Published in final edited form as:

Science. 2018 February 16; 359(6377): . doi:10.1126/science.aao4798.

Enantioselective C(sp³)–H Bond Activation by Chiral Transition Metal Catalysts

Tyler G. Saint-Denis¹, Ru-Yi Zhu¹, Gang Chen¹, Qing-Feng Wu¹, and Jin-Quan Yu^{1,†}

¹The Scripps Research Institute, 10550 N. Torrey Pines Road, La Jolla, California 92037, USA

Abstract

Background—The ultimate goal of synthetic chemistry is the expedient and efficient assembly of molecules from readily available starting materials and reagents with minimal waste generation. The synthesis of organic molecules – *i.e.* compounds containing multiple carbon hydrogen bonds and as well as carbon heteroatom (*i.e.* oxygen, nitrogen, sulfur, phosphorus, halogens, and boron) bonds – has greatly improved our quality of life: pharmaceuticals that can treat disease, agrochemicals that enhance crop yields, and organic materials used in computer engineering are but three illustrative examples. And yet, more often than not, the syntheses of these substances have proved challenging due to restrictions on how molecules can be constructed.

Major advances in organic chemistry over the last century have relied on the discovery of novel disconnections, which has dramatically altered the approach chemists take to building molecules. These disconnections have been enabled by reaction discovery, including, but not limited to, the Grignard reaction, the Diels-Alder reaction, the Brown asymmetric allylation, the Wittig reaction, and more recently cross-coupling, olefin and alkyne metatheses, and asymmetric catalysis. Given that organic molecules possess an abundance of C–H bonds, it should be no surprise that C–H functionalization (*i.e.* the select conversion of C–H bonds into C–X bonds, where X ≠ H) has, over the last few decades, garnered considerable attention as a technique that could dramatically alter synthetic disconnections, by enabling relatively unreactive C–H bonds to be viewed as dormant functionality. And yet, to date, application of C–H functionalization logic is dampened by considerable limitations in terms of chemoselectivity, regioselectivity, and stereoselectivity (*i.e.* the construction of chiral centers).

Advances—Though numerous approaches to chemoselective and regioselective C–H functionalization have been extensively reported, only recently has attention been placed on addressing the issues of stereoselectivity. One such solution, entails the use of chiral transition metal catalysts for enantioselective C–H activation, in which a chiral transition metal catalyst directly reacts with a C–H bond, forming a chiral organometallic intermediate that may be diversified into various functionality. A variety of transition metal catalysts have been shown to affect the asymmetric metalation of C–H bonds of enantiotopic carbons (C–H bonds on different carbons) or enantiotopic protons (C–H bonds on the same carbon). The major driving force behind the development of enantioselective C–H activation has been the design of chiral ligands that bind to transition metal catalysts that both (A) create a steric environment that affords stereocontrol and

[†]Corresponding author. yu200@scripps.edu.

(B) increase reactivity of a transition metal catalyst, thereby accelerating the rate of the C–H activation.

Outlook—Although enantioselective C–H activation is still in its infancy, preliminary data is promising and the recent progress of the field is reminiscent of the early stages of now mature sciences such as asymmetric hydrogenation which is now routinely used in synthesis. In order for enantioselective C–H activation to become a standard disconnection in asymmetric syntheses, the efficiency, catalytic turnovers, and breadth of transformations must be dramatically improved. Though the specific requirements to this end are unclear, given the tremendous impact of ligand design on the emergence of this field, we argue that improved ligand design will be instrumental to further progress, until any C–H bond of any molecule can be converted into any functionality with high efficiency and enantioselectivity. The impact of such progress will no doubt have rippling effect in seemingly dissonant fields such as biology, medicine, and materials science by enabling the synthesis of otherwise unimaginable forms of matter.

Organic molecules are rich in carbon-hydrogen bonds; consequently, the transformation of C–H bonds to new functionalities (*e.g.* C–C, C–N, and C–O, *etc.*) has garnered a wealth of attention by the synthetic chemistry community. The utility of C–H activation in organic synthesis, however, cannot be fully realized until chemists achieve stereocontrol in the modification of C–H bonds. This review highlights recent efforts to enantioselectively functionalize C(sp³)–H bonds *via* transition metal catalysis, with an emphasis on both (A) the development of chiral ligand scaffolds that can accelerate metalation of C(sp³)–H bonds and (B) stereomodels for asymmetric metalation of prochiral C–H bonds by these catalysts. Several different approaches and the profound impact such reactions will have on the endeavors of organic chemists are herein discussed.

Enantioselective C(sp³)–H activation

Chiral transition metal catalysts can selectively functionalize both enantiotopic carbons (**top arrow**) and enantiotopic protons (**bottom arrow**) through asymmetric metalation.

Introduction

One of the long-standing objectives of organic chemistry is the selective functionalization of carbon–hydrogen bonds (1). This is because organic molecules consist of carbon–carbon frameworks (occasionally containing heteroatoms, *e.g.* oxygen in ethers, *etc.*) bearing hydrogen atoms on the majority of carbon centers. Traditionally the synthetic manipulations possible in organic synthesis have been limited by the availability of functional groups (*e.g.* π -bonds, *etc.*) at specific carbon centers; consequently, synthetic transformations are not possible at the majority of carbon centers containing inert C–H bonds. Such limitations have often forced synthetic chemists to pursue indirect, multi-step manipulations to introduce

functionality in a reaction sequence, and have restricted the use of simple starting materials in synthetic endeavors.

The intrigue of C–H functionalization in the synthesis of complex synthetic targets thus stems from the potential to view inert C–H bonds as “masked” reactive functionalities, which may be unlocked under appropriate reaction conditions. By virtue of the abundance of C–H bonds in organic molecules, C–H bond functionalization, in principle, could allow structural modification at any carbon center of an organic molecule thereby altering synthetic chemistry’s *modus operandi* by enabling novel disconnections, shortening synthetic routes, increasing atom economy (*i.e.* the conversion efficiency of a reaction), and expediting the production of target molecules. Further, in the arenas of drug discovery and drug design C–H functionalization may allow chemists to take relatively complicated molecules and in a single step introduce diverse range of functionalities to previously inaccessible carbon centers so as to afford analogues with potentially improved biological properties.

