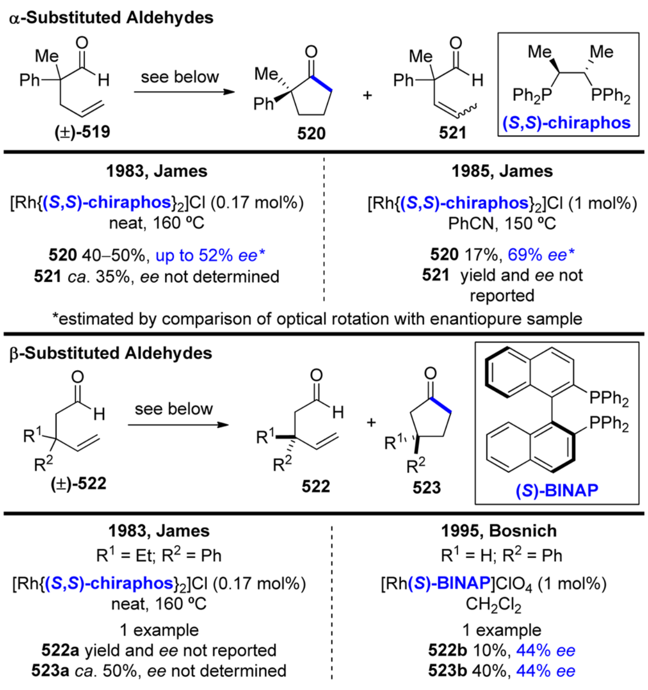
All methodologies discussed thus far have involved the preferential recognition of one prochiral functional group, or one enantiotopic face of a π-bond, by a chiral catalyst. Kinetic resolutions are conceptually distinct and require a chiral catalyst to interact differently with each enantiomer in a racemic mixture. Several resolution methodologies that incorporate a transition-metal-catalyzed C−H activation event have been developed, and these can be classified on the basis of the nature of the overall process (Scheme 108). A standard kinetic resolution relies upon different reaction rates of enantiomers in the same transformation. In an ideal case, a maximum 50% yield of unreacted enantiopure starting material and 50% yield of the enantiopure product is obtainable. Dynamic kinetic resolutions also rely upon different reaction rates of enantiomers; however, reactions of this type incorporate a process whereby the two enantiomeric substrates can interconvert rapidly. If this process is sufficiently faster than the functionalization reaction, a 100% yield of enantiopure material is theoretically obtainable. In contrast, a parallel kinetic resolution[324,325] takes advantage of differing regio-, chemo-, or stereoselectivity between enantiomers, producing two new nonenantiomeric products in a maximum 50% yield each (shown as a regiodivergent parallel kinetic resolution).

7.1. Standard Kinetic Resolutions

The earliest kinetic resolution methodologies involving a C−H activation process focused on the hydroacylation of chiral aldehydes with tethered alkenes (Scheme 109). The first example was disclosed by James and Young, in 1983, and to the best of our knowledge represents the first transition-metal-catalyzed enantioselective hydroacylation reaction.[326] The transformation was discovered fortuitously during attempts to decarbonylate 2-methyl-2-phenylpent-4-enal (**519**) with [Rh{(*S*,*S*)-chiraphos}$_2$]-Cl, neat, at 160 °C. Instead, enantioenriched cyclopentanone **520** was isolated in 40−50% yield and 52% ee (estimated by comparison of the optical rotation with that of an enantiopure sample), along with approximately a 35% yield of the isomerized starting material **521**. Two years later, James and Young reported that the reaction proceeded with a higher level of enantiocontrol when conducted in benzonitrile at 150 °C, although the cyclized product was obtained in only 17% yield.[327] In their earlier 1983 study, they also demonstrated the hydroacylation of β-substituted aldehyde 3-methyl-3-phenylpent-4-enal (**522a**, where R^1 = Et, R^2 = Ph), thus eliminating the potential for alkene isomerization. Although an optically active product was obtained, the ee was not determined.[326] The Bosnich research group later disclosed a related reaction, in this case reacting 3-

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 109. First Kinetic Resolutions Incorporating a Transition-Metal-Catalyzed C−H Activation

