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Palladium-Catalyzed Alkyl C–H Bond Activation

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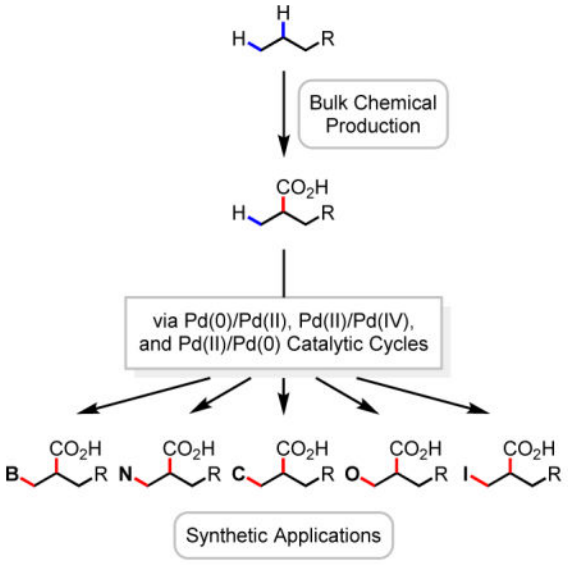
Abstract

This Review summarizes the advancements in Pd-catalyzed C(sp^3)–H activation via various redox manifolds, including Pd(0)/Pd(II), Pd(II)/Pd(IV), and Pd(II)/Pd(0). While few examples have been reported in the activation of alkane C–H bonds, many C(sp^3)–H activation/C–C and C–heteroatom bond forming reactions have been developed by the use of directing group strategies to control regioselectivity and build structural patterns for synthetic chemistry. A number of mono- and bidentate ligands have also proven to be effective for accelerating C(sp^3)–H activation directed by weakly coordinating auxiliaries, which provides great opportunities to control reactivity and selectivity (including enantioselectivity) in Pd-catalyzed C–H functionalization reactions.

Graphical Abstract



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Notes

The authors declare no competing financial interest.

1. INTRODUCTION

Despite intensive efforts to advance new synthetic methods in organic chemistry, the development of effective strategies to convert C–H bonds to other functional groups *en route* to a wide range of more complicated materials, such as polymers and bioactive molecules, remains a central challenge in catalysis.[1–16] In particular, selective activation/functionalization of alkyl C(sp^3)–H bonds presents both a fundamental and a practical challenge to chemists due to the robust nature of such bonds.[17–27] C(sp^3)–H bonds are among the most ubiquitous chemical bonds in nature. However, the development of methods to selectively functionalize these abundant bonds has faced tremendous difficulties. The poor reactivity of C(sp^3)–H bonds is often attributed to their high bond energies (typically 90–100 kcal/mol), low acidity (estimated pK_a = 45–60), and unreactive molecular orbital profile.[1–31]

Although C(sp^3)–H bonds are more difficult than other types of linkages to cleave, they are not completely inert. In the last several decades, there has been a renaissance in transition metal-catalyzed C–H activation reactions.[1–27] While this type of reaction has proven to be effective for the selective functionalization of aryl C(sp^2)–H bonds, the focus of this review is on recent developments in the realm of Pd-catalyzed alkyl C(sp^3)–H activation/functionalization. Pd-mediated C(sp^3)–H cleavage poses a unique set of challenges because the system possesses added conformational degrees of freedom and because the metal cannot engage with the target C–H bond via an initial π-orbital interaction, which is able to occur in the initial step of C(sp^2)–H cleavage. A review on C(sp^3)–H activation reactions with Pd catalysts is provided herein. A special focus is placed on early developments in alkyl C–H cleavage using stoichiometric amount of Pd, which served as the intellectual foundation for recent emergence of catalytic processes.

2. C(sp^3)–H ACTIVATION OF ALKANES

Among the thousands of reagents in the arsenal of the modern synthetic organic chemists, few reaction systems have been developed that are capable of carrying out selective reactions on C(sp^3)–H bonds of alkanes.[1–16] A rare example involves Pd(II)-catalyzed C(sp^3)–H carboxylation of cyclohexane **1** by Fujiwara and coworkers (Scheme 1).[32–42] With **1** in large excess as solvent, treatment with high pressure CO (20–40 atm) and a Pd(II)/Cu(II) catalytic system in trifluoroacetic acid (TFA) at 80 °C afforded cyclohexanecarboxylic acid **2** in 4.3% based on cyclohexane (Scheme 1).[33] Subsequently, the same laboratory reported C(sp^3)–H carboxylation reactions of gaseous acyclic alkanes to give the corresponding aliphatic acids.[36] For instance, propane **3** reacted with CO (20 atm) in the presence of 0.05 mmol $Pd(O_2CEt)_2$, $CuSO_4$, and $K_2S_2O_8$ in TFA at 80 °C to give isobutyric acid **4a** and butyric acid **4b** in 360% and 300% yield, respectively, calculated based on the amount of added Pd. The mechanism of C(sp^3)–H activation in these processes was proposed to involve the initial generation of cationic $[Pd(TFA)]^+$ species in TFA, which is strongly electrophilic and can be attacked by C(sp^3)–H bonds of alkanes to give [alkyl–Pd(II)–TFA] species. The potential involvement of radical species was also proposed.[36]

The use of chelating bis(*N*-heterocyclic carbene) ligands to promote Pd(II)-catalyzed C(sp^3)–H activation of methane was first reported by Strassner and co-workers (Scheme

2).[43] A suspension of $K_2S_2O_8$ in a mixture of TFA and trifluoroacetic anhydride (TFAA) at a methane pressure of 30 bar led to the formation of trifluoroacetic acid methyl ester in 3000% yield relative to Pd. The same bis(NHC) palladium catalyst **5** was later applied to the oxidation of propane in the presence of $NaVO_3$ and dioxygen.[44] The mechanism involving C(sp^3)–H cleavage by Pd(II) and subsequent oxidation of Pd(II) to Pd(IV) by bromine was proposed.[45] In addition, the Pd(II)-catalyzed aerobic oxidation of methane was also achieved using benzoquinone and $NaNO_2$ as cocatalysts.[46]

Alkanes are nonpolar and hydrophobic and thus interact very weakly with polar Pd species. To overcome this weak affinity and drive metal-mediated C(sp^3)–H cleavage, alkane substrates must generally be used in large excess (as solvent when liquid, or under high pressure when gaseous), as in the previous examples. Because highly reactive Pd species are needed to cleave C(sp^3)–H bonds, controlling the regioselectivity and chemoselectivity of the reaction to avoid over-functionalization has traditionally been difficult.[1–16] Additionally, because both the substrates and products are comparatively low-value chemicals, developing homogeneous catalysts with exceptionally high turnover numbers (TONs) that are competitive with alternatives (including heterogeneous catalysts) is commercially unattractive. As a consequence, to date Pd(II)-catalyzed functionalization of alkanes is limited to the aforementioned carbonylation and trifluoroacetoxylation, with no extension of this methodology to other C(sp^3)–C or C(sp^3)–heteroatom bond formation.[1–16,47–52] In the following sections, the Pd-mediated C(sp^3)–H activation methods that have emerged since the 1960s that use pre-existing functional groups to coordinate Pd and position it for efficient and regioselective C(sp^3)–H activation will be highlighted.

3. C(sp^3)–H ACTIVATION DIRECTED BY CARBON–HALOGEN BONDS (VIA Pd(0)/Pd(II) CATALYSIS)

Pd catalysts are unique in that the overall catalytic process can be tailored to mimic that of traditional Pd(0)-catalyzed cross-coupling reactions of organohalides and organometallic reagents, which are known for their remarkable utility, practicality, and reliability. Indeed, a number of groups have exploited Pd(0) catalysts to effect *intramolecular* C–H activation reactions of organohalide substrates, as summarized below. Based on the knowledge acquired from these works, we sought to develop improved directing groups in the context of Pd(0)/ligand (L)-catalyzed *intermolecular* C(sp^3)–H activation reactions, with the long term vision that any insights regarding reactivity could then be extended to other Pd(II)-catalyzed C(sp^3)–H activation systems.

3.1. Intramolecular Activation of C(sp^3)–H Bonds

A seminal report on the synthesis of polycyclic systems by Pd-catalyzed C(sp^3)–H activation from aryl iodides was published by Dyker in 1994 (Scheme 3).[53] Synthesis of 1,2-dihydrocyclobutabenzene derivative **13** was effected when 2-iodo-*tert*-butylbenzene **7** was reacted with catalytic $Pd(OAc)_2$, arylbromide, potassium carbonate, and a quaternary ammonium salt in DMF. The reaction was proposed to involve a complex sequence of events, starting with oxidative addition of the aryl iodide to a Pd(0) species followed by intramolecular C(sp^3)–H activation. The resulting five-membered palladacycle **9** undergoes

intermolecular coupling to forge a new C(sp^2)–Ar bond via Pd(II)/Pd(IV) catalysis to give **10**. Subsequent C(sp^2)–H activation by the [alkyl–Pd(II)] species forms the cyclopalladated intermediate **12**, which undergoes reductive elimination to forge the 1,2-dihydrocyclobutabenzene product **13** and regenerate catalytically active Pd(0).