The greatest hindrance to the widespread application of C–H activation is selectivity: In molecules with multiple C–H bonds of comparable electronic strengths and steric environments it has been traditionally difficult to control chemo-, regio-, and stereoselectivity in C–H activation processes. Though recent advances have been made in the regioselective modification of C–H bonds using directing effects or electronic biases by several different groups (2–4), practical stereoselective C–H activation has received considerable less attention. The lack of attention towards enantioselective C–H activation is striking, given the paramount importance of chirality in organ chirality in organic molecules: for example, pharmaceuticals often require chiral components, owing to the inherent chirality of life (5). The development of such enantioselective C–H activation methodologies would make it possible to precisely modify C–H bonds and generate new stereocenters in a single step, providing synthetic chemists with the power to specify *where*, *what*, and *when* stereocenters are introduced in a reaction sequence.

To date, several different approaches have been developed to enantioselectively modify C–H bonds (Figure 1). These include (A) biomimetic approaches (6), akin to the H-atom abstraction of cytochrome P450 (7) as well as other enzymatic processes (metal-oxo H-atom abstractions) (8, 9) (Fig 1A); (B) metallonitrene (10), and metallocarbene (11–12) insertions (Fig 1B); and (C) transition-metal mediated C–H activation (13) (Fig 1C) which is typified by a C–H cleavage event preceding generation of a well-characterized carbon-metal bond; the topic of this review (14). In terms of the final approach, two main methods have emerged, including desymmetrizing C–H activation (*e.g.* isopropyl desymmetrization; *i.e.* chiral carbon center is not bound to transition metal, Figure 1C) and transition-metal complex recognition of enantiotopic methylene C–H bonds (*i.e.* chiral carbon center is bound to transition metal) (Figure 1C). Further, C–H activation kinetic resolution of racemic (*i.e.* a one-to-one ratio of enantiomers) substrates has been demonstrated and is an active area of research (Fig 1C). Transition metal-catalyzed C–H activation has largely been enabled by select catalytic cycles, including palladium (Pd)(II/0), Pd(II/IV), Pd(0/II), Pd(II/II) and rhodium (Rh) or iridium (Ir)(I/III), though other preliminary examples do exist (15). Herein we highlight recent major achievements (Fig 1D) in the development of

enantioselective C–H bond activation with an emphasis on stereochemistry-generating C–H activation (as opposed to enantioselection occurring in other non-C–H activation steps), the design of chiral ligands and stereomodels to enable these technologies. For a comprehensive review covering enantioselective C(sp²)–H and C(sp³)–H activation reactions up to 2016, we encourage the reader to see a review by Newton and Wang (13).

Enantioselective C–H Activation by Desymmetrization

Enantioselective desymmetrization C–H activation reactions primarily fall into two categories: (A) the desymmetrization around a point (*i.e.* a single atom) in a substrate and (B) the desymmetrization of a plane or axis of a substrate, exemplified by the desymmetrization of metallocene compounds (16, 17) and atroposelective C–H activation (18), respectively. That said, because planar and axial desymmetrization do not encompass C(sp³)–H activation, the corresponding stereomodels will not be discussed here. Enantioselective C–H point desymmetrization involves the generation of a stereocenter either distal (*i.e.* more than two bonds away) to the C–H bond undergoing activation, as is the case with C(sp²)–H desymmetrization, or involves the generation of a stereocenter adjacent (*i.e.* two bonds away/vicinal) to the C–H bond undergoing activation (Fig 2A). These examples are in contrast to methylene C–H activation, in which the newly formed stereocenter is formed on the same carbon of the C–H bond that was functionalized. The earliest examples of enantioselective catalytic C–H activation relied on the use of mono-*N*-protected amino acid (MPAA) ligands to desymmetrize pyridine-containing substrates by Pd(II)/Pd(0) catalysis (19). This work exploited the well-established directing group (DG) nature of pyridine (20) to direct palladation of both C(sp²)–H and C(sp³)–H bonds as well as chiral carboxylates to induce asymmetric cyclopalladation. MPAA ligands were investigated given their (A) easy preparation from commercially available and naturally occurring amino acids as well as their (B) ability to coordinate Pd(II) serving as chiral carboxylate surrogates, as originally proposed by Sokolov *et al.* (21), or as bidentate ancillary ligands as studied by Navarro *et al.* (22) (Fig 3A). Initial stoichiometric studies with Pd(OAc)₂ yielded a racemic cyclometallated dimer in 85% yield (Fig 3A), and it was proposed that by replacing the bridging acetates with amino acid ligands would lead to the formation of a chiral cyclometallated dimer; however, thorough variation in amino acid substitution elucidated a different mechanism for stereocontrol: unprotected leucine amino acids (Entry 1) suppressed catalysis and double *N*-protected amino acids (Entry 2) – though affording product in high yield – gave minimal stereocontrol (7% enantiomeric excess [*ee*]). Mono-*N*-protection was critical for both yield and enantiocontrol (Entry 3, 90% *ee*) and conversion of the carboxylate to the corresponding methyl ester (Entry 4) afforded racemic product in 86% yield. Entries 2, 3, and 4 suggest that the operative mechanism of enantiocontrol induced by MPAA relies on bidentate coordination by both the carboxylate and the mono-protected amine to the metal center. Though bidentate cyclopropyl MPAA (Entry 5) was capable of moderate enantiocontrol and yield, the C₂-symmetric bidentate cyclopropyl MPAA (Entry 6) only afforded racemic product. This was a surprising and important finding, given the dominance of C₂-symmetric ligands in transition metal catalysis (23) and suggested a radically different approach would be needed to effectively induce stereocontrol in C–H activation (note: monodentate C₂ ligands are discussed later). Further optimization of ligand

design yielded the (–)-Menthol derivative of Leucine (Entry 7) as the most effective ligand. ^1H NMR, mass spectroscopy, and density functional theory computational studies elucidated the mechanism of stereoinduction in these reactions (24), and have led to the proposal of a stereomodel consistent with reactivity and stereochemistry observed in this reaction as well as the necessary requirements (Fig 3B). The pre-transition state intermediate, in which Pd is both bound to the MPAA ligand as well as the directing group of the substrate may proceed through two distinct pathways: in the disfavored pathway (*S*), it is proposed that a high-energy transition state is formed in which there is steric clashing between the bulky chain of the MPAA ligand and a large aryl group of the substrate; in the favored pathway (*R*), this steric clashing is avoided, resulting in a lower-energy transition state and thus the major product.