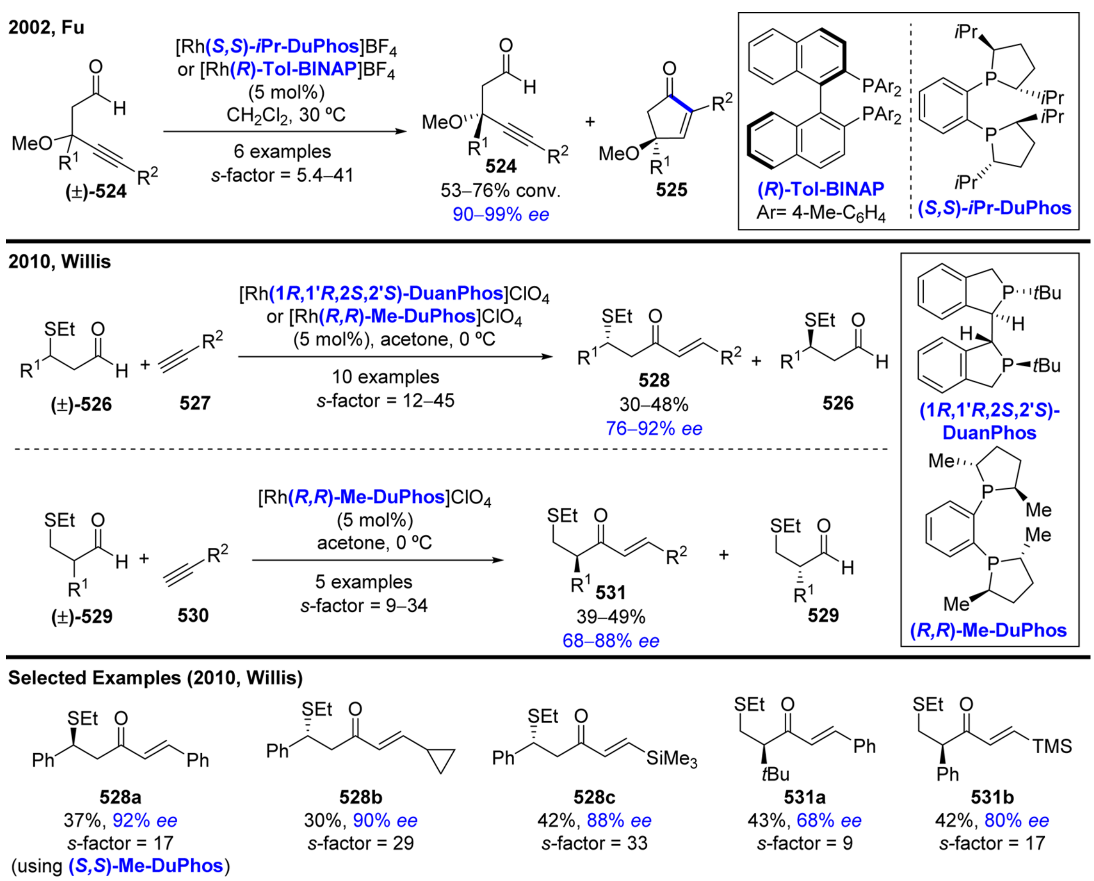


phenylpent-4-enal (**522b**, where R^1 = H, R^2 = Ph) with a more reactive cationic Rh(I)−BINAP complex. As with the earlier study by James and Young, unproductive olefin isomerization was the major competitive pathway. Despite this, enantioenriched staring material was isolated in 10% yield and 44% ee, and the cyclized product (*R*)-3-phenylcyclopentanone (**523b**, where R^1 = H, R^2 = Ph) was isolated in 44% yield and 44% ee.

Two research groups have since disclosed hydroacylation reactions incorporating an alkyne coupling partner (Scheme 110). In 2002, Tanaka and Fu demonstrated the kinetic resolution of 4-alkynals **524**, employing chiral rhodium complexes derived from either (*S,S*)-*i*Pr-DuPhos or (*R*)-Tol-BINAP.[246] The former ligand was best-suited for substrates bearing a tertiary stereocenter (where R = H) and the latter for those with a quaternary stereocenter (R ≠ H). The enantiopurity of the recovered aldehydes **524** ranged from 90 to 99% ee, with 53−76% conversion (the enantiopurity of cyclized products **525** was not disclosed). In the same study, the enantioselective desymmetrization of achiral diynes was also accomplished (Scheme 84). An intermolecular alkyne hydroacylation was later reported by the Willis group in 2010.[328] *β*-Ethylthio substituted aldehydes **526** were reacted with terminal alkynes **527**, providing the corresponding *α*,*β*-unsaturated ketones **528** in up to 48% yield and 92% ee. These conditions were also suitable for *β*-ethylthio-substituted aldehydes **529**, although lower enantioselectivities for the formation of the corresponding hydroacylated products **531** were generally observed. The Willis group demonstrated that various alkyne substituents were tolerated, enabling the synthesis of *α*,*β*-unsaturated ketone derivatives incorporating conjugated aromatic (**528a** and **531a**), alkyl (**528b**), and trimethylsilyl (**528c** and **531b**) functionality.

Kinetic resolution by means of aryl C−H functionalization has recently been achieved. The two earliest reports apply catalytic