In 2003, Baudoin reported the first example of Pd(0)/phosphine-catalyzed synthesis of fused four-membered carbocycles by intramolecular C(sp^3)–H arylation from aryl bromides (Scheme 4).[54] In contrast to Dyker's previous work, no oligomerization was observed due to the effect of the phosphine ligand. Importantly, [Ar–Pd(II)–X] species generated upon oxidative addition of the aryl bromide **16** could cleave methylene C(sp^3)–H bonds. However, sluggish reductive elimination to forge the C(sp^3)–Ar bond led to competitive β-hydride elimination giving a mixture of unsaturated products **17a** and **17b**. The reaction yields and turnover frequency (TOF) numbers of this alkane dehydrogenation were further increased by using a more electron-deficient triarylphosphine ligand (Scheme 4).[55]

Several related reports described the formation of analogous fused five-membered heterocycles by intramolecular C(sp^3)–H arylation from aryl halides (Scheme 5). First, Fagnou reported the synthesis of 2,2-dialkyldihydrobenzofurans **21** by using *in situ*-generated Pd(0)/PCy_3, cesium carbonate, and pivalic acid as an additive.[56] Ohno also described the synthesis of indolines **23** from functionalized 2-bromoanilines **22** under nearly identical conditions.[57] More recently, the research groups of Fagnou and Baudoin jointly reported the use of aryl chlorides **24** to effect intramolecular C(sp^3)–H arylation reactions.[58] Interestingly, Fagnou also reported a rare example of cyclopropyl C–H activation for the synthesis of dihydroquinoline **27**, which was treated with DDQ to give quinoline derivatives **28**.[59] The cyclopropyl group can be extended by one more carbon from aryl halides, as demonstrated by Cramer in the activation of a methine C(sp^3)–H bond of cyclopropanes, to access spiroindoline scaffolds **30** using similar reaction conditions.[60]

In 2012, starting from cycloalkenyl bromides **31**, the Baudoin group realized Pd(0)-catalyzed intramolecular C(sp^3)–H alkenylation to efficiently build up the octahydroindole cores.[61] This gram-scale reaction was later applied to the synthesis of aeruginosin marine natural products (Scheme 6).[62]

For the activation of benzylic C(sp^3)–H bonds, the substrates are not limited to aryl halides in Pd(0)-catalyzed intramolecular cyclization reactions (Scheme 7).[63–65] In 2012, the Takemoto group developed a chemoselective lactam formation reaction to synthesize various oxindoles using carbamoyl chloride precursors **36**.[63] In order to achieve high reaction efficiency, the intramolecular cyclization needs to be carried out under CO atmosphere with PivNHOH as an additive. This illustrates an early example utilizing [ArNHCOPd(II)L_n] complexes to activate and aminocarbonylate benzylic C(sp^3)–H bonds. The Cramer group subsequently employed Pd(0)-catalyzed C(sp^3)–H activation of trifluoroacetimidoyl chlorides to synthesize a range of valuable 2-(trifluoromethyl)indoles (**39**).[64]

In the course of a study on the Suzuki–Miyaura coupling of bulky aryl bromides, Buchwald observed the formation of an unexpected arylation product that arose from C(sp^3)–H activation of the *ortho-tert*-butyl group in **40** (Scheme 8).[66] This represents a rare example of

intermolecular C–H functionalization process enabled by a [Ar–Pd(II)L_n] species formed via oxidative addition of an aryl halide. In 2011, the Buchwald laboratory also used the same classes of substrates (**40**) to perform analogous intermolecular C(sp^3)–H amination.[67] Reductive elimination to form a C(sp^3)–N bond from a Pd(II) species was unprecedented prior to this report.

3.2. Enantioselective Intramolecular C(sp^3)–H Activation

Recently, Kündig applied optically active NHC ligands derived from chiral 2,2-dimethyl-1-arylpropane-1-amines to the synthesis of highly enantioenriched *trans*-fused indolines **44a** by Pd(0)-catalyzed C(sp^3)–H activation of cycloalkanes (**43**) (Scheme 9).[68] Despite the need for reaction temperatures of 140–160 °C, high asymmetric recognition of one of the two enantiotopic C(sp^3)–H bonds on the unactivated methylene unit could be achieved. Shortly after this seminal report by Kündig, Kagan reported the desymmetrization of prochiral *gem*-dimethyl C(sp^3)–H bonds in **45** using optically active (*R*,*R*)-Me-DUPHOS as the ligand to obtain ee values as high as 93%.[69] Intriguingly, less than 50% ee could be obtained for asymmetric intramolecular arylation of cyclic C(sp^3)–H bonds. Further development of this method by Cramer described the cooperative effects of chiral monodentate phosphines and bulky carboxylic acids in Pd(0)-catalyzed desymmetrization of *gem*-dimethyl and cycloalkyl C(sp^3)–H bonds in **47** and **49** to obtain ee values up to 95%.[70]

Using monodentate TADDOL-derived phosphoramidites and phosphonites as chiral ligands, the Cramer group also developed several enantioselective Pd(0)-catalyzed intramolecular cyclization reactions of cyclopropanes (Scheme 10).[71–73] The direct C(sp^3)–H arylation of cyclopropylmethyl anilines led to the formation of the chiral tetrahydroquinolines (**52**). The phosphoramidite ligand and pivalic acid additive are essential for achieving both excellent reactivity and enantioselectivity.[71] Similarly, the combination of a bulky phosphonite ligand with adamantane-1-carboxylic acid enabled a highly enantioselective C(sp^3)–C(sp^3) bond forming reaction of the chloroacetamides **53**, providing a concise route for the synthesis of chiral cyclopropane-fused γ-lactams.[73]

4. C(sp^3)–H ACTIVATION DIRECTED BY STRONGLY COORDINATING AUXILIARIES

Recent developments in Pd-catalyzed C–H activation reactions have depended on the use of substrates containing one or more pre-existing functional groups that chelate the Pd catalyst and position it for selective cleavage of a proximate C–H bond.[17–27] Precoordination can overcome the unreactive “paraffin” nature of C–H bonds by increasing the effective concentration of the substrate so that it need not be used in stoichiometric excess. Traditionally, nitrogen-, sulfur-, or phosphorous-containing moieties (*e.g.*, pyridine, oxazoline, sulfide, and phosphine), which are relatively strong σ-donors and/or π-acceptors, have been employed as auxiliaries to direct Pd-mediated C–H activation because they are capable of coordinating strongly to Pd and forming stable, well-defined metallacycles.[3]

4.1. Syntheses and Characterization of Palladacycles

The term "cyclometalation" was first introduced by Trofimenko,[74] and reactions of this type involving cleavage of C(sp^2)–H and C(sp^3)–H bonds by late transition metals to form defined [M–R] species have been known for several decades, with examples of well characterized cyclometalated complexes appearing in the literature as early as the 1960s.[3] These inner-sphere processes are known to proceed by a variety of different mechanisms depending on the metal species, the substrates, and the reaction conditions; they include oxidative addition, electrophilic activation, concerted metalation/deprotonation, and σ-bond metathesis.[6]

Since the initial discovery of σ-chelation-directed cleavage of C–H bonds in 1960s, substantial efforts have been invested into making this stoichiometric process synthetically useful.[75–85] Because organopalladium compounds are valuable intermediates in organic synthesis, cyclopalladation has been extensively studied. Numerous examples of cyclopalladation reactions involving aromatic or benzylic C(sp^2)–H bonds have been reported, but only a few cases have involved unactivated aliphatic C(sp^3)–H bonds. These early stoichiometric studies on cyclopalladation involving C(sp^3)–H activation have served as the intellectual foundation for our group in developing catalytic processes, and key findings will be summarized herein.

In 1978, Shaw and coworkers reported a pioneering example on the palladation of oximes (Scheme 11).[75] Treatment of *tert*-butyl methyl ketone oxime **55** with a stoichiometric amount of Na_2PdCl_4 and NaOAc induced cleavage of the C(sp^3)–H bond of the *tert*-butyl group to give the palladacycle **56**, which was identified as a chloride-bridged dimer. Subsequent to this discovery, a number of nitrogenous auxiliaries were also scrutinized for their potential to direct C(sp^3)–H activation.[75–80] Pyridine (**57**, **59**)[78,79] and *N*,*N*-dimethylamine (**61**)[80] were demonstrated to be effective auxiliaries for C(sp^3)–H cleavage. Interestingly, unlike the chloride-bridged dimer obtained by Shaw using the oxime auxiliary (**56**)[75] and the acetate-bridged dimer using the pyridine auxiliary (**58**),[78] Hiraki reported that the cyclopalladated complex obtained using *N*,*N*-dimethylamine-containing substrate **61** was a trinuclear complex (**62**) based on NMR and IR studies.[80] Hiraki also revealed that in substrate **59**, the joint directing effect of two pyridine groups facilitated Pd(II) insertion into methylene C(sp^3)–H bonds.[79]

In 1979, Shaw also described that heating 1,5-bis(di-*tert*-butylphosphino)pentane **63** with a stoichiometric amount of $PdCl_2(PhCN)_2$ in ethanol yielded a monomeric cyclopalladated complex **64**, which was isolated in 12% yield and characterized by elemental analysis, IR and NMR spectroscopic analysis (Scheme 12).[76] Importantly, the bidentate bis-phosphine functionality was also shown to be capable of directing the Pd(II) insertion to methylene C(sp^3)–H bonds.