The original discovery of MPAA ligands for enantioselective C–H activation also reported the enantioselective $\text{C}(\text{sp}^3)\text{--H}$ activation of 2-isopropyl pyridine (19) (Fig 3C); however, both the yield and the *ee* reported were low (38% and 37%, respectively). One reason the alkyl substrate has such poor selectivity may be due to the fact that the catalyst has to differentiate between a methyl group and a hydrogen atom, which are relatively close in size compared to the differentiation required in Figure 3B (between an aryl group and a hydrogen atom). Additionally, pyridine-directed C–H activation persisted in the absence of chiral ligand (*i.e.* a racemic background reaction proceeds). This example underscores two significant pitfalls of conventional directed C–H activation: typically, innate functionality (*e.g.* carboxylic acids, amines, alcohols, ethers, *etc.*) fail to interact sufficiently with a transition metal catalyst to direct metallation, such that strong directing groups must be installed prior to C–H activation so as to effectively direct metallation. When strong directing groups (*e.g.* pyridine, 8-amino quinoline, *etc.*, Fig 4B) are present in a substrate, (A) the substrate may outcompete ligand binding to a transition metal center (substrate is usually an order of magnitude greater in concentration than ligand) or (B) the substrate may enable a reaction to occur in the absence of a chiral ligand, therefore affording racemic product (Fig 4A). Moreover, strong directing groups may lead to a thermodynamically stable cyclopalladation intermediate, thereby hindering subsequent functionalization steps.

These so-called background reactions are detrimental to enantiocontrol; one solution to this problem has been the use of weakly-coordinating monodentate directing groups (25) which, ideally, in the absence of a chiral bidentate ligand fail to afford any product. The key principles of ligand design for enantioselective C–H activation reaction are thus twofold: ligands must both be capable of creating a steric environment that affords stereocontrol *and* must increase reactivity of a transition metal catalyst, thereby accelerating the rate of the reaction.

Fortunately, it was discovered early on that MPAAAs are capable of dramatically accelerating a wide variety of C–H activation transformations (26,27) This discovery compounded with the facile syntheses of diverse MPAAAs motivated the use of MPAA ligands in the presence of weakly-coordinating monodentate directing groups for the desymmetrization of cyclopropyl and cyclobutyl compounds using Pd(II)/Pd(0) catalysis (Fig 5A, eq 1) (28,29). Cyclopropyl and cyclobutyl compounds were chosen as substrates since the requisite $\text{C}(\text{sp}^3)\text{--H}$ bonds have similar electronic properties to that of $\text{C}(\text{sp}^2)\text{--H}$ bonds and because

these rigid systems would allow for precise elucidation of the mechanism of stereoinduction. Because of the conformation of the substrates, only single *cis*-diastereomers were observed and through fine-tuning of MPAA ligand side chain and *N*-protecting group, enantioselective cross coupling of cyclopropyl compounds could be achieved in up to 70% yield with up to 94% ee (28). Further modification of MPAA ligand side chain to a 2,6-diarylated phenyl compound as well as conversion of the carboxylate to an *N*-hydroxamic ester (Fig 5A, eq 2) allowed for the desymmetrization of cyclobutyl compounds in up to 77% yield as well as 95% ee (29). The stereomodels proposed to rationalize stereochemical induction in these systems are shown in Fig 5A and are based on computational studies (30) as well as assignment of the absolute configuration: in both cases it is believed that the repulsive interaction between the sterically bulky *N*-protecting group and the large MPAA side chain forces the MPAA side chain to be orthogonal to the square plane of Pd(II), and that the rigid position of the MPAA side chain forces the substrate cyclopropane/cyclobutane to be also orthogonal to the square plane and *trans* to the MPAA side chain, in order to avoid unfavorable steric clashing. These models have also proven reliable in rationalizing enantioinduction imparted by MPAA ligands for Pd(II)/Pd(IV) C(sp³)-H arylation of cyclopropylmethylamines (31), which has different steric requirements in the functionalization step (*i.e.* a high energy octahedral Pd(IV)) compared to Pd(II)/Pd(0) catalyses.

Several complementary approaches to the aforementioned enantioselective Pd(II)/Pd(0) or Pd(II)/Pd(IV) catalyses for C(sp³)-H desymmetrization have been developed, including enantioselective Pd(0)/Pd(II) catalyses (32–35) as well as Rh(I)/Rh(III) (36,37) catalyses. The only examples of these point desymmetrization are intramolecular (*i.e.* the target C(sp³)-H bond and the to-be-installed functionality are linked by a covalent tether); due to the rigidity imparted by intramolecularity, C₂-symmetric ligands have had success in these catalytic arenas. In the Pd(0)/Pd(II) systems, oxidative addition by Pd(0) to substrate aryl-iodides, -bromides, or -triflates generates a Pd(II) intermediate which then proceeds to cleave an intramolecular C(sp³)-H bond (Fig 5B). In this regard, the aryl-iodide, -bromide, or -triflate serves as a *pseudo*-directing group, but one that is consumed during the course of the reaction; the aryl-iodide, -bromide, or -triflate both relay chiral transition metal catalysts to a target C-H bond *and* serve as the source of functionality installed during a reaction. It is worth noting that these catalytic regimes are capable of desymmetrizing *gem*-dimethyl substrates, as well as cyclic substrates with high ee (up to 93% and 95%, respectively). Unfortunately, the stereomodels for these reactions are still under investigation; in almost all cases the ligands required to enable reactivity and enantioselectivity are monodentate phosphines, phosphoramidites, or *N*-heterocyclic carbenes (NHCs) which enable Pd(0) to oxidatively add to substrates, though a single example of the bidentate phosphine (*R,R*)-Me-DUPHOS imparting enantioselectivity has been reported (33). In the few examples of enantioselective Rh(I)/Rh(III) C(sp³)-H activation, bidentate C₂-symmetric ligands have afforded enantioenriched products (Fig 5C) (36, 37), the most notable example by Hartwig entails the two-step sequence of *in-situ* alcohol protection of cyclopropylmethyl alcohols to the corresponding alkoxy silane followed by intramolecular C-H cyclization (up to 90% yield and up to 90% ee) (36). As is the case for Pd(0)/Pd(II) chemistry, the stereomodels for these reactions are remain to be established, and the precise

enantiocontrol imparted by C_2 -symmetric ligands is unknown and are currently under rigorous investigation.