Scheme 110. Kinetic Resolution via Hydroacylation of Alkynals



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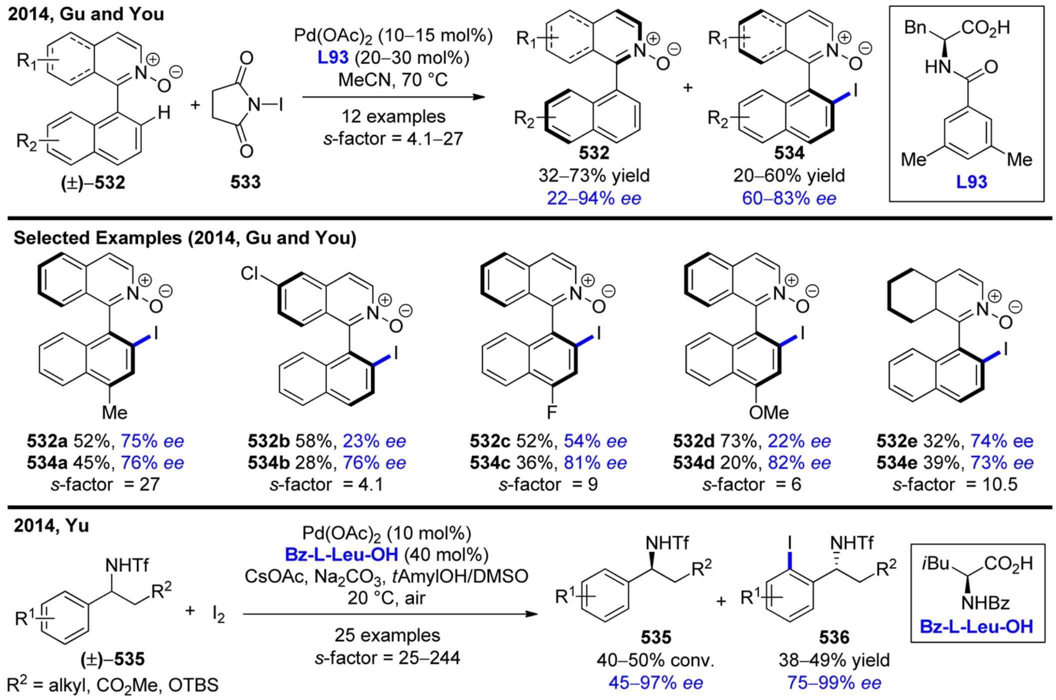
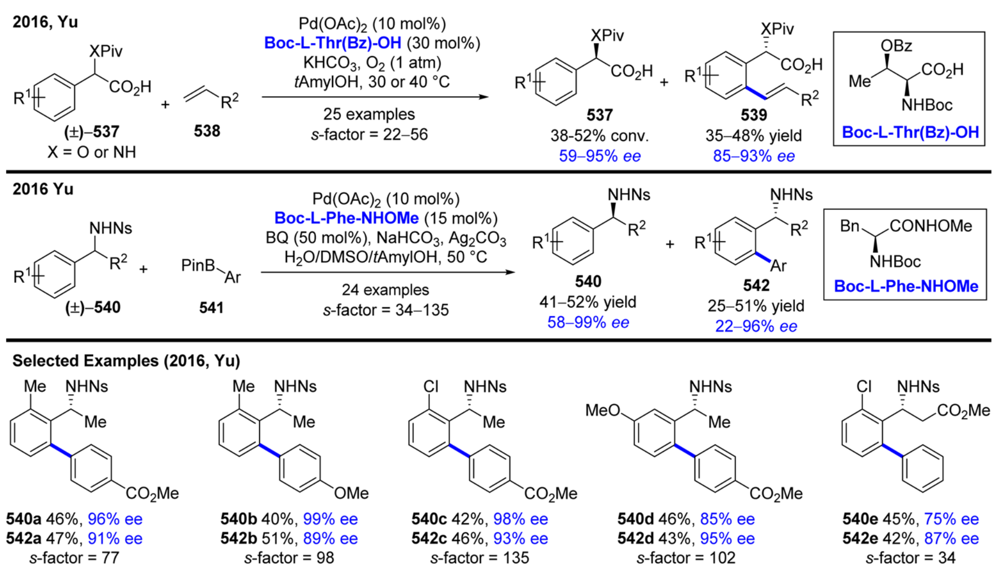
Scheme 111. Aryl C−H Iodination via a Pd-Catalyzed Kinetic Resolution



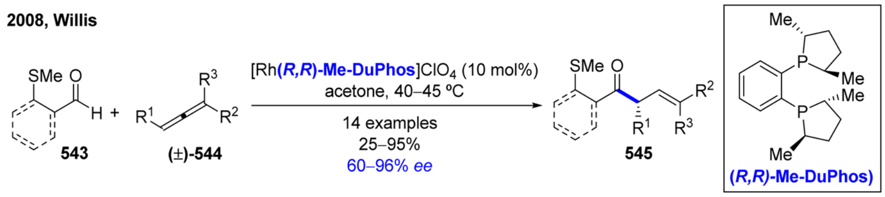
Scheme 112. Pd(II)/Pd(0)-Catalyzed Kinetic Resolution via Aryl C−H Functionalization



systems developed by the Yu group (introduced in sections 2.1.1.2 and 2.1.1.3), in a directed C−H iodination process (Scheme 111). In 2014, Gu, You, and their co-worker disclosed a kinetic resolution of axially chiral aryl isoquinoline *N*-oxides **532**, yielding enantioenriched iodinated biaryls **534**.[329] Following a brief screening of MPAA ligands, phenylalanine derivative **L93** provided the best selectivity, with *s*-factors ranging from 4.1 to 27 under optimized conditions. Methyl-substituted derivative **532a** provided the best selectivity (*s*-factor = 27), and aryl chloride (**532b**), aryl fluoride (**532c**), electron-rich (**532d**), and partially reduced substrates (**532e**) could all be accessed. Both the starting materials and products were found to be configurationally stable when held at 80 °C for 24 h, enabling C−I arylation of the products without reduction in enantiopurity. Later that same year, Yu and co-workers reported an exceptionally selective C−H iodination of benzylic amine derivatives **535** (*s*-factors up to 244).[330] By employing the MPAA ligand Bz-L-Leu-OH, at ambient temperature in the presence of a Pd(II) source, a variety of arylalkylamines, *β*-amino esters, and protected *β*-amino alcohols could be successfully resolved. With the exception of substrates containing bulky aryl substituents, the iodinated products **536** could be isolated with high levels of enantioselectivity (typically 91−97% ee), although notably, 40 mol % of chiral ligand is required to achieve high yields. The authors went on to demonstrate the utility of the functionalized products in a variety of transformations, including deprotection of the *N*-triflyl group, without any degree of racemization. A recent computational mechanistic study by Dang and co-workers proposed that the reaction proceeds through a Pd(II)/Pd(IV) catalytic cycle, rather than a Pd(II) redox-neutral mechanism.[331]