4.2. Reactions of Palladacycles

Isolated palladacycles have been subjected to a variety of reaction conditions in an effort to convert the C(sp^3)–Pd bonds into C(sp^3)–C and C(sp^3)–heteroatom bonds. Functionalization of the C(sp^3)–Pd bond in Shaw's oxime-derived palladacycle **56** was achieved by Baldwin in

1985 (Scheme 13).[81] Chlorination of complex **56** with chlorine in carbon tetrachloride, followed by reduction with sodium cyanoborohydride led to the expected palladium–chlorine exchange, and product **65** was isolated in 64% yield. The reduction of **56** with sodium cyanoborodeuteride afforded β-deuterated product **66** in 41% yield. Oxidation of **56** under various conditions failed to give the desired product. However, when oxidation was attempted on the monomeric pyridine complex **67** with lead tetraacetate, followed by reduction with sodium borohydride, quantitative yield of the acetoxylated product **68** was obtained. This acetoxylation protocol was exploited by Gribble in his synthesis of β-Boswellic acid analogues.[83] In addition, Sutherland also disclosed a C(sp^3)–I bond-forming process using an oxime-derived palladacycle and I_2.[82]

Transformations of C(sp^3)–Pd bonds into a diverse collection of C(sp^3)–C bonds was achieved by Clinet in 1990 (Scheme 14).[84] The reaction of 2-*tert*-butyl-4,4-dimethyl-2-oxazoline **69** with $Pd(OAc)_2$ in acetic acid at 95 °C for 1 hour afforded yellow crystals of the dimeric palladacycle **70a** in 62% yield. Interestingly, in addition to **70a**, trinuclear species **70b** was also obtained in 16% yield. Treatment of complex **70a** with an excess of a 1-iodoalkane led to C(sp^3)–C(sp^3) bond formation to provide **71**. Furthermore, **70a** was reacted with lithium chloride in acetic anhydride to give the chloride-bridged dimer **72**. Carbonylation of **72** was effected by treatment with CO (1 atm) in methanol, giving ester **73** in 68% yield. In addition, reaction of **72** and methyl vinyl ketone in DMF and triethylamine gave the α,β-unsaturated ketone **74** in 52% yield. The C(sp^3)–Pd alkylation, carbonylation and olefination reactions in this work represent novel methods for selective "remote" functionalizations of β-C(sp^3)–H bonds in aliphatic carboxylic acid derivatives.

The potential utility of C(sp^3)–C bond-forming methods via heteroatom-directed C(sp^3)–H activation with stoichiometric Pd(II) in a more complex setting was demonstrated in synthesis of the Teleocidin B-4 core by the research group of Sames (Scheme 15).[85] The key sequence of the synthesis consisted of two C(sp^3)–H bond functionalization reactions. The imine and methoxy groups of **75** coordinated with stoichiometric $PdCl_2$ in a bidentate fashion, which triggered C(sp^3)–H bond cleavage of the proximate *tert*-butyl group. The resulting stable palladacycle **76** was treated with a substituted vinyl boronic acid; transmetalation followed by reductive elimination forged the desired C(sp^3)–vinyl bond, giving the cross-coupled product **77**. Methanesulfonic acid promoted the Friedel–Crafts cyclization reaction of **77** to yield **78**, which was then treated with another batch of $PdCl_2$ to form palladacycle **79**. Reaction of **79** with CO in methanol forged the C(sp^3)–CO_2Me bond. This intermediate was not isolated; instead the imine auxiliary was hydrolyzed, and spontaneous cyclization gave the lactam products **80a** (teleocidin B-4 precursor) and **80b**.

Transformations of C(sp^3)–Pd bonds in palladacycles into a wide range of C(sp^3)–C and C(sp^3)–heteroatom bonds provide nontraditional disconnections in retrosynthetic analyses. However, when our laboratory initiated our research program in 2002, catalytic C(sp^3)–H activation reactions using proximate directing groups were relatively undeveloped. In the following sections, the early explorations and recent developments in C(sp^3)–H functionalization using Pd catalysts to forge C(sp^3)–C and C(sp^3)–heteroatom bonds will be summarized. The versatility and practicality of these types of reactions in their current forms

are evaluated with respect to the efficiency of catalysis, substrate scope, and operational costs. Key problems and potential solutions in this field are also discussed.

4.3. C(sp^3)–H Activation via Pd(II)/Pd(IV) Catalysis

Cyclopalladation with molecules containing C(sp^3)–H bonds has been achieved using strongly coordinating nitrogen- or phosphine-containing auxiliaries.[75–85] However, strongly chelating substrates give cyclometalated intermediates that are thermodynamically stable and thus are less reactive in the subsequent functionalization step, which limits the range of nucleophiles and electrophiles with which they can react. One way to circumvent this problem is to employ highly electrophilic coupling partners that oxidize the Pd(II) center of the palladacycle to generate a high-energy Pd(IV) species that undergoes rapid reductive elimination to release Pd(II) and the desired functionalized product.[86–88]

Indeed, functionalization of aryl C(sp^2)–H bonds has been achieved using Pd(II)/Pd(IV) catalysis as early as 1971, when Fahey described Pd(II)-catalyzed *ortho*-C(sp^2)–H chlorination of strongly coordinating azobenzene **81** (Scheme 16).[87] Reaction of the putative palladacycle with Cl_2 leads to a high oxidation state Pd(IV) intermediate, which then undergoes C–Cl reductive elimination to release product **82**. Another important finding came in 1984 when Tremont found that acetanilide **83** could undergo *ortho*-C(sp^2)–H methylation with MeI in good yields and demonstrated that TONs up to 10 could be achieved by using AgOAc as an additive.[88]

Despite these seminal advances in C(sp^2)–H functionalization that proceed via Pd(II)/Pd(IV) catalysis, as well as reactions of palladacycles to forge various C(sp^3)–C and C(sp^3)–heteroatom bonds, developing methods to catalytically convert more inert C(sp^3)–H bonds remained a significant challenge. An early paper by Sanford reported that oxime and pyridine directing groups in substrates **85** and **87** are capable of effecting catalytic acetoxylation of unactivated C(sp^3)–H bonds using iodobenzene diacetate as a stoichiometric oxidant (Scheme 17).[89] Physical evidence implicating the involvement of Pd(IV) intermediates has been obtained by the same laboratory through X-ray crystallography, based on the seminal work of Canty.[86] This strategy was later applied to the synthesis of 1,2-diols, cyclic ethers, and 1,2-amino alcohols by the Dong group.[90–92] In 2006, the research group of Che also disclosed an example of oxime-directed Pd(II)-catalyzed intermolecular C(sp^3)–H amidation (Scheme 18).[93] The reaction was proposed to proceed via intramolecular C(sp^3)–H activation followed by insertion of a nitrene generated *in situ* from the corresponding amide or sulfonamide and potassium persulfate; however, a Pd(II)/Pd(IV) catalytic cycle could still be a possible mechanistic route.

In our efforts to achieve effective Pd-catalyzed C(sp^3)–H functionalization, our laboratory has aimed to address a number of specific challenges in this field. When starting our research program in 2002, we focused our efforts on exploring the Pd(II)-catalyzed asymmetric functionalization of C(sp^3)–H bonds through diastereoselective C–H activation using a chiral auxiliary. The asymmetric C–H activation/functionalization process generates a chiral organometallic intermediate that can be cross-coupled with diverse nucleophiles or electrophiles, provided that asymmetric induction during C–H cleavage is robust and that the chiral auxiliary is compatible with the respective reaction conditions.

In 2005, we reported $Pd(OAc)_2$-catalyzed $C(sp^3)$–H iodination and acetoxylation protocols that proceed via Pd(II)/Pd(IV) catalysis.[94,95] Cleavage of unactivated aliphatic and cyclopropyl C–H bonds proceeded under mild conditions with moderate to excellent levels of diastereoselectivity (Scheme 19). Installation of an optically pure oxazoline auxiliary provides a high level of asymmetric induction during the $C(sp^3)$–H insertion event to form the corresponding palladacycle, which is oxidized to a Pd(IV) species by reaction with IOAc or lauroyl peroxide. Rapid reductive elimination releases Pd(II) and the desired enantioenriched iodination or acetoxylation products. The presence of steric bulk on both the auxiliary and the α-position of the carboxylic moiety of the oxazoline substrates have effects on both the degree of diastereoselective induction and the reactivity. A decrease in steric hindrance at the α-position of the substrates resulted in only moderate levels of diastereoselectivity. Significantly lower de values along with diminished product yields were similarly obtained as the *tert*-butyl group on the chiral oxazoline was replaced by smaller groups such as isopropyl and methyl groups. The chiral auxiliary in conjunction with the resulting bicyclic transition state induces a high level of stereoselectivity during C–H bond activation via the steric repulsion model depicted in Scheme 20. Based on the characterization of a trinuclear C–H insertion intermediate **96** by ^1H NMR and X-ray crystallography, we have proposed detailed structures of the intermediate formed following the diastereoselective C–H insertion step. When the R_L group is larger than the methyl group, transition state **97a** will be favored over **97b** as a result of increased steric repulsion between R_L and the *tert*-butyl group on the chiral oxazoline. Therefore, the conformation of **97a** controls the stereochemical course of C–H insertion and hence the overall stereochemical outcome of the C–H functionalization reaction.