The reader will notice that the majority of $C(sp^3)$ -H point desymmetrization has been performed on cyclic systems. Several examples of enantioselective desymmetrization of acyclic systems (*i.e.* *gem*-dimethyl groups) using the above methodologies were reported (29, 29, 37); however, yields and enantioselectivities are generally poor (Fig 3C, 6A). These results highlight two major challenges of C-H activation enantioinduction of acyclic systems: (A) in cyclic systems, hydrogen atoms and target C-H bonds have restricted rotational freedom and, consequently, restricted conformations; acyclic systems possess many more accessible conformational states; (B) in acyclic systems a catalyst needs to recognize the steric difference between relatively similar methyl groups and hydrogen atoms, as opposed to cyclic systems, in which a catalyst needs to recognize the difference between the target C-H bond and the conformationally locked rest of the molecule (Fig 6A). Insofar as the relevance of *gem*-dimethyl desymmetrization is concerned, one of the most important biological pathways used in the synthesis of myriad natural products entails the enzyme-catalyzed enantioselective hydroxylation of isobutyric acid (38). We elected to engineer a ligand that could enable an analogous transformation; namely, the robust Pd(II)/Pd(IV)-catalyzed desymmetrization of isobutyramides. Inspired by our previous work on the diastereoselective iodination of α -dialkyl groups enabled by a chiral oxazoline auxiliary (Fig 6B) (39) as well as the bidentate coordination mode of mono-*N*-protected amino acids, we synthesized bidentate *N*-acetyl protected aminomethyl chiral oxazoline ligands (APAO), which were capable of enantioselective arylation, alkenylation, and alkynylation of isobutyramides in moderate yields with high enantioselectivities (Fig 6C) (40). Since the original report of APAO ligands, they have also been exploited for the enantioselective borylation of cyclic amide substrates enabled by Pd(II)/Pd(0) chemistry (41). The proposed stereomodel rationalize the general high enantioselectivity imparted by the APAO ligands is shown in Figure 6D: it is believed that (A) the bulky phenyl substitution on the oxazoline ring and the *tert*-butyl group side chain orient themselves perpendicular to the square plane of Pd(II) in such a way so as to evade steric clashing; (B) the *tert*-butyl group then forces the *N*-acetyl group into the square plane of Pd(II) thereby engaging with the target C-H bond. In the disfavored C-H cleavage transition state, the methyl group of the substrate has intense steric clashing with the phenyl substitution of the APAO ligand; in the favored C-H cleavage transition state, this interaction is avoided by positioning of the methyl *trans* to the sterically-encumbering phenyl group. This preliminary stereomodel has yet to be validated and is under scrupulous computational investigation. The generality of transformations enabled by APAO ligands (including Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalyses) parallels that of MPAA ligands. Further, the ease by which these ligands may be diversely prepared as well as the success so far reported in the steric differentiation of a hydrogen atom and a relatively small methyl group will no doubt provide invaluable insight for the further development of desymmetrizing enantioselective C-H activation.

Enantioselective Methylene C-H Activation

The C-H activation of methylene (*i.e.* secondary) enantiotopic C-H bonds is a significant synthetic challenge for two main reasons: In terms of reactivity, secondary C-H bonds are

substantially less stereoelectronically prone to C–H cleavage/C–H insertion than their primary counterparts as they are both less sterically accessible (kinetic) and possess greater heterolytic bond dissociation energies (thermodynamic). It is worth noting that there are several examples of enantioselective point-desymmetrization (presented above) on methylene C–H bonds; however, the reader will be quick to note that these are only in cyclobutyl and cyclopropyl substrates, and do not entail the chiral differentiation of enantiotopic methylene C–H bonds, but rather entail the desymmetrization of enantiotopic carbons, as only the *syn*-product can be formed. Moreover, cyclopropane and cyclobutane C–H bonds possess electronic properties comparable to those of aromatic C–H bonds, therefore making these C–H bonds more prone to reactivity (42). In terms of stereochemical induction in methylene C–H activation of acyclic substrates, a catalyst must be capable of differentiating a relatively small hydrogen atom and a relatively large R-group (Figure 7A); as the size of this R- group decreases, catalyst differentiation of the hydrogen and R-group becomes increasingly more difficult.

Despite these challenges, significant progress has been made in enantioselective methylene C–H activation: At present, there are three different substrate categories in directed enantioselective methylene C–H activation (Fig 7A), including C–H bonds α -to-heteroatom, benzylic C–H bonds, and unbiased methylene C–H bonds of linear systems. The majority of methylene C–H activation reactions have been of the first two categories, and multiple transition metal catalysts and ligands have enabled these reactions. For example, enantioselective Ir(I)/Ir(III)-catalyzed alkylation/olefination of methylene C–H bonds adjacent to nitrogen atoms have been reported in both acyclic and cyclic substrates, affording products in high yield and high ee (Fig 7B, Eq. 1) (43–45). Mechanistically, the target methylene C–H bond undergoes oxidative addition by an Ir(I) catalyst ligated with a C_2 -symmetric bidentate phosphine ligand, and the requisite organometallic intermediate then undergoes insertion into olefins or alkynes, affording the alkylated and alkenylated species, respectively. In all of these cases a precise stereomodel has yet to be proposed so as to rationalize stereochemical induction, and it is worth noting that, as seen above in desymmetrization C–H activation, the role of bidentate C_2 -symmetric ligands in imparting stereochemical induction is not well-defined and that the hemilabile nature of bidentate phosphines may need to be invoked. Monodentate C_2 -symmetric phosphoramidites (46) and phosphoric acid (47) ligands have been shown to enable Pd(0)-catalyzed intramolecular cyclization and Pd(II)-catalyzed intermolecular arylation of α -methylene C–H bonds, respectively (Fig 7B, Eq 2). Though the yields and enantioselectivities of these reactions are high, the corresponding stereomodels are ambiguous and under investigation.

Insofar as enantioselective benzylic methylene C–H activation is concerned, two distinct approaches have been reported. The first approach was inspired by the highly enantioselective C–H desymmetrization imparted by amino acid-derived ligands: Our group developed a transient-chiral auxiliary approach for enantioselective benzylic methylene C–H activation of 2-alkyl benzaldehyde substrates in which the chiral element is covalently attached to the substrate prior to the chiral induction step (Fig 7C, Eq 3) (48). This technique relied on the *in situ* formation of an imine intermediate between the amine moiety of amino acids and the aldehyde component of substrates. The corresponding transient aldehyde-amino acid imine intermediates then ligate Pd(II) and C–H activation and subsequent

functionalization proceed in high yield and high enantioselectivity. The stereomodel for this reaction follows the principle of diastereoselection and it is believed that the steric repulsion between the bulky *tert*-butyl group of the chiral amino acid and the R-group of the substrate forces the two to adopt a *trans*-conformation in the transition state, which proceeds to form product; were the intermediate to adopt a *cis*-conformation (highly disfavored) the opposite enantiomer would be favored.