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 113. Intermolecular Hydroacylation of Allenes via a Dynamic Kinetic Resolution



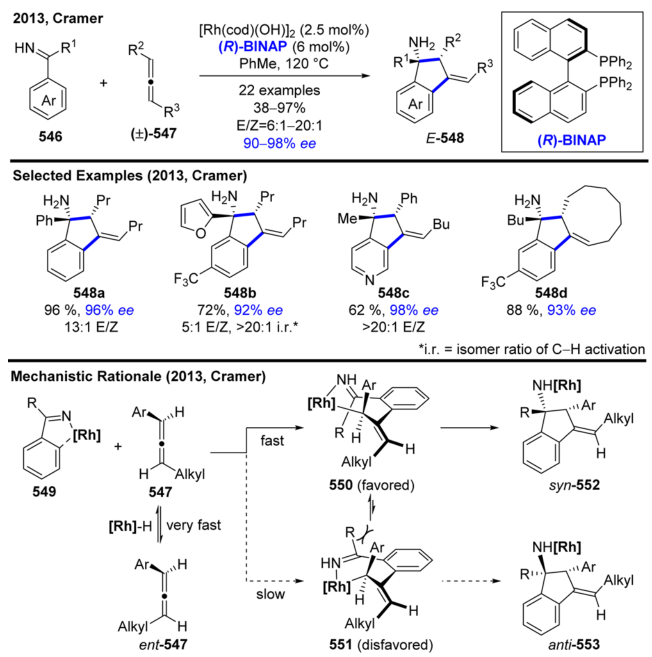
Two reports, both from the Yu group, employ their earlier described Pd(II)/Pd(0) catalytic system in a directed functionalization of aryl C−H bonds (Scheme 112). Racemic mandelic and phenylglycine pivalate derivatives **537** (X = O and NH, respectively) were successfully olefinated to provide valuable enantioenriched α-hydroxy and α-amino phenylacetic acid derivatives, important structural motifs in pharmaceuticals and biologically active compounds.[332] Optimization studies identified that steric bulk on the ligand backbone was beneficial for enantioselectivity, as too was *O*-benzyl and *N*-Boc protection. The reactions were conducted using $Pd(OAc)_2$, under weakly basic conditions and employing oxygen as the terminal oxidant. Mostly electron-deficient alkene coupling partners were screened, including acrylates, vinyl amides, phosphates, and ketones, although one example employing styrene was also disclosed. That same year, Yu and co-workers described the kinetic resolution of *N*-nosyl benzylamine derivatives **540** via cross-coupling with arylboronic acid pinacol esters **541**.[333] In this methodology, methylhydroxamic acid ligand Boc-L-Phe-NHOMe provided the best results. In general, the boronic acid structure had little impact on the *s*-factor of the transformation (e.g., **540a** and **542a** versus **540b** and **542b**), which is to be expected given that the enantioselectivity is determined by the C−H activation event. In terms of benzylamine substrate scope, a wide variety of functionality was well-tolerated, and selected examples include *o*-aryl chloride **542c** (*s*-factor 135), electron-rich derivative **542d** (*s*-factor 102), and β-amino acid **542e** (*s*-factor 34)

7.2. Dynamic Kinetic Resolutions

The first intermolecular asymmetric hydroacylation employing acyclic coupling partners was described by Willis and co-workers in 2008 (Scheme 113).[232] Both aryl and alkyl β-*S*-aldehydes **543** were reacted with racemic allenes **544**, under Rh(I) catalysis in acetone at 40−45 °C. The more conformationally restricted aryl derivatives performed better, and aside from one example, enantioselectivities were ≥89% ee. Both di- and trisubstituted allenes provided high levels of enantiocontrol; however, yields were significantly lower for the latter. Mechanistic experiments indicate that allene isomerization occurs under the reaction conditions, suggesting a dynamic kinetic asymmetric transformation; however, no further mechanistic details were provided.

In 2013, Tran and Cramer reported an extension to their Rh-catalyzed enantioselective [3 + 2]-annulation of ketimines with achiral allenes and alkynes (Scheme 52). In this case, aryl ketimines **546** were coupled with racemic allenes **547** via a C−H activation/[3 + 2]-annulation sequence (Scheme 114).[334] Employing $[Rh(cod)(OH)]_2$ with (*R*)-BINAP, highly functionalized indenylamines **548** were isolated in up to 97% yield and up to 98% ee. The regioselectivity of the C−H activation was kinetically controlled, and excellent *E*/*Z*-selectivity and diastereo- and enantioselectivity were generally observed. The cyclization exhibits broad functional group tolerance for both

Scheme 114. Dynamic Kinetic Asymmetric Transformation of Racemic Allenes via a [3 + 2]-Annulation with Aryl Ketimines