As an extension to Pd(II)-catalyzed $C(sp^3)$–H activation reactions using oxazoline auxiliaries, we employed an achiral oxazoline auxiliary in **98** to direct sequential di-iodination of *gem*-dimethyl carboxylate derivatives (Scheme 21).[96] The resulting di-iodinated compound **99** could be subjected to radical-mediated cyclization in the presence of benzoyl peroxide in benzene at 115 °C to provide cyclopropane product **100**. As a net transformation, this reaction represents conversion of a *gem*-dimethyl group into a cyclopropane ring.

Another pivotal class of $C(sp^3)$–H functionalization reactions that employs Pd(II)/Pd(IV) catalysis is reactions that couple $C(sp^3)$–H bonds with organohalides to forge $C(sp^3)$–C bonds. In 2005, Daugulis and coworkers reported the arylation of a $C(sp^3)$–H bond of 2-ethylpyridine **101** with 4-iodotoluene in the presence of silver acetate and $Pd(OAc)_2$ (Scheme 22).[97] The reaction was sluggish even at an elevated temperature, and only a modest yield of the arylated product **102** was obtained. In the same year, the Daugulis group described the use of bidentate auxiliaries to affect highly efficient β-arylation of carboxylic acid derivatives **103** and γ-arylation of amine derivatives **105** with iodoarenes.[98] For these transformations, the authors proposed a mechanism involving the formation of a tricoordinate palladacycle by $C(sp^3)$–H activation, followed by oxidative addition of the iodoarenes to form a Pd(IV) intermediate that would undergo reductive elimination to form the new $C(sp^3)$–C bond with concomitant generation of [I–Pd(II)–L]. Superstoichiometric quantities of AgOAc were necessary to abstract iodide from [I–Pd(II)–L] and regenerate

catalytically active $Pd(OAc)_2$. Importantly, the 8-aminoquinoline amide auxiliary was able to effect arylation of methylene C(sp^3)–H bonds; the monodentate oxime and oxazoline directing groups[89,93,94–96,99–105] employed by the Sanford group and our group have not been demonstrated to promote cleavage of acyclic methylene C(sp^3)–H bonds to date.

In 2010, Daugulis reported the development of a novel bidentate 2-methylthioaniline-amide auxiliary (**107**) to effect β-arylation of C(sp^3)–H bonds in absence of Ag salts, instead using inexpensive K_2CO_3 (Scheme 23).[106] Importantly, benzyl-protected lactic acid derivative **109** could also be arylated in 65% yield, albeit with partial racemization. The lactic acid derivatives are among one of the most challenging substrates in C(sp^3)–H activation directed by weakly coordinating auxiliaries, as the coordination of α-oxygen atoms to Pd(II) prevents the catalyst from activating C(sp^3)–H bonds. Furthermore, the 8-aminoquinoline-amide auxiliary (**111**) was employed to effect alkylation of C(sp^3)–H bonds with alkyl iodides. In 2012, the same laboratory also reported the monoselective arylation of β-C(sp^3)–H bonds in proteinogenic amino acids by installing the 2-methylthioaniline-amide auxiliary (**113**).[107]

Recently, the group of Duan demonstrated the enantioselective version of β-methylene C(sp^3)–H arylation of 8-aminoquinoline amides (Scheme 24).[108] Chiral monodentate phosphoramides were used to control the stereoselectivity in the C(sp^3)–H cleavage step. Although the hydrocinnamic acid-derived amides could furnish the desired products in 47–82% ee, the use of aliphatic acid derivatives led to very poor enantioselectivity.

The high efficiency and impressive functional group tolerance of Daugulis' methodology to couple aryl halides with C(sp^3)–H bonds using bidentate auxiliaries[109–120] have attracted several groups seeking to extend the coupling partner scope of this chemistry. For instance, Corey and coworkers developed a C(sp^3)–H acetoxylation protocol of α-amino acid derivatives (**117**) in the presence of a $Pd(OAc)_2$ catalyst, manganese(II) acetate, oxone, and acetic anhydride in nitromethane to give **118** with good diastereoselectivity (Scheme 25).[121] An efficient arylation protocol of **117** was also reported in the same manuscript. In 2011, Chatani and coworkers achieved catalytic alkynylation of β-methylene and γ-methyl C(sp^3)–H bonds in **115** using TIPS-alkynyl bromide and AgOAc (Scheme 26).[122,123] Methylene C(sp^3)–H alkenylation of aliphatic amide substrates with vinyl iodides[124] was later realized by the Rao group (Scheme 27).[125] While (*E*)-vinyl iodides gave excellent stereoselectivity of (*E*)-olefin products, (*Z*)-olefin coupling partners led to isomerization, furnishing a mixture of (*Z*)- and (*E*)-product isomers (**121a**, **121b**).

The Chen group expanded the substrate scope of C(sp^3)–H alkylation to picolinamide-protected aliphatic amine substrates **122**, using a newly identified organic phosphate promoter (Scheme 28).[126] Under similar reactions conditions, they could also achieve methylene C(sp^3)–H alkylation of aliphatic acid-derived amides **103**.[127] In the latter case, the alkyl halide partners are limited to methyl iodide and α-haloacetates. To broaden the scope with respect to the coupling partners,[128,129] Shi group developed a robust catalytic system using NaOCN and 4-chlorobenzenesulfonamide as effective additives.[128] The alkylation of α-amino acid substrates **125** is tolerant of various alkyl halides, and proceeds with high levels of diastereoselectivity.

In 2012, Daugulis and Chen independently reported examples of intramolecular amination with picolinamide-protected amine substrates **127** and **129** via Pd(II)-catalyzed C(sp^3)–H activation for the syntheses of β- or γ-lactams (Scheme 29).[130,131] Following Pd(II)-mediated C(sp^3)–H cleavage to form the tricoordinate palladacycle, iodobenzene diacetate oxidizes the Pd(II) center to Pd(IV). Reductive elimination to forge the C(sp^3)–N bond is faster than C(sp^3)–OAc bond formation, thus giving the desired lactam product.[130–132] In a subsequent manuscript, Chen also reported an example of C(sp^3)–H alkoxylation using the same substrate **122**, in which C(sp^3)–OR bond-forming reductive elimination to give **131** is more facile than the C(sp^3)–N bond-forming cyclization when the reaction was carried out in the presence of alcohols.[133] Using cyclic hypervalent iodine as the oxidant, Rao and co-workers further optimized the protocols to cleave β-methyl as well as β-methylene C(sp^3)–H bonds of aliphatic acid-derived amides, constructing C(sp^3)–O bonds with broad substrate scopes.[134,135]

Oxidative addition of palladacycle intermediates to N–halogen bonds would generate Pd(IV)–halogen species which could readily undergo reductive elimination to forge C(sp^3)–halogen bonds.[136–138] Using 8-amino quinoline amide auxiliaries, Xu reported an early example of C(sp^3)–H fluorination reactions in the presence of *N*-fluorobenzenesulfonimide (NFSI) (Scheme 30).[136] The method is more efficient in the functionalization of benzylic methylene C(sp^3)–H bonds than other types of methylene and methyl C(sp^3)–H bonds. The β-C(sp^3)–H bonds of amide substrates **133** containing α-tertiary or α-quaternary carbon centers could also be chlorinated, brominated, and iodinated in AcOH when treated with *N*-halosuccinimides (NXS) at room temperature (Scheme 30).[138] Using a similar strategy, the group of Besset developed Pd-catalyzed β-C(sp^3)–H trifluoromethyl-thiolation of aliphatic acid derivatives with *N*-SCF_3-phthalimide and PivOH.[139]

Pd(II)-catalyzed C(sp^3)–C bond-forming reactions using these bidentate auxiliaries and aryl or vinyl halides have also found applications in natural product synthesis.[140–146] In the synthesis of celogentin C (**136**), Chen utilized this approach to couple 6-iodo-1-tosyl-1*H*-indole with the β-methylene C(sp^3)–H bond of a valine-derived substrate to give **135** in 80% yield (Scheme 31).[140] In 2012, Baran and coworkers reported the total synthesis of piperaborenine B (**141**) using sequential, diastereoselective arylation reactions of cyclobutyl C(sp^3)–H bonds as the key steps (Scheme 32).[143] Subsequently, Maimone reported a short total synthesis of podophyllotoxin via Pd(II)-catalyzed arylation of cyclohexyl C(sp^3)–H bonds.[145] Very recently, Reisman and co-workers accomplished the first enantioselective total synthesis of (+)-psiguadial B.[146] The directed C(sp^3)–H alkenylation of a chiral cyclobutane **142** could provide the key intermediate **143** in 72% yield on a gram scale (Scheme 33).