The second approach to benzylic methylene C–H activation (Fig 7C, Eq 4), has relied on strong bidentate directing groups and monodentate chiral C_2 -symmetric phosphoramidites/phosphoric acids (49–50). The yields and enantioselectivities of these reactions are moderate-to-good, and the shortcomings of these approaches may be attributed to the strongly coordinating bidentate nature of the directing group, such that background reactions may proceed in the absence of chiral ligand, thereby preventing high stereocontrol. The limitations of strong bidentate directing group/monodentate ligand approaches to enantioselective C–H activation are exemplified by attempts to adopt this approach for electronically unbiased (*i.e.* non-benzylic) substrates: both yields and enantioselectivities were low, suggesting that substrate-driven cyclopalladation is a major hindrance to high enantioselectivity (Fig 8A) (49). Our group was motivated by our previous successes in the use of monodentate weakly-coordinating directing groups/bidentate chiral ligands for enantioselective C(sp³)–H activation. Inspired by previous reports of monodentate quinoline-enabled Pd(II)-catalyzed racemic methylene C–H activation as well as privileged structure of bidentate MPAA ligands (Fig 8B) (51), we began a campaign on the synthesis of chiral bidentate quinoline-based ligands (52). Extensive ligand design revealed that an acetyl-protected aminoethyl quinoline (APAQ) ligand could not only enable Pd(II)-catalyzed methylene C–H arylation to proceed with a weak directing group but also afford the corresponding products with high enantioselectivity (Fig 8C). Systematic ligand modification revealed that (A) six-membered chelation was critical for reactivity (note: the corresponding five-membered chelating quinoline/acetyl-protected amine ligands failed to afford any product) and (B) *cis*-substitution was necessary for high reactivity and enantioselectivity; the corresponding diastereomeric ligands failed to afford the desired product in reasonable yields or enantioselectivities. The best ligand for this reaction is shown in Figure 8C, and contains *both* a bulky 3,5-di *tert*-butyl phenyl group at C1 and an ethyl group at C2. The stereochemical induction imparted by APAQ ligands has been the subject of computational studies (52–53) and the proposed stereomodel of APAQ-enabled enantioselective methylene C–H activation is shown in Figure 8D. In the favored transition state, the combined action of the sterically encumbering 3,5-di *tert*-butyl phenyl of the ligand and the bulky directing group of the substrate is believed to force the quinoline portion of the APAQ ligand perpendicular to the square plane of Pd(II), which in turn forces the bulky R-group of the substrate to orient itself *trans*- to the quinoline. In the disfavored transition state, the perpendicular quinoline has an intense steric interaction with the *cis*-situated R-group of the substrate. Though substitution at the C2 position of the APAQ ligands is not a prerequisite for high reactivity and high enantioselectivity (52), it is believed that the ethyl group shown in the competing transition states of Figure 8D helps orient the 3,5-di *tert*-butyl phenyl group in such a way that forces the quinoline to adopt a geometry perpendicular to the square planar of Pd(II). The breadth of methylene C–H bonds that may

be enantioselectively functionalized by APAQ-ligated Pd(II) will no doubt provide invaluable insight for the development of new ligand classes for enantioselective methylene C–H activation on diverse substrates involving both different redox cycles as well as transformations.

Kinetic Resolution

The discussions above on point desymmetrization C(sp³)–H activation and enantioselective methylene C(sp³)–H activation involved the recognition – and subsequent functionalization – of prochiral carbon centers by transition metal complexes. In contrast, kinetic resolution entails the different recognition of enantiomers of a racemic mixture by a chiral catalyst (Fig 1C, Fig 9A) (54). Though kinetic resolution has been established in C(sp²)–H activation (55–58) (Fig 9B), there are considerably fewer examples in C(sp³)–H substrates. Those examples that do exist involve intramolecular Pd(0)/Pd(II) catalyses and there are many opportunities for ligand and catalyst design to enable improved and novel C(sp³)–H activation *via* kinetic resolution. Parallel kinetic resolution has been reported for the regiodivergent synthesis of indolines from racemic carbamates (Fig 9C, Eq 1) (59). Interestingly in this reaction, each enantiomer proceeds to form different constitutional isomers. This reaction was enabled with a monodentate C₂-symmetric NHC ligand, and it is believed that the active chiral catalyst forms diastereomeric intermediates when binding with each enantiomer of the starting material and that these diastereomeric intermediates proceed to different products. A single example of kinetic resolution of C(sp³)–H bonds was recently reported using intramolecular Pd(0)/Pd(II) catalysis and chiral phosphonate ligands, though yield and ee were low (Fig 9C, Eq 2) (60). To date, intermolecular kinetic resolution by C–H activation of methylene C(sp³)–H bonds or point desymmetrization has yet to be reported; through rigorous catalyst and ligand design, such synthetically useful processes necessarily will reach fruition.

Conclusions and Future Outlook

In the past century, asymmetric catalysis has dramatically changed the way chemists construct chiral molecules and has made the synthesis of various pharmaceuticals, agrochemicals, pesticides, materials, and natural products possible (61, 62). Moreover, rationalization of chiral induction in asymmetric catalysis has been one of the most powerful tools to elucidate molecular mechanisms of these reactions and has contributed substantially to our understanding of the underpinnings of catalysis (63). Enantioselective C–H activation is but one sub-category of asymmetric catalysis, and yet the interest it has garnered, both academic and industrial, has grown exponentially over the past decade. The examples of enantioselective C(sp³)–H activation herein presented should attest to this growth and underscore the promise this field holds to (A) enrich synthetic disconnections, (B) expedite chemists' endeavors to make synthetic targets, (C) construct chiral molecules from simple feedstock chemicals, and (D) elucidate various mechanisms of organometallic processes, thereby providing guidance for the development of superior catalysts. Though the field of enantioselective C(sp³)–H activation by chiral transition metal catalysts is young, the breadth of substrates, transformations, catalyses, and ligand platforms involved in these reactions is impressive and will continue to expand. No doubt the field will continue to grow

and overcome current limitations, such as scope and reactivity, until any C–H bond of any molecule can be converted into any C–X bond with high yield, regiocontrol, and enantioselectivity. Most importantly, however, is that this growth may have tremendous impact on seemingly dissonant fields by enabling the synthesis of hitherto unfathomable forms of organic matter.

Acknowledgments

The authors would like to thank The Scripps Research Institute (TSRI) and the NIH (NIGMS, 2R01GM084019) as well as NSF under the CCI Center for Selective C–H Functionalization, CHE-1205646 for financial support. We thank the NSF GRFP and TSRI for financial support of Tyler G. Saint-Denis. Ru-Yi Zhu was funded by TSRI and the Boehringer Ingelheim Fellowship. Gang Chen thanks The Shanghai Institute of Organic Chemistry, Zhejiang Medicine, and Pharmaron. The authors thank A. N. Herron and N. Chekshin for thoughtful discussions.