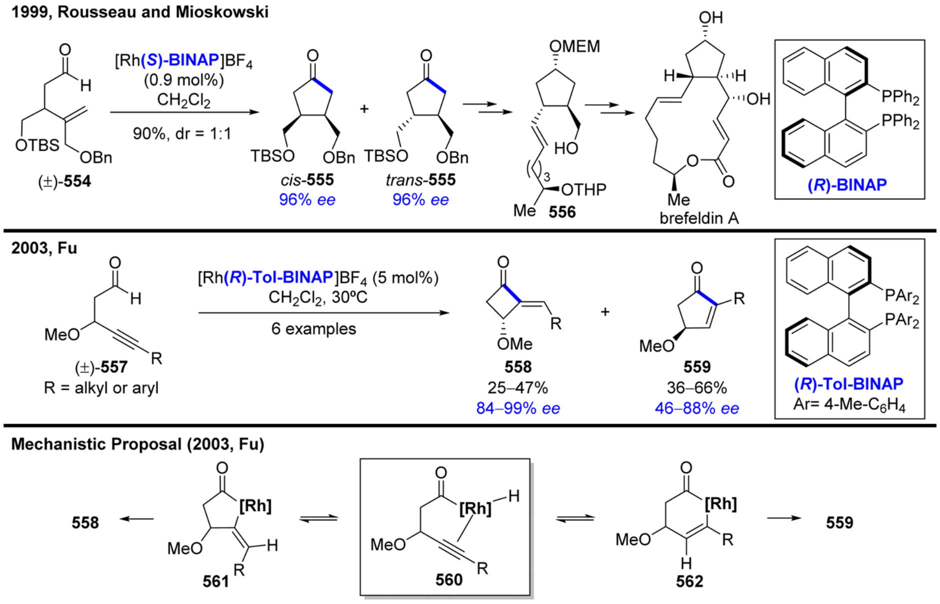
coupling partners, and interestingly, the enantioselectivity was mostly independent of the ketimine moiety. The reaction worked well with both symmetrical (**548a**) and unsymmetrical ketimines (**548b**−**548d**), including those with heteroaromatic or alkyl substitution (**548b** and **548c**, **548d**). Cyclic allenes enabled complete control of *E*/*Z*-selectivity (**548d**), and a significant kinetic isotope effect indicates that the C−H activation is rate-determining. Further mechanistic investigations revealed that the racemic allenes can interconvert through a hydrorhodation-type mechanism (e.g., **547** to *ent*-**547**)[138,335] via reaction with a [Rh]−hydride species generated directly from $[Rh(cod)(OH)]_2$, as demonstrated by Baba and co-workers.[336] To rationalize the diastereochemical outcome of the reaction, the authors proposed two competing modes of cyclization based on the two possible orientations of allene addition to rhodacycle **549**. The more sterically favorable intermediate places the allene Ar substituent away from the ketimine R group, leading to *syn*-intermediate **552** (exclusively observed). The alternate allene orientation places these groups closer to each other and would lead to the *anti*-isomer **548**.

7.3. Parallel Kinetic Resolutions

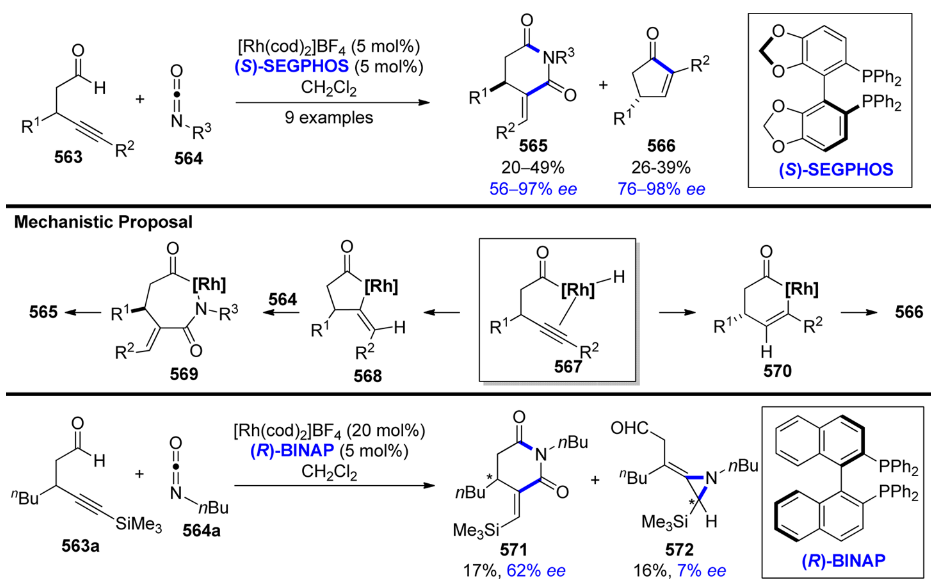
The two earliest parallel kinetic resolution methodologies proceed via an intramolecular hydroacylation reaction (Scheme 115). In 1999, Rousseau, Mioskowski, and their co-worker reported a stereodivergent resolution as part of an enantioconvergent formal synthesis of bredfeldin A.[337] Silyl-protected alcohol **554** was treated with $[Rh(S)\text{-BINAP}]BF_4$, producing the

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

Scheme 115. Hydroacylation Reactions Proceeding via a Parallel Kinetic Resolution