Following Daugulis' pioneering work on C(sp^3)–H arylation by the use of strongly coordinating aminoquinoline amides and picolinamides,[98] many other bidentate auxiliaries containing diamide or heterocyclic moieties have been developed to construct C(sp^3)–C bonds as well as C(sp^3)–O bonds of carboxylic acid, amine, and alcohol derivatives.[147–169] There are several directing groups also capable of facilitating C(sp^3)–H activation/carbon–halogen bond forming reactions. For example, Sahoo and co-workers reported methyl C(sp^3)–H bromination and chlorination of α-quaternary aliphatic acid derivatives **145** with

N-halophthalimides assisted by *S*-methyl-*S*-2-pyridyl-sulfoximine (Scheme 34).[170] Sequential double C(sp^3)–H activation of a single substrate was made possible through sluggish halogenation on the additional β-methyl moiety at 60–65 °C. Using *N*-((2-pyridyl)isopropyl)amide as the bidentate directing group and Selectfluor as the fluorine source, the Shi group developed diastereoselective fluorination of β-methylene C(sp^3)–H bonds of α-amino acid derivatives **147** (Scheme 35).[171] The substrate scope was further expanded by using $Fe(OAc)_2$ as the additive.[172]

In 2014, our group achieved site-selective arylation of inert C(sp^3)–H bonds of N-terminal amino acids in di-, tri-, and tetrapeptides (Scheme 36).[173] The native amino acid moiety serves as the bidentate directing group to promote C(sp^3)–H activation.[173,174] Considering that the amino acid could be reversibly tethered to an aldehyde or ketone substrate via an imine linkage to mimic the coordinating mode in our dipeptide chemistry, we utilized it as a transient directing group in C(sp^3)–H activation of aldehydes and ketones (Scheme 36).[175] By using 50 mol% glycine and a 3:1 mixture of HFIP:AcOH as the solvent, a variety of aliphatic ketones could be activated to give β-arylated products (**152**). γ-Arylation was also feasible when β-C(sp^3)–H bonds were absent in the substrate. Furthermore, based on the steric interaction between the R group and the bulky side chain of the amino acid, we were able to realize enantioselective benzylic C(sp^3)–H arylation of 2-alkyl benzaldehydes **153** in 90–96% ee with the aid of 20 mol% L-*tert*-leucine.

4.4. C(sp^3)–H Activation via Pd(II)/Pd(0) Catalysis

Encouraged by our initial successes on oxazoline substrates through Pd(II)/Pd(IV) catalysis,[94–96] we attempted to harness the reactivity of these strongly coordinating auxiliaries to establish a proof of concept for an unprecedented catalytic cross-coupling reactions between C(sp^3)–H bonds and organometallic reagents proceeding through Pd(II)/Pd(0) catalysis. The advent of cross-coupling reactions between organohalides and organometallic reagents has had a lasting impact in synthetic chemistry, as well as in scientific research more broadly.[176–189] These cross-coupling reactions are compatible with a vast array of organometallic coupling partners, including aryl-, vinyl-, alkyl-, allyl- and alkynyl-metal reagents. Given that traditional cross-coupling reactions require that both of the two reactants have a reactive functional group, a logical improvement would be to develop methodology in which installation of one of the two functional groups is obviated. In particular, this could be accomplished by utilizing Pd(II)-mediated C–H activation as a means of entering the catalytic cycle, rather than oxidative addition of the aryl or alkyl halide to Pd(0).

In the early stages of our investigations, we benefited from understanding the reaction mechanisms at play in the Pd(0)-catalyzed Stille–Migita and Suzuki–Miyaura reactions,[176,178] which allowed us to identify potential problems that we could encounter (Scheme 37). These reactions proceed through a sequence of oxidative addition by the organohalide to Pd(0), transmetalation of the organometallic reagent, and finally reductive elimination to form the desired C–C bond in the product.

Based on this knowledge, we aimed to design a novel catalytic cycle in which Pd(II)-catalyzed C–H activation would generate an analogous [Pd(II)–R] species. Following

transmetalation and reductive elimination, the resulting Pd(0) species would be reoxidized by a terminal oxidant to close the catalytic cycle (Scheme 38). Comparing the two catalytic cycles, we realized that there were three major obstacles for establishing this new mode of catalysis. Firstly, it was evident that the commonly-used phosphine and NHC ligands, which play a critical role in Pd(0) catalysis, would be incompatible with the Pd(II)-catalyzed C–H cleavage step. These ligands would reduce the Pd(II) catalysts necessary for C–H cleavage, to Pd(0)/L species.[176–189] Secondly, a reoxidation system would be required to regenerate catalytically active Pd(II) from Pd(0) by a terminal oxidant, and this oxidant would need to be compatible with all other steps in the cycle. Thirdly, Pd(II) could react competitively (or predominantly) with the organometallic reagents, rather than engaging with the auxiliary and inserting into the proximal C–H bond, which would result in formation of the undesired homocoupling product. We approached each of these challenges in turn during the course of our efforts to merge C–H activation technology with cross-coupling chemistry.

We attempted to overcome these three obstacles by making logical choices of substrate (*i.e.*, directing group), organometallic reagent, and terminal oxidant. Pd(II)-catalyzed cross-coupling of C–H bonds with organometallic reagents was initially established using aryl C(sp^2)–H activation, which was better understood and more predictable. When we initiated our investigation in 2004, we had already established that oxazolines gave excellent reactivity as directing groups in the diastereoselective iodination of C–H bonds via Pd(II)/Pd(IV) catalysis.[94] Thus, we chose to take advantage of the facile and robust reactivity of the oxazoline directing group in our efforts to establish proof of concept for C–H activation/C–C cross-coupling via Pd(II)/Pd(0) catalysis. Our initial aim was to establish reaction conditions in which oxazoline-directed Pd(II)-catalyzed C–H activation would take place preferentially over organostannane homocoupling. Subsequently, transmetalation and reductive elimination would fashion the desired product. Each step would need to take place without the aid of the phosphine ligand.

As predicted, our efforts to devise Pd(II)-catalyzed C–H activation/C–C cross-coupling reaction with organostannanes faced tremendous challenges (Scheme 39).[190] Our initial attempts to treat oxazoline substrates **155** with $Pd(OAc)_2$ and organotin reagents under various conditions consistently resulted in full recovery of Pd(0) precipitates and homocoupling products. We made a crucial discovery that this could be remedied by batchwise addition of organotin reagents. In addition, effecting the C(sp^2)–C bond-forming reductive elimination from thermodynamically stable Pd(II) species **157** without the aid of bulky phosphine ligands was a significant challenge. We found that reductive elimination can be promoted by the addition of 1 equivalent of 1,4-benzoquinone (BQ), which presumably serves as an electron-withdrawing ligand, to furnish the desired cross-coupling product **159**. It is crucial to note that C(sp^3)–H bonds could not be coupled with organotin reagents under these conditions; C(sp^3)–H cleavage is far less facile than C(sp^2)–H cleavage, therefore homocoupling of organotin reagents became the predominant reaction pathway.

The Pd(II)-catalyzed C(sp^2)–H activation/C–C cross-coupling reaction with organotin reagents left several key problems to be addressed, including application of the method to C(sp^3)–H activation and use of more environmentally benign organometallic reagents. Addressing these problems required that we devise reaction conditions in which C(sp^3)–H

activation occurs faster than competitive homocoupling of the organometallic reagent. We viewed the use of organoboron reagents as advantageous because the transmetalation rate (and hence, the rate of undesired homocoupling) would be slower than in the case of organotin reagents, which we thought would prove beneficial by potentially allowing us to avoid the cumbersome batchwise addition protocol. In addition, organoboron reagents are generally safe, stable, and a large number of them are commercially available. Hence, we postulated that it would be possible to address the homocoupling problem by using the highly efficient C(sp^3)–H activation systems established in previous reports in conjunction with organoboron reagents, which are known to undergo homocoupling more slowly.

We first attempted to perform Pd(II)-catalyzed oxazoline-directed coupling of C(sp^2)–H bonds with organoboron reagents but found that this reaction gave a mere 10% yield. As we explored other directing groups, we were pleased to find that reactions between substrates containing a pyridine directing group, such as 2-phenylpyridine, and methylboroxine gave improved results (40–93% yield).[191] After establishing this reaction in the context of aryl C(sp^2)–H activation, we then proceeded to apply this novel transformation to C(sp^3)–H bonds using pyridine as a directing group to develop the first example of catalytic C(sp^3)–H/R–boron cross-coupling via Pd(II)/Pd(0) catalysis (Scheme 40).[191] Again, the addition of 1,4-benzoquinone (BQ) was found to be crucial for promoting reductive elimination from putative Pd(II) intermediate **162**. The use of Ag(I) as the reoxidant was also found to be critical for catalytic turnover and for promoting transmetalation.

Using this novel cross-coupling protocol as a platform, we reported in 2008 an asymmetric C(sp^3)–H/R–M cross-coupling procedure using a chiral amino acid ligand, through desymmetrization of prochiral *gem*-dimethyl-containing substrate **87** (Scheme 41). However, only 38% yield and 37% ee of enantioenriched product **164** was obtained.[192] Our rationale for the poor ee was that an elevated reaction temperature was necessary for the reaction to take place, which may have led to erosion in stereoinduction. Additionally, the strongly chelating pyridine substrate would outcompete the amino acid ligand for coordination sites on the Pd(II) center, which would facilitate the background racemic cross-coupling reaction without the involvement of the ligand.

With the aid of thioamide directing groups, the α-arylation of saturated azacycles and *N*-methylamines was accomplished via Pd(II)-catalyzed C(sp^3)–H cross-coupling with boronic acids.[193] This method enabled highly monoselective as well as sequential diastereoselective diarylation of pyrrolidines **165** (Scheme 42). In accordance with our early discovery of Pd(II)-catalyzed C–H cross-coupling,[191,192] BQ is essential as a promoter for reductive elimination and a suitable oxidant to regenerate Pd(II).