References and Notes

1. Arndtsen BA, Bergman RG, Mobley TA, Peterson TH. Selective intermolecular carbon-hydrogen activation by synthetic metal complexes in homogeneous solution. *Acc Chem Res.* 1995; 28:154–162.
2. Engle KM, Yu JQ. Developing ligands for palladium(II)-catalyzed C–H functionalization: intimate dialogue between ligand and substrate. *J Org Chem.* 2013; 78:8927–8955. [PubMed: 23565982]
3. Leow D, Li G, Mei TS, Yu JQ. Activation of Remote *meta*-C–H Bond Assisted by an End-on Template. *Nature.* 2012; 468:518–522.
4. Hartwig JF, Larsen MA. Undirected, homogeneous C–H bond functionalization: challenges and opportunities. *ACS Cent Sci.* 2016; 2:281–292. [PubMed: 27294201]
5. Carey JS, Laffan D, Thomson C, Williams MT. Analysis of the reactions used for the preparation of drug candidate molecules. *Org Biomol Chem.* 2006; 4:2337–2347. [PubMed: 16763676]
6. Shugrue CR, Miller SJ. Applications of nonenzymatic catalysts to the alteration of natural products. *Chem Rev.* ASAP.
7. Murahashi SI. Development of biomimetic catalytic oxidation methods and non-salt methods using transition metal-based acid and base ambiphilic catalysts. *Proc Jpn Acad Ser B Phys Biol Sci.* 2011; 87:242–253.
8. Groves JT, Viski P. Asymmetric hydroxylation by a chiral iron porphyrin. *J Am Chem Soc.* 1989; 111:8537–8538.
9. Zalatan D, Du Bois J. A chiral rhodium carboxamidate catalyst for enantioselective C–H amination. *J Am Chem Soc.* 2008; 130:9220–9221. [PubMed: 18582043]
10. Nishioka Y, Uchida T, Katsuki T. Enantio- and regioselective intermolecular benzylic and allylic C–H bond amination. *Angew Chem Int Ed.* 2013; 52:1739–1742.
11. Anada M, Mita O, Watanabe H, Kitagaki S, Hashimoto S. Catalytic enantioselective synthesis of the phosphodiesterase type IV inhibitor (R)-(–)-rolipram *via* intramolecular C–H insertion process. *Synlett.* 1999; 11:1775–1777.
12. Liao K, Negretti S, Musaev DG, Bacsá J, Davies HML. Site-selective and stereoselective functionalization of unactivated C–H bonds. *Nature.* 2016; 533:230–234. [PubMed: 27172046]
13. Newton CG, Wang SG, Oliveira CC, Cramer N. Catalytic enantioselective transformations involving C–H Bond cleavage by transition-metal complexes. *Chem Rev.* 2017; 117:8908–8976. [PubMed: 28212007]
14. The term “C–H activation” is often used incorrectly to refer to the general functionalization of C–H bonds; strictly speaking, “C–H activation” is defined as a reaction, either catalytic or stoichiometric, between a transition metal complex with the unreactive C–H bonds of alkanes, alkenes, or arenes to form a putative intermediate or product containing a new metal-carbon bond. This definition thus excludes biological processes, Friedel-Crafts reactions, metal-oxo/H-atom abstraction processes, metallonitrene reactions, and metallocarbene reactions, instead defining them as “C–H functionalization” processes. For an in-depth discussion on this dichotomy, please

see: Hartwig JF. *Organotransition Metal Chemistry: From Bonding to Catalysis*. University Science Books 2010

15. Su B, Zhou TG, Xu PL, Shi ZJ, Hartwig JF. Enantioselective borylation of aromatic C–H bonds with chiral dinitrogen ligands. *Angew Chem Int Ed*. 2017; 25:7205–7208.
16. Pi C, Cui X, Liu X, Guo M, Zhang H, Wu Y. Synthesis of ferrocene derivatives with planar chirality *via* palladium-catalyzed enantioselective C–H bond activation. *Org Lett*. 2014; 16:5164–5167. [PubMed: 25247387]
17. Gao DW, Gu Y, Wang SB, Gu Q, You SL. Pd-catalyzed highly enantioselective synthesis of planar chiral ferrocenylpyridine derivatives. *Organometallics*. 2016; 35:3227–3233.
18. He C, Hou M, Zhu Z, Gu Z. Enantioselective synthesis of indole-based biaryl atropisomers *via* palladium-catalyzed dynamic kinetic intramolecular C–H cyclization. *ACS Catal*. 2017; 7:5316–5320.
19. Shi BF, Maguel N, Zhang YH, Yu JQ. Pd(II)-catalyzed enantioselective activation of sp^2 and sp^3 C–H bonds using mono protected amino acids as chiral ligands. *Angew Chem Int Ed*. 2008; 47:4882–4886.
20. Liu YL, Xu H, Kong WJ, Shang M, Dai HX, Yu JQ. Overcoming the limitations of directed C–H functionalizations of heterocycles. *Nature*. 2014; 515:389–393. [PubMed: 25383516]
21. Sokolov VI, Troitskaya LL, Reutov OA. A new route to enantiomeric 1,2-disubstituted ferrocenes. *Dokl Akad Nauk USSR*. 1979; 246:124.
22. Navarro R, García J, Urriolabeitia EP, Cativiela C, Diaz-de-Villegas MD. Metal complexes of biologically important ligands: synthesis of amino acidato complexes of Pd(II) containing a C, N-cyclometallated group as an ancillary ligand. *J Organomet Chem*. 1995; 490:35–43.
23. Pfaltz A, Drury WJ III. Design of chiral ligands for asymmetric catalysis: from C_2 -symmetric P,P and N,N-ligands to sterically and electronically nonsymmetrical P,N-ligands. *Proc Natl Acad Sci USA*. 2004; 101:5723–5726. [PubMed: 15069193]
24. Musaev DG, Figg TM, Kaledin AL. Versatile reactivity of Pd-catalysts: mechanistic features of the mono-*N*-protected amino acid ligand and cesium-halide base in Pd-catalyzed C–H bond functionalization. *Chem Soc Rev*. 2014; 43:5009–5031. [PubMed: 24626313]
25. Engle KM, Mei TS, Wasa M, Yu JQ. Weak coordination as powerful means for developing broadly useful C–H functionalization reactions. *Acc Chem Res*. 2012; 45:768–802.
26. Engle KM, Wang DH, Yu JQ. Ligand-accelerated C–H olefination reactions: evidence for a switch of mechanism. *J Am Chem Soc*. 2010; 132:14137–14151. [PubMed: 20853838]
27. Engle KM, Thuy-Boun PS, Dang M, Yu JQ. Ligand-accelerate cross-coupling of $C(sp^2)$ –H bonds with arylboron reagents. *J Am Chem Soc*. 2011; 133:18183–18193. [PubMed: 21913636]
28. Wasa M, Engle KM, Lin DW, Yoo EJ, Yu JQ. Pd(II)-catalyzed enantioselective C–H activation of cyclopropanes. *J Am Chem Soc*. 2011; 133:19598–19601. [PubMed: 22059375]
29. Xiao KJ, Lin DW, Miura M, Zhu RY, Gong W, Wasa M, Yu JQ. Palladium(II)-catalyzed enantioselective $C(sp^3)$ –H activation using a chiral hydroxamic acid ligand. *J Am Chem Soc*. 2014; 136:8138–8142. [PubMed: 24815880]
30. Cheng GJ, Chen P, Shun TY, Zhang X, Yu JQ, Wu YD. A combined IM-MIS/DFT study of Pd(MPAA)-catalyzed enantioselective C–H activation: relay of chirality through a rigid framework. *Chem Eur J*. 2015; 21:11180–11188. [PubMed: 26186414]
31. Chan KSL, Fu HY, Yu JQ. Palladium(II)-catalyzed highly enantioselective arylation of cyclopropylmethylamines. *J Am Chem Soc*. 2015; 137:2042–2046. [PubMed: 25581489]
32. Nakaniski M, Katayev D, Besnard C, Kündig EP. Fused indolines by palladium-catalysed asymmetric C–C coupling involving an unactivated methylene group. *Angew Chem Int Ed*. 2011; 50:7438–7441.
33. Anas S, Cordi A, Kagan HB. Enantioselective synthesis of 2-methyl indolines by palladium catalyzed $C(sp^3)$ –H activation/cycisation. *Chem Commun*. 2011; 47:11483–11485.
34. Saget T, Lemouzy SJ, Cramer N. Chiral monodentate phosphines and bulky carboxylic acids: cooperative effects in palladium-catalyzed enantioselective $C(sp^3)$ –H functionalization. *Angew Chem Int Ed*. 2012; 51:2238–2242.