Scheme 116. Parallel Kinetic Resolution of 3-Substituted 4-Alkynals with Isocyanates



two diastereomeric cyclopentanones *cis*-**555** and *trans*-**555** in a 1:1 ratio and both in 96% ee. This mixture was carried through several synthetic steps, eventually converging into **556** via the selective epimerization of the *cis*-diastereomer into the more stable *trans*-derivative. This compound could subsequently be converted into an intermediate from Gais and Lied's synthesis of the natural product.[338] The second example was published by the Fu group in 2003. During their earlier cationic Rh(I)-catalyzed kinetic resolution of alkynals via hydroacylation (Scheme 110),[246] it was observed that the replacement of (*S*,*S*)-*i*Pr-DuPhos with (*R*)-Tol-BINAP provided an unanticipated product in good yield.[339] Careful examination determined that a regiodivergent parallel kinetic resolution was occurring, enabling the synthesis of cyclobutanones **558** in 25−47% yield and up to 99% ee, as well as cyclopentenones **559** in 36−66% yield and up to 88% ee. The authors further demonstrated the matched/mismatched nature of the catalyst by employing enantiopure alkynals substrates, observing that either the four- or five-membered ring analogue could be favored depending on which absolute configuration of ligand was employed. The mechanistic rationale for the regiochemical outcome of the transformation hinges upon the divergent reactivity of the oxidative addition intermediate **560**. Migratory insertion into the Rh−hydride bond to form the six-membered rhodacycle **562** (proceeding with net *trans*-addition) leads to the initially anticipated cyclopentenone **559**. Alternatively, if the migratory insertion proceeds to the five-membered rhodacycle **561** (in this case with net *cis*-addition), then reductive elimination provides cyclobutane **558**.

As an extension to their earlier reported intramolecular enantioselective hydroacylation of achiral 4-alkynals (see Scheme 89), Tanaka and co-workers reported a Rh-catalyzed regiodivergent parallel kinetic resolution of chiral 3-substituted 4-alkynals **563** with isocyanates **564**, incorporating a [4 + 2]-annulation process, to generate enantiomerically enriched glutarimides **565** and cyclopentenones **566** (Scheme 116).[340] A

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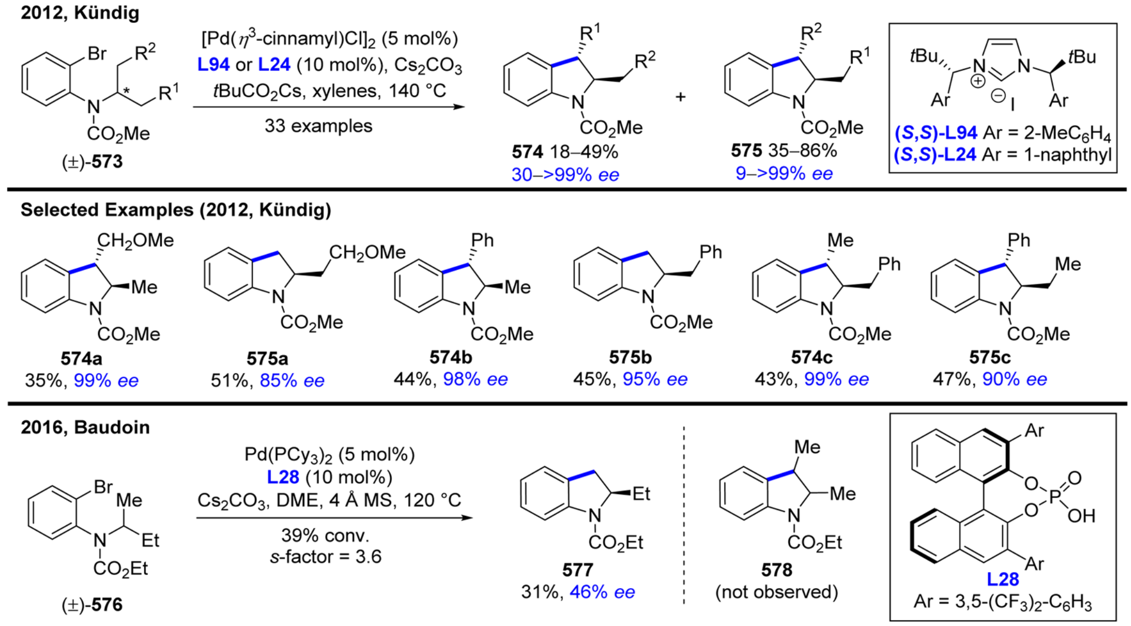
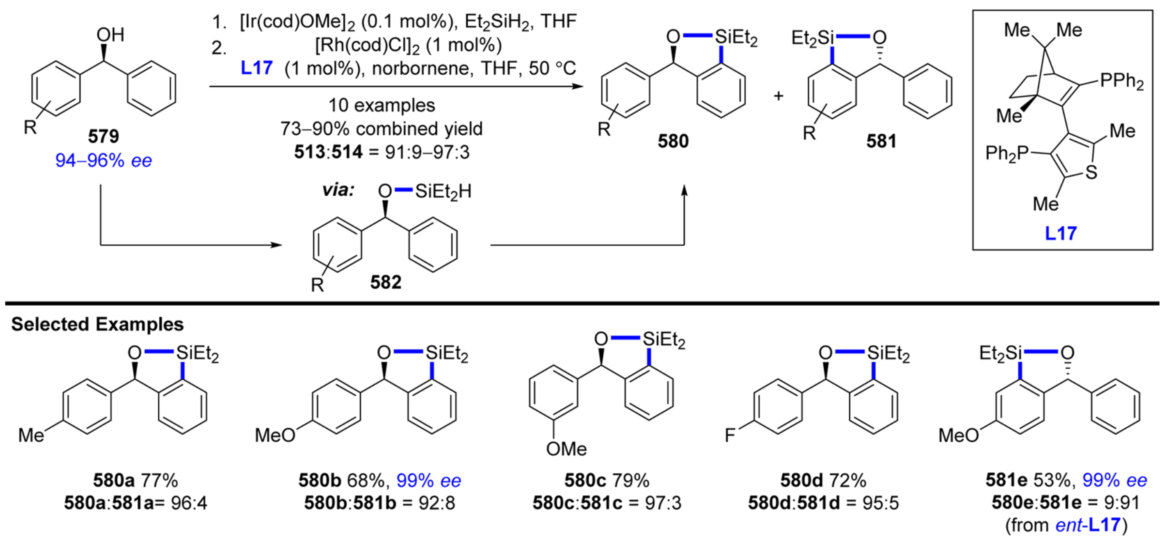
Chem. Rev. 2017, 117, 8908−8976