Apart from Pd(II)-catalyzed cross-coupling reactions of C(sp^3)–H bonds,[191–193] monodentate nitrogen heterocycles could also act as effective directing groups to promote C(sp^3)–H olefination with acrylates (Scheme 43).[194,195] In 2011, Sanford and co-workers reported pyridine-directed aerobic olefination to construct 6,5-*N*-fused bicyclic heterocycles **168**. The intramolecular conjugate addition prevented the product from overfunctionalization. Molybdovanadophosphoric acids serve as the reoxidation catalysts to generate Pd(II) during the reaction course.[196] A rare example of Pd-catalyzed pyrazole-

directed C(sp^3)–H olefination was reported by our group.[195] The mono-protected amino acid ligands (MPAA) were shown to promote C(sp^3)–H olefination for the first time. In contrast to previous work which reported the formation of aza-Michael cyclization products (**168**), this C(sp^3)–H olefination method can provide immediate access to products **170** with intact olefins. Due to the steric hindrance of the olefinated pyrazoles, the reaction rendered high mono-selectivity when multiple methyl groups were present.

Recently, a few examples of Pd(II)/Pd(0) catalytic systems have been developed using bidentate directing groups (Scheme 44).[197–201] With the help of the picolinamide auxiliary and a mixture of multiple bases, Shi and co-workers achieved γ-methyl C(sp^3)–H borylation of amine derivatives **129**.[197] Diisopropyl sulfide is essential for improving the reaction efficiency, as it stabilizes the Pd(0) species generated *in situ*. While amino acid and amino alcohol derivatives could be borylated in good yields, the reaction always required the use of a substantial amount of Pd catalyst and significant excess of bis(pinacolato)diboron (B_2pin_2). The first example of Pd-catalyzed C(sp^3)–H sulfonylation with sodium sulfinates was reported by the group of Shi.[198] The β-C(sp^3)–H bonds of aminoquinoline amides **172** bearing α-tertiary carbon centers were functionalized in the presence of silver oxidant and benzoic acid additive, affording a wide range of aryl alkyl sulfones. In 2015, Pd-catalyzed γ-C(sp^3)–H carbonylation of alkyl amines **174** was reported by Wang, in which (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) was used as the crucial sole oxidant. γ-Lactams and γ-amino acids could be readily accessed by using this synthetic strategy.[199] In 2016, Ge demonstrated a single example of Pd-catalyzed C(sp^3)–H cyanomethylation with acetonitrile assisted by the bidentate 8-aminoquinoline auxiliary.[201] The use of 40 mol% 5,5′-dimethyl-2,2′-bipyridine to bind to copper salts could dramatically increase the yield. In their proposed mechanism, the palladacycle intermediate generated from C(sp^3)–H cleavage undergoes transmetalation with cyanomethyl copper(II) species followed by C(sp^3)–C(sp^3) reductive elimination to furnish the product **176**. Both β-methyl and methylene C(sp^3)–H bonds of aliphatic acid derivatives are reactive under the reaction conditions.

Using Pd(II), a large number of strongly coordinating nitrogen- and phosphine-containing directing groups have been reported to effect stoichiometric[75–85] and catalytic activation/functionalization[89–175,190–201] of unactivated C(sp^3)–H bonds. The thermodynamic stability of the corresponding palladacycles has enabled detailed characterization and has provided a platform for developing reactions to forge C(sp^3)–carbon and C(sp^3)–heteroatom bonds. Altogether, this body of work provided important early precedents for the development of directed C(sp^3)–H functionalization reactions based on Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalysis.

However, at the same time, there are inherent problems of using strongly chelating directing groups, particularly in catalytic processes. First, substrates containing these functional groups are often synthetically restrictive either because they must be installed then removed, or because they are a permanent part of the substrate. Second, C–C and C–heteroatom reductive elimination from Pd(II) centers of thermodynamically stable palladacycles remains a significant challenge; thus many C–H functionalization reactions using strong directing groups require the generation of reactive Pd(IV) intermediates through the use of powerful oxidants and/or harsh conditions. Finally and most importantly, strong directing groups

chelate predominantly to the empty coordination sites of Pd(II), thereby outcompeting external ligands which could potentially control enantio- and regioselectivity and accelerate the rate of C(sp^3)–H activation and later functionalization steps. This is particularly problematic when using the bidentate auxiliaries such as those developed by Daugulis,[98,106–146,197–199,201] as initial coordination of the directing group occupies two coordination sites at Pd(II). In the following section, we describe our approach to developing a diverse range of Pd-catalyzed C(sp^3)–H functionalization reactions using weakly coordinating directing groups.

5. C(sp^3)–H ACTIVATION DIRECTED BY WEAKLY COORDINATING AUXILIARIES: LIGAND ACCELERATION AND ENANTIOSELECTIVITY

The classical cyclometalation/functionalization approach has proven to be indispensable for designing and developing new Pd(II)-catalyzed C(sp^3)–H activation reactions. In the preceding section, examples of Pd(II)-catalyzed C(sp^3)–H functionalization reactions were described in which the substrate contained an electron-rich, strongly chelating auxiliary which served both to promote C(sp^3)–H cleavage and to control positional selectivity. However, this approach can be disadvantageous for the reasons outlined above. In reflecting upon these limitations, we hypothesized that weaker coordinating functional groups could also be employed to trigger C(sp^3)–H cleavage. The enhanced reactivity of the thermodynamically less stable palladacycle intermediates could then be harnessed for more facile coupling to various reaction partners. This could improve the scope of compatible coupling partners, and hence increase the number of new reactions that could be developed. Furthermore, we envisioned that reactions using weakly coordinating directing groups could incorporate external ligands more easily than reactions with strong directing groups because the directing group would not outcompete the ligands for coordination sites around the Pd(II) center.

5.1. Carboxylate-Directed C(sp^3)–H Activation

Based on these hypotheses, our laboratory focused on identifying common functional groups to direct C(sp^3)–H cleavage through weak coordination. In this regard, organic molecules that contain carboxylic acid moieties are versatile, ubiquitous, and inexpensive. Thus, using carboxylic acids to direct C–H functionalization seemed appealing to us in charting a path forward. Despite the attractiveness of this line of inquiry, our preliminary forays to establish carboxylate-directed Pd(II)-mediated cleavage of inert alkyl C(sp^3)–H bonds were largely unsuccessful. The key discovery that propelled our efforts in a productive direction was the observation that a wide range of countercations, including Na^+, promoted carboxylate-directed Pd(II)-mediated cleavage of C–H bonds (Scheme 45).[202] In our working model, the sodium cation coordinates with the carboxylate group in a κ^2 fashion, which forces Pd(II) to coordinate with the unhindered lone pair of electrons on the oxygen atom. This finding enabled us for the first time to apply our C–H/R–M cross-coupling protocol to substrates that did not contain strongly coordinating directing groups.

Based on these findings, our laboratory in 2007 reported the first example of carboxylate-directed Pd(II)-catalyzed C(sp^3)–H activation/C–C cross-coupling with both alkyl- and

arylboron reagents (Scheme 46).[203] This report demonstrated that a functional group as simple and ubiquitous as a carboxylic acid could serve as a directing group for cleaving inert β-C(sp^3)–H bonds and subsequent cross-coupling with organoboron reagents to forge a wide variety of C(sp^3)–C bonds. Despite these significant steps forward, this research program also revealed several problematic aspects of carboxylate-directed Pd-catalyzed C(sp^3)–H activation.

Firstly, the isolated yield of **178** was only 38%, implying that the carboxylate group had low efficacy as a directing group for promoting facile C(sp^3)–H activation by Pd(II). A major obstacle in these coupling reactions is the undesired Pd(II)-mediated homocoupling of the organometallic reagents. This side reaction becomes predominant if C–H activation of the substrate is not sufficiently fast. Extensive screening was carried out in an effort to find suitable reaction conditions for carboxylate-directed Pd(II)-catalyzed C(sp^3)–H activation/C–C cross-coupling with organoboron reagents; however, success was limited. Even under the best conditions, Pd(0) was observed to precipitate out of solution in the form of Pd black or other aggregates after only three hours. After this point, no further C–H functionalization was found to take place.

Secondly, carboxylic acid–directed C(sp^3)–H activation reactions were ineffective with substrates containing α-hydrogen atoms, such as **179** (Scheme 47). This restricts the range of starting materials to those possessing quaternary carbon centers at the α-position, such as **177**. The lack of reactivity can be explained by the loss of a favorable Thorpe–Ingold effect (comparing substrates with quaternary carbon centers at the α-position to those containing α-hydrogen atoms).[204] In addition, for α-hydrogen-containing substrates, following Pd(II)-mediated C–H activation, the resulting palladacycle can undergo β-hydride elimination with the α-hydrogen atom. As a consequence, many synthetically important carboxylic acid substrates, such as alanine and lactic acid, could not be functionalized.