35. Martin N, Pierre C, Davi M, Kazzar R, Baudoin O. Diastereo- and enantioselective intramolecular C(sp³)-H arylation for the synthesis of fused cyclopentanes. *Chem Eur J*. 2012; 18:4480–4484. [PubMed: 22407525]
36. Lee T, Hartwig JF. Rhodium-catalyzed enantioselective silylation of cyclopropyl C-H bonds. *Angew Chem Int Ed*. 2016; 55:8723–8727.
37. Murai M, Takeshima J, Morita H, Kuninobu Y, Takai K. Acceleration effects of phosphine ligands on the rhodium-catalyzed dehydrogenative silylation and germylation of unactivated C(sp³)-H bonds. *J Org Chem*. 2015; 80:5407–5414. [PubMed: 25961415]
38. Goodhue CT, Schaeffer JR. Preparation of L(+) β-hydroxyisobutyric acid by bacterial oxidation of isobutyric acid. *Biotechnol Bioeng*. 1971; 13:203–214. [PubMed: 5580680]
39. Giri R, Chen X, Yu JQ. Palladium-catalyzed asymmetric iodination of unactivated C-H bonds under mild conditions. *Angew Chem Int Ed*. 2005; 44:2112–2115.
40. Wu Q-F, Shen P-X, He J, Wang X-B, Zhang F, Shao Q, Zhu R-Y, Marcelli C, Qiao JX, Poss MA, Yu J-Q. Formation of β-chiral centers by asymmetric β-C(sp³)-H arylation, alkenylation, and alkynylation. *Science*. 2017; 355:499–503. [PubMed: 28154075]
41. He J, Shao Q, Wu QF, Yu JQ. Pd(II)-catalyzed enantioselective C(sp³)-H borylation. *J Am Chem Soc*. 2017; 139:3344–3347. [PubMed: 28209055]
42. Bach RD, Dmitrenko O. Strain energy of small ring hydrocarbons. Influence of C-H bond dissociation energies. *J Am Chem Soc*. 2004; 126:4444–4452. [PubMed: 15053635]
43. Pan SG, Endo K, Shibata T. Ir(I)-catalyzed enantioselective secondary sp³ C-H bond activation of 2-(alkylamino)pyridines with alkenes. *Org Lett*. 2011; 13:4692–4695. [PubMed: 21812393]
44. Pan SG, Matsuo Y, Endo K, Shibata T. Cationic iridium-catalyzed enantioselective activation of secondary sp³ C-H bond adjacent to nitrogen atom. *Tetrahedron*. 2012; 68:9009–9015.
45. Tahara Y, Michino M, Ito M, Kanyiva KS, Shibata T, Tahara Y, Michino M, Ito M, Kanyiva KS, Shibata T. Enantioselective sp³ C-H alkylation of γ-butyrolactam by a chiral Ir(I) catalyst for the synthesis of 4-substituted γ-amino acids. *Chem Commun*. 2015; 51:16660–16663.
46. Pedroni J, Boghi M, Saget T, Cramer N. Access to β-lactams by enantioselective palladium(0)-catalyzed C(sp³)-H alkylation. *Angew Chem Int Ed*. 2014; 53:9064–9067.
47. Jain P, Verma P, Xia G, Yu JQ. Enantioselective amine α-functionalization *via* palladium-catalysed C-H arylation of thioamides. *Nat Chem*. 2017; 9:140–144. [PubMed: 28282045]
48. Zhang FL, Hong K, Li TJ, Park H, Yu JQ. Functionalization of C(sp³)-H bonds using a transient directing group. *Science*. 2016; 351:252–256. [PubMed: 26816374]
49. Yan SB, Zhang Z, Duan WL. Palladium-catalyzed asymmetric arylation of C(sp³)-H bonds of aliphatic amides: controlling enantioselectivity using chiral phosphoric amides/acids. *Org Lett*. 2015; 17:2458–2461. [PubMed: 25937267]
50. Wang H, Tong HR, He G, Chen G. An enantioselective bidentate auxiliary directed palladium-catalyzed benzylic C-H arylation of amines using BINOL phosphate ligand. *Angew Chem Int Ed*. 2016; 55:15387–15391.
51. Wasa M, Chan KSL, Zhang XG, He J, Miura M, Yu JQ. Ligand enabled methylene C(sp³)-H bond activation with a Pd(II) catalyst. *J Am Chem Soc*. 2012; 134:18570–18572. [PubMed: 23116159]
52. Chen G, Gong W, Zhuang Z, Andrä MS, Chen YQ, Hong X, Yang YF, Liu T, Houk KN, Yu JQ. Ligand-accelerated enantioselective methylene C(sp³)-H bond activation. *Science*. 2016; 353:1023–1027. [PubMed: 27701111]
53. Yang YF, Chen G, Hong X, Yu JQ, Houk KN. The origins and dramatic differences in five-membered vs six-membered chelation of Pd(II) on efficiency of C(sp³)-H bond activation. *J Am Chem Soc*. 2017; 139:8514–8521. [PubMed: 28578572]
54. Huerta FF, Minidis ABE, Bäckvall JE. Racemisation in asymmetric synthesis. Dynamic kinetic resolution and related processes in enzyme and metal catalysis. *Chem Soc Rev*. 2001; 30:321–331.
55. Chu L, Xiao KJ, Yu JQ. Room-temperature enantioselective C-H iodination *via* kinetic resolution. *Science*. 2014; 346:451–455. [PubMed: 25342799]
56. Xiao KJ, Chu L, Yu JQ. Enantioselective C-H olefination of α-hydroxy and α-amino phenylacetic acids by kinetic resolution. *Angew Chem Int Ed*. 2016; 55:2856–2860.