Scheme 117. Regiodivergent Synthesis of Indolines from Racemic Carbamates



Scheme 118. Regiodivergent Synthesis of Silylated Arenes



cationic [Rh(cod)$_2$]BF$_4$/(S)-SEGPHOS catalytic system provided the best combination of yield and enantioselectivity, enabling a small library of alkyl-, alkenyl-, and aryl-substituted derivatives to be synthesized. As with the work of Fu above (Scheme 115), the migratory insertion of the alkyne into the Rh−hydride bond of **567** can proceed to give either a five- (**568**) or six-membered (**570**) rhodacycle. In the former case, complexation followed by migratory insertion of isocyanates **564** leads to metallacycle **569**, which subsequently undergoes reductive elimination to furnish enantioenriched glutarimides **565**. Alternatively, the six-membered rhodacycle intermediate directly undergoes reductive elimination to form chiral cyclopentenones **566**. Interestingly, when trimethylsilyl derivative **563a** is reacted with isocyanate **564a**, in this case using (R)-BINAP as ligand, enantioenriched gluatarimide **571** and aziridine **572** are generated.

In 2012, the Kündig group extended their Pd(0)/Pd(II)-catalyzed C(sp^3)−H functionalization of achiral carbamates (Scheme 30) to the regiodivergent functionalization of racemic branched derivatives **573** (Scheme 117).[341] In this reaction, one enantiomer of **573** reacts preferentially to yield **574**, whereas the opposite enantiomer leads to constitutional isomers **575**. Notably, in favorable cases extremely high enantioselectivities were observed (>99% ee). In substrates where either R^1 or R^2 = H, the ligand selectively controls the C−H activation event so that one enantiomer undergoes methylene activation and the other methyl activation (e.g., **574a** and **575a**, and **574b** and **575b**). However, in substrates where neither R^1 nor R^2 = H, divergent reactivity is still observed, as exemplified by **574c** and **575c**. Interestingly, as part of their studies focused on the enantioselective synthesis of indolines using chiral phosphoric acid **L28** (see Scheme 31), Baudoin and co-workers screened their reaction conditions in the same parallel kinetic resolution process.[106] However, in this case a standard kinetic resolution of racemic substrate **576** was observed (functionalized product **577** isolated in 31% yield and 46% ee; the yield and enantiopurity of

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

the recovered starting material were not reported), and the constitutional isomer **578** was not observed.

As part of their 2015 study focused on the enantioselective silylation of arene C−H bonds (Scheme 25), Ryberg, Hartwig, and their co-workers disclosed a regiodivergent parallel kinetic resolution of nonsterically biased diarylmethanols **579** (Scheme 118).[93] Although this example does not strictly adhere to the definition of a kinetic resolution, as it does not involve the reaction of a racemic mixture, it is conceptually the same principle applied to an enantioenriched sample. The reaction proceeds with catalyst control; thus, a preference for the major enantiomer **579** to form the (*R*)-configured product **580** and for the minor enantiomer to form the (*R*)-configured constitutional isomer **581** is observed, thus amplifying enantiomeric excess according to the Horeau principle.[342] Alkyl (**580a**), *p*- and *m*-methoxy (**580b** and **580c**), as well as aryl fluoride functionality (**580d**) were all amenable to the reaction. In addition, the researchers demonstrated that the divergent nature of the catalytic system by employing *ent*-**L17**, thus switching the reaction selectivity to the isomeric **581**. Notably, regardless of which substrate enantiomer was employed, the enantiopurity of the major product was determined to be 99% ee (however, enantiopurity measurements were only reported for substrates **580b** and **581e**).