Thirdly, β-methylene C(sp^3)–H bonds could not be activated under the reported conditions (Scheme 48). Methylene C–H bonds are substantially more resistant to Pd(II) insertion than methyl C–H bonds due to increased steric hindrance. Furthermore, following the hypothetical methylene C(sp^3)–H cleavage step to form the putative palladacycle, with substrates containing α-hydrogen atoms, undesired β-hydride elimination could occur due to the presence of C–H bonds at the α- and γ-positions, and could become predominant if subsequent steps (*e.g.*, transmetalation and reductive elimination) are sluggish. Therefore, only methyl C(sp^3)–H bonds could be functionalized using carboxylate directing groups. These severe limitations with carboxylate directing groups in C(sp^3)–H activation prompted us to reconsider alternative strategies towards developing a diverse collection of C(sp^3)–H functionalization reactions. To improve these rather challenging but potentially powerful transformations, we elected to pursue two related approaches: (1) develop new weakly coordinating auxiliaries and (2) identify ligands capable of improving reactivity.

We initially aimed to improve significantly the rate of C(sp^3)–H activation, which would ideally allow us to reduce the reaction temperature, improve the yield, expand the substrate scope to include α-hydrogen-containing starting materials, and functionalize methylene C(sp^3)–H bonds. In particular, we sought to design an auxiliary that would improve

reactivity but would be synthetically versatile. To this end, we revisited a simple aliphatic acid substrate and converted the carboxylic acid group into a hydroxamic acid (CONHOMe) moiety. Due to its structural similarity to a carboxylic acid, we hypothesized that this amide could mimic the coordination mode of an acid while also providing improved reactivity by offering stronger coordination.

5.2. Hydroxamic Acid-Directed C(sp^3)–H Activation

After an extensive survey of possible reaction conditions, we established an improved protocol for β-C–C bond formation using a hydroxamic acid auxiliary (**184**), which gave substantially higher yields of **185** at lower reaction temperatures (70 °C) (Scheme 49).[205] However, under the reported reaction conditions, substrates containing α-hydrogen atoms (**186**) and methylene C(sp^3)–H bonds (**188**) could not be functionalized. Nevertheless, in light of our observation that a hydroxamic acid auxiliary was capable of promoting facile C(sp^3)–H activation, we conjectured that by systematically modifying the steric and electronic properties of related amide auxiliaries, we could find a solution to our reactivity problems.

5.3. *N*-Arylamide-Directed C(sp^3)–H Activation

5.3.1. Pd/PR_3 and Pd/NHC-Catalyzed C(sp^3)–H Activation—A systematic electronic and steric optimization of amide directing groups was initiated by preparing an assortment of *N*-arylamide compounds **190** by reacting isobutyryl chloride with an array of commercially available anilines. These amides were reacted with $Pd(OAc)_2$ and (2-biphenyl)dicyclohexylphosphine (cyclohexyl JohnPhos) in the presence of iodobenzene, CsF and 3Å molecular sieves in toluene (Scheme 50).[206] While the substrates containing electron-donating substituents gave no β-C(sp^3)–H arylated product, product formation was observed with substrates containing electron-withdrawing groups. It was found that the highly electron-withdrawing pentafluoroaryl-substituted amide gave the product with highest efficiency of 88% (34% mono- and 54% di-arylation). These results showed that the amide containing an acidic N–H bond could be readily deprotonated by CsF to yield the corresponding Cs–amidate. The *in situ*-generated [Ph–PdL_n–X] complex was first hypothesized to coordinate to the sp^2-hybridized nitrogen atom of Cs–amidate; this coordination mode was later verified by X-ray crystallographic analysis of a Pd/amidate complex (Scheme 51).[207] Upon the palladacycle formation, subsequent C(sp^3)–C(sp^2) bond forming reductive elimination yielded the desired product and Pd(0). A range of *N*-arylamide substrates containing an α-quaternary or α-tertiary carbon center gave the corresponding β-arylation products in good to excellent yields.[59] This catalytic system was later applied to β-methylene C(sp^3)–H arylation of 1-admantanecarboxylic acid-derived amides[208] as well as γ-C(sp^3)–H arylation of acrylamide derivatives.[209]

One of the key findings made during the development of this method is that both steric and electronic properties of Pd(II) center could be fine-tuned to promote facile C(sp^3)–H cleavage/reductive elimination sequence by the cooperative effect of two ligands: amidate directing group and organophosphines. The ability to readily optimize the reactivity by such a cooperative effect is a fundamental advantage over the previous methods that only used strongly coordinating directing groups. To be specific, substrates containing strongly

coordinating moieties could outcompete the catalytic quantity of ligands (such as PR_3 and *N*-protected amino acid) for the coordination site(s) of the Pd(II) center. As a consequence, reactivity is predominantly controlled by the directing group and limited ligand effect can be observed. To the best of our knowledge, there has been no report of Pd/PR_3-catalyzed transformations of C(sp^3)–H bonds using oxazoline and pyridine directing groups. Low enantioselectivity (37% ee, Scheme 41) obtained in Pd(II)/amino acid-catalyzed enantioselective cross coupling reaction of 2-isopropylpyridine and *n*-butylboronic acid[192] could be another evidence for such outcompeting of the chiral ligand by the directing group. In contrast, we have demonstrated that weaker coordinating Cs–amidate does not outcompete the PR_3 ligand but instead promote Pd(II)-catalyzed C(sp^3)–H functionalization cooperatively.

Our laboratory has also reported that Pd(0)/phosphine and Pd(0)/NHC complexes are capable of facilitating alkynylation of C(sp^3)–H bonds with alkynyl halides without the use of external oxidants (Scheme 52).[210] Carboxylic acid derivatives containing α-hydrogen atoms give good yields, and ethers are also well tolerated (**195a**). This method is also effective for the activation of cyclohexyl and tetrahydropyranyl C(sp^3)–H bonds (**195b**) with high levels of diastereoselectivity, and allows for the installation of two different alkynyl groups in product **195c**.

Encouraged by these advancements on ligand-promoted C(sp^3)–H activation,[206,210] we designed an analogous Pd(0)/Pd(II) catalytic cycle to achieve intermolecular C(sp^3)–H amination reactions with *O*-benzoyl hydroxylamines (Scheme 53).[211] The use of an electron-deficient triarylphosphine ligand is crucial for this transformation to proceed, as it stabilizes the Pd–amido species (**198**) and facilitates C(sp^3)–N reductive elimination. This method allows for the direct amination of C(sp^3)–H bonds in a variety of substrates from the lipid-lowering drug gemfibrozil (**197a**) to the natural product dehydroabietic acid (**197b**), as well as providing access to novel β-amino acids including synthetic precursors for several bioactive molecules (**197c**). *O*-Benzoyl hydroxylamines were later applied to the Pd(II)-catalyzed C(sp^3)–H amination of bidentate carboxylic acid-derived amides bearing α-hydrogen atoms.[212]

Very recently, NHC ligand-enabled C(sp^3)–H arylation of saturated heterocycles with a wide range of aryl iodides was reported by our group (Scheme 54).[213] Experimental data is consistent with a Pd(II)/NHC complex insertion into C(sp^3)–H bonds, followed by subsequent functionalization with aryl iodides, which is distinct from the Pd(0)/NHC/ArI catalysis. Both C3 and C4 C(sp^3)–H bonds of piperidine and tetrahydropyran derivatives could be successfully arylated. The diastereoselectivity of this transformation is controlled by the conformation of the six-membered rings during the C(sp^3)–H cleavage step.

5.3.2. $Pd(OAc)_2$-Catalyzed C(sp^3)–H Activation—We were also successful in reacting *N*-arylamides with $Pd(OAc)_2$, iodobenzene, Cs_2CO_3, and AgOAc to give the desired arylated products (Scheme 55).[214] These results indicate that $Pd(OAc)_2$ is capable of activating β-C(sp^3)–H bonds of Cs–amidate without the aid of PR_3 or NHC ligands via a Pd(II)/Pd(IV) catalytic system. The reaction could proceed through the activation of C(sp^3)–H bonds by $Pd(OAc)_2$ coordinating with Cs–amidate to generate a palladacycle. Oxidative

addition of aryl iodides onto the palladacycle gives Pd(IV), followed by C(sp^3)–Ar bond forming reductive elimination to provide the desired product and L_nPd(II)–I, which undergoes ligand exchange with AgOAc to give L_nPd(II)–OAc.

Very recently, Sanford and co-workers attached the perfluorinated amide auxiliary onto saturated nitrogen-containing heterocycles to facilitate a remote site-selective C(sp^3)–H arylation reaction (Scheme 56).[215] In order to suppress α-oxidation of amines, non-oxidizing cesium salts served as an effective additive to promote the transformation.[106] A variety of alicyclic amines could be functionalized through this transannular approach, giving quick access to new amino-acid derivatives as well as analogues of the pharmaceutical candidates.

In 2010, our laboratory reported an example of the Pd(II)-catalyzed olefination of C(sp^3)–H bonds with acrylates which proceeds via Pd(II)/Pd(0) catalysis (Scheme 57).[216] After β-C–H olefination, the amide products underwent 1,4-conjugate addition to give the corresponding lactam compounds. The reaction conditions could also be applied to effect olefination of cyclopropyl C–H bonds and substrates containing α-hydrogen atoms. Thus, the *N*-arylamide directing group was demonstrated to robustly effect C(sp^3)–H activation even in the presence of competitively coordinating ligands (*i.e.*, acrylate, DMF) that often detrimentally influence the steric and electric properties of the Pd catalyst.

Subsequently in 2010, we disclosed a protocol to effect Pd(II)-catalyzed carbonylation of C(sp^3)–H bonds under 1 atm CO (Scheme 58).[217] The introduction of a highly oxidized carbonyl group at the β-position of carbonyl compounds (**205**) via C(sp^3)–H activation to yield 1,4-dicarbonyl compounds offers a versatile handle for further structural elaboration. Use of non-polar solvent (*n*-hexane) and use of TEMPO/AgOAc for reoxidation of Pd(0) were found to be essential for obtaining high product yield.

These examples demonstrated the versatility of *N*-arylamides in directing Pd(II)-catalyzed C(sp^3)–H cleavage and transformations of palladacycles into various C(sp^3)–C bonds. With these results in hand, we proceeded to investigate chiral ligands that could induce enantioselective C(sp^3)–H cleavage.

5.3.3. Pd(II)/Amino Acid-Catalyzed Enantioselective C(sp^3)–H Activation—

Enantioselective C–H activation of cyclopropanes was achieved through systematic tuning of the mono-*N*-protected amino acid (MPAA) ligand and reaction conditions.[218] Enantioselective C–H/R–BX_n cross-coupling with aryl-, vinyl-, and alkylboron reagents provided a new disconnection for the synthesis of *cis*-substituted chiral cyclopropanecarboxylic acids (Scheme 59).

In our continuous efforts to develop enantioselective C(sp^3)–H activation reactions, chiral mono-*N*-protected α-amino-*O*-methylhydroxamic acid (MPAHA) ligands were synthesized to achieve desymmetrization of cyclobutyl C–H bonds through Pd(II)-catalyzed cross-coupling with arylboron reagents (Scheme 60).[219] Although the presence of an α-hydrogen (relative to the amide carbonyl group) decreased the yield and ee, the reaction worked well with various 1-substituted 1-cyclobutanecarboxylic acid derivatives **210**. This new class of

chiral ligands have also shown promises for enantioselective functionalization of prochiral methyl C(sp^3)–H bonds. Using the MPAHA ligand derived from *N*-Boc leucine, cross-coupling of **212** proceeded with an aryltrifluoroborate coupling partner in moderate yield (61%) and enantioselectivity (80% ee).

5.3.4. Pd(II)/Pyridine- or Quinoline-Catalyzed C(sp^3)–H Activation—The *N*-arylamide moiety serves as a powerful auxiliary to effect a diverse array of Pd-catalyzed C(sp^3)–H functionalization reactions of aliphatic acids.[206–214,216–219] However, the monodentate auxiliaries developed in our laboratory, including the *N*-arylamide, have been unable to activate acyclic β-methylene C(sp^3)–H bonds. Selective functionalization of not only methyl but also methylene C(sp^3)–H bonds would offer an indispensable handle for elaborating carboxylic acid substrates. Our laboratory in 2012 reported the *N*-arylamide-directed Pd(II)-catalyzed arylation of acyclic and cyclic β-methylene C(sp^3)–H bonds using 2-alkoxy-quinoline ligands (Scheme 61).[220]

Further exploiting pyridine- and quinoline-based libraries allowed us to establish a catalyst-controlled system for C(sp^3)–H arylation (Scheme 62).[221] 2-Picoline ligand was able to promote highly mono-selective C(sp^3)–H arylation of alanine-derived amide **216** with a wide range of aryl iodide coupling partners, while a newly developed tricyclic quinoline ligand dramatically improved the reaction efficiency in methylene C(sp^3)–H arylation of α-amino acid derivatives. Successive application of these ligands enables the sequential hetero-diarylation of amide **216** with two different aryl iodides, affording a wide range of β-Ar-β-Ar′-α-amino acids with excellent levels of diastereoselectivity. Both configurations of the β-chiral center can be accessed by choosing the order in which the aryl iodides are installed (**220a**, **220b**). The use of a catalytic amount of trifluoroacetic acid improved both mass balance and conversion, while the absence of extra inorganic bases prevented the racemization of arylated products. The intramolecular kinetic isotope effect and ligand acceleration implicate the intimate involvement of the ligand in the C(sp^3)–H cleavage step. This strategy has also been applied to the gram-scale syntheses of various unnatural α-amino acids, bioactive molecules, and chiral bis(oxazoline) ligands using a simple *N*-methoxyamide auxiliary.[222]

Very recently, our collaboration with the Jones group demonstrated the feasibility of using an immobilized pyridine-based ligand to promote Pd(II)-catalyzed C(sp^3)–H monoarylation of alanine-derived amide **216** (Scheme 63).[223] This polymer-supported catalyst showed selectivity towards less hindered aryl iodides, and was reusable with an identical catalytic yield in a second cycle. In addition to the modification of substituents on the pyridine rings, the reactivity of Pd catalyst can also be controlled by changing the ratio between the monomer and styrene in polymer synthesis.

Starting from simple propionamide **221**, we then developed an unprecedented pyridine ligand-promoted triple sequential C–H activation reactions to prepare diverse 4-aryl-2-quinolinones in one pot (Scheme 64).[224] The monoarylated product of **221** underwent methylene C(sp^3)–H insertion, followed by β-hydride elimination to generate a cinnamide intermediate. After subsequent Heck coupling with a second aryl iodide, intramolecular C(sp^2)–H amidation would then provide product **222**. The cascade reaction sequence

involved the cleavage of five C–H bonds, two C–I bonds, and one N–H bond, and the formation of three C–C bonds and one C–N bond via four different types of palladium catalytic cycles.

As Pd(II)-catalyzed alkylation reactions go through a similar mechanism to Pd(II)-catalyzed arylation reactions, we tested the feasibility of ligand-promoted C(sp^3)–H alkylation under the previously established neutral reaction conditions. The use of quinoline-based ligands and AgOPiv increased the yields of alkylated products **217**. Various alkyl iodides could be coupled to afford numerous unnatural α-amino acids using this methodology (Scheme 65).[225] It worths mentioning that strongly basic cesium salts which are crucial in Pd(0)/Pd(II) catalysis cause *N*-alkylation of the amide directing group. Our attempts to achieve C(sp^3)–H alkylation via oxidative addition of Pd(0) to alkyl halides have not met with success so far.

A tricyclic quinoline-based ligand also enabled β-C(sp^3)–H fluorination of phenylalanine-derived amide **223** through a Pd(II)/Pd(IV) catalytic cycle (Scheme 66).[226] Using Selectfluor as the fluorinating reagent and Ag_2CO_3 as the base, this reaction proceeded in a highly diastereoselective fashion.

As Pd(II)/Pd(IV) and Pd(II)/Pd(0) catalytic systems share the identical C(sp^3)–H cleavage by $L_nPd(II)$ species as the initiation step, we hypothesized that the pyridine- or quinoline-based ligands might also effect Pd(II)-catalyzed C(sp^3)–H activation reactions via Pd(II)/Pd(0) catalysis. Under slightly modified reaction conditions based on the catalyst-controlled C(sp^3)–H arylation, we observed efficient reactivity in the olefination of alanine-derived amide substrate **216** (Scheme 67).[221] The subsequent lactamization *in situ* also ensured the mono-selectivity of the reaction.

Given that quinoline-based ligands facilitated C(sp^3)–H olefination,[221] we launched our efforts to develop new ligands that could promote β-C(sp^3)–H cross-coupling of carboxylic acid derivatives with organometallic reagents. With the new ligands, Pd(II)-catalyzed cross-coupling of C(sp^3)–H bonds with organosilicon coupling partners has been realized for the first time (Scheme 68).[227] The use of tricyclic quinoline-based ligands accelerates the C(sp^3)–H cross-coupling efficiently so as to outcompete the homo-coupling process of arylsilanes. The reaction protocol is tolerant of substrates containing α-hydrogen atoms. The development of this coupling reaction further demonstrates the potential utility of quinoline-based ligands in Pd-catalyzed C–H activation reactions, especially in Pd(II)/Pd(0) catalytic systems.

Based on the observed ligand effect, we exploited another Pd(II)/Pd(0) catalytic cycle, namely Pd(II)-catalyzed β-C(sp^3)–H borylation, using our pyridine and quinoline ligand libraries. Oxygen serves as the sole oxidant to reoxidize Pd(0) to Pd(II). Methyl β-C(sp^3)–H bonds in carboxylic acids containing α-tertiary and α-quaternary carbon centers, as well as methylene C(sp^3)–H bonds in a variety of carbocyclic rings are borylated. (Scheme 69).[228] The borylated products can thereafter be converted into various organic synthons through carbon–carbon and carbon–heteroatom bond formation.

Despite the extensive investigation of β-C(sp^3)–H functionalization of aliphatic acids in recent years, γ-C(sp^3)–H bond activation of these substrates is extremely challenging due to the instability of six-membered palladacycle intermediates. The combination of a quinoline-based ligand and a weakly coordinating amide directing group significantly lowers the energy of the transition state during the C(sp^3)–H cleavage step, allowing for Pd-catalyzed γ-C(sp^3)–H olefination and carbonylation of carboxylic acid-derived amide **231** (Scheme 70).[229,230] The diastereoselective γ-C(sp^3)–H arylation of a valine derivative (**234**) was also achieved in the presence of the tricyclic ligand (Scheme 70), which provides an alternative way to synthesize chiral unnatural amino acids.

5.4. Amine-Directed C(sp^