57. Xiao KJ, Chu L, Chen G, Yu J-Q. Kinetic resolution of benzylamines *via* palladium(II)-catalyzed C–H cross-coupling. *J Am Chem Soc.* 2016; 138:7796–7800. [PubMed: 27249208]
58. Gao DW, Gu Q, You SL. Pd(II)-catalyzed intermolecular direct C–H bond iodination: an efficient approach toward the synthesis of axially chiral compounds *via* kinetic resolution. *ACS Catal.* 2014; 4:2741–2745.
59. Katayev D, Nakanishi M, Burgi T, Kündig EP. Asymmetric C(sp³)–H/C(Ar) coupling reactions. Highly enantio-enriched indolines *via* regiodivergent reaction of a racemic mixture. *Chem Sci.* 2012; 3:1422–1425.
60. Yang L, Melot R, Neuburger M, Baudoin O. Palladium(0)-catalyzed asymmetric C(sp³)–H arylation using a chiral binol-derived phosphate and an achiral ligand. *Chem Sci.* 2017; 8:1344–1349. [PubMed: 28451275]
61. Trost BM. Asymmetric catalysis: An enabling science. *Proc Natl Acad Sci USA.* 2004; 101:5348–5355. [PubMed: 14990801]
62. Taylor MS, Jacobsen EN. Asymmetric catalysis in complex target synthesis. *Proc Natl Acad Sci USA.* 2004; 101:5368–5373. [PubMed: 15020767]
63. Knowles RR, Jacobsen EN. Attractive noncovalent interactions in asymmetric catalysis: Links between enzymes and small molecule catalysts. *Proc Natl Acad Sci USA.* 2010; 107:20678–20685. [PubMed: 20956302]

Fig. 1. Overview of mechanistic differentiation in transition metal-mediated enantioselective C-H functionalization

(A) Biomimetic approaches/metal-oxo H-atom abstraction. (B) Metallonitrene and metalcarbene insertion into C-H bonds. (C) Topic of this review: transition metal-mediated C-H activation. Me = methyl, *t*-Bu = *tert*-butyl, *L = chiral ligand, [M] = transition metal, BPin = pinacolatoboron, X = aryl, alkyl, alkynyl, N, O, B.

Fig. 2. Overview of enantioselective C–H activation

(A) Point desymmetrization of $C(sp^2)$ –H and $C(sp^3)$ –H substrates. (B) Planar and axial desymmetrization of $C(sp^2)$ –H substrates. DG = Directing group, [M] = transition metal, L^*-L = chiral ligand, $M' = Fe, Ru$.

Fig. 3. Discovery of mono-*N*-protected amino acids

(A) Initial discovery and ligand examples. (B) Corresponding stereomodels. (C) Preliminary results of enantioselective C(sp³)–H activation. *n*-Bu = *n*-Butyl, Boc = *tert*-butyloxycarbonyl, *i*-Pr = isopropyl, OAc = acetate.

Fig. 4. Strong versus weak directing group

(A) Reaction coordinate comparing strong directing groups, weak directing groups, and weak directing groups with ligand. (B) Typical strong directing groups encountered in the literature.

Fig. 5. Representative examples of enantioselective C(sp³)-H point desymmetrization
 (A) Examples and stereomodels of Pd(II)/Pd(0) chemistry. (B) Examples of Pd(0)/Pd(II) chemistry. (C) Examples of Rh(I)/Rh(III) chemistry. *n*-Pr = *n*-propyl, EWG = electron-withdrawing group, COD = 1,5-cyclooctadiene, Ar = aryl, OTf = triflate, NHC = *N*-heterocyclic carbene.

Fig. 6. Desymmetrization of acyclic systems and desymmetrization of geminal-dimethyl amides
(A) Examples and limitations of enantioselective C-H activation of acyclic systems. (B) Inspiration for a novel ligand design. (C) Desymmetrization of geminal dimethyl amide substrates. (D) Proposed stereomodel of APAO ligands. IOAc = iodoacetate, Ph = phenyl, TIPS = triisopropylsilyl, APAO = acetyl-protected, amino oxazoline.

Fig. 7. Overview of methylene C–H activation

(A) Overview of major challenges in methylene C–H activation. (B) Representative C–H activation of methylene C–H bonds α -to heteroatoms (C) Representative examples of benzylic C–H activation. dba = dibenzylideneacetone, MeCN = acetonitrile.

Fig. 8. Unbiased methylene C–H activation

(A) Significant problems of bidentate directing groups. (B) Inspiration for novel bidentate APAQ ligands. (C) APAQ-enabled enantioselective methylene C–H activation. (D) Proposed stereomodel for APAQ-enabled enantioselective methylene C–H activation. TFA = trifluoroacetic acid, APAQ = acetyl-protected amino quinoline.

A. Kinetic resolution and parallel kinetic resolution **B. Initial report of MPAA-enabled C(sp²)-H kinetic resolution** **C. Intramolecular Pd(0)/Pd(II) Parallel Kinetic Resolution and Kinetic Resolution** **Fig. 9. Kinetic resolution C-H activation**

(A) Overview of kinetic resolution and parallel kinetic resolution. (B) Initial report on MPAA-enabled C(sp²)-H kinetic resolution. (C) Early examples of C(sp³)-H kinetic resolution. PG = protecting group, Cy = cyclohexyl,