8. CONCLUSION AND FUTURE OUTLOOK

The transition-metal-catalyzed enantioselective functionalization of unactivated C−H bonds has progressed enormously over the past decade. With the exception of a handful of pioneering examples, the vast majority of methodologies were disclosed from 2008 onward, undoubtedly driven by breakthroughs concerning the general understanding of transition-metal-catalyzed C−H activation processes. Although still a relatively young field, a diverse set of reactions, chiral ligand families, and catalysts has already been developed, enabling the synthesis of numerous enantioenriched structural motifs. Nevertheless, a great number of challenges still remain. Currently Pd-, Rh-, and Ir-based systems are the most commonly employed and well understood. Although they certainly still have much to offer, the development of more readily available transition-metal catalysts, such as those incorporating Ni, Co, Fe, and Cu, could significantly enhance the practicality and versatility of asymmetric C−H functionalization reactions. In addition, studies in this direction would likely create new opportunities for the design of novel ligand families and the exploration of new C−H activation processes. The direct functionalization of C−H bonds is frequently touted as being both highly atom- and step-economic, whereas in reality most methodologies require the stoichiometric introduction and removal of specialized directing groups. The discovery and development of more diverse and synthetically useful groups would greatly enhance the value of current C−H functionalization methodologies. From a reaction optimization standpoint, further computational investigations into catalyst/substrate interactions will help guide ligand design, while also leading to a deeper understanding of reaction mechanisms. Although the field of C−H functionalization already allows for novel retrosynthetic disconnections, application of these methodologies is significantly lagging behind the development of new methods. For many synthetic chemists, the maturity of the field will be defined by its application in target oriented synthesis. As yet, only a handful of examples have been disclosed, most commonly on relatively simple substrates. However, given the rapid progress the field is currently experiencing, we have no doubt that this shortcoming will soon be addressed.

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Author Contributions

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

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Notes

The authors declare no competing financial interest.

Biographies

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Shou-Guo Wang received his B.Sc. in chemistry from Soochow University in 2010. From 2010 to 2015 he conducted his Ph.D. at the Shanghai Institute of Organic Chemistry in China under the supervision of Prof. Shu-Li You, before moving to Switzerland as a postdoctoral research fellow in the group of Prof. Nicolai Cramer. His research interests concern the development of catalytic asymmetric transformations and their application in the synthesis of biologically active targets.

Caio C. Oliveira graduated with a degree in pharmacy from the Federal University of Bahia in 2009 and earned his Master's degree at the same institution under the guidance of Prof. Silvio Cunha in 2010. From 2010 to 2015 he conducted his Ph.D. at the University of Campinas in the group of Prof. Carlos Roque Duarte Correia, working on the development of stereoselective intermolecular Heck reactions. During this period, he spent 1 year in the group of Prof. Andreas Pfaltz, at the University of Basel (Basel, Switzerland), developing new chiral ligands for the enantioselective arylation of acyclic olefins. Following a short postdoc at Unicamp, he returned to Switzerland in 2016 to start a new position as a postdoc in the group of Prof. Nicolai Cramer.

Nicolai Cramer studied chemistry at the University of Stuttgart (Stuttgart, Germany) and earned his Ph.D. in 2005 under the guidance of Prof. Sabine Laschat. After a research stage at Osaka University (Suita, Japan), he joined the group of Prof. Barry M. Trost at Stanford University as a Feodor-Lynen postdoctoral fellow in 2006. From 2007 to 2010, he worked on his habilitation at ETH Zurich (Zurich, Switzerland) associated with the chair of Prof. Erick M. Carreira and received the venia legendi. In 2010, he started as assistant professor at the EPF Lausanne (Lausanne, Switzerland) and was promoted to associate professor in 2013 and to full professor in 2015. His general interests encompass enantioselective metal-catalyzed transformations

DOI: 10.1021/acs.chemrev.6b00692
Chem. Rev. 2017, 117, 8908−8976

and their implementation for the synthesis of biologically active molecules. A key focus of his research is the development of asymmetric C−H and C−C bond functionalizations enabled by designed and tailored ligands.

ACKNOWLEDGMENTS

This work is supported by the EPFL and the Swiss National Science Foundation Consolidator Grant no 157741. C.G.N. acknowledges support from the "EPFL Fellows" fellowship program cofunded by Marie Skłodowska-Curie, Horizon 2020 grant agreement no. 665667.

ABBREVIATIONS USED

Ac	acetyl
Acac	acetylacetonate
$AgNTf_2$	silver bis(trifluoromethanesulfonyl)imide
AgTFA	silver trifluoroacetate
BARF	tetrakis[3,5-bis(trifluoromethyl)phenyl]borate
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	benzoquinone
Bz	benzoyl
CMD	concerted metalation−deprotonation
cod	1,5-cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
DABCO	1,4-diazabicyclo[2.2.2]octane
DBPO	dibenzoyl peroxide
DCE	dichloroethane
DFT	density functional theory
DME	1,2-dimethoxyethane
dba	dibenzylideneacetone
DMA	*N*,*N*-dimethylacetamide
DMF	*N*,*N* -dimethylformamide
2,6-DMBQ	2,6-dimethoxybenzoquinone
DYKAT	dynamic kinetic asymmetric transformation
ee	enantiomeric excess
Fmoc	fluorenylmethyloxycarbonyl
HFIP	hexafluoroisopropanol
MPAA	mono-*N*-protected amino acids
Ms	mesyl, methanesulfonyl
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
NaTFA	sodium trifluoroacetate
nbd	norbornadiene
NHC	*N*-heterocyclic carbene
Ns	nosyl, 2-nitrobenzenesulfonyl
OFBA	2-fluorobenzoic acid
Phth	phthalimido
Pin	pinacol, 2,3-dimethyl-2,3-butanediol
Piv	pivalate
*t*AmOH	*tert*-butyldimethylsilyl
TBAB	tetrabutylammonium bromide
TBS	*tert*-amyl alcohol, 2-methylbutan-2-ol
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Tf	trifluoromethanesulfonyl
Ts	tosyl, *p*-toluenesulfonyl

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DOI: 10.1021/acs.chemrev.6b00692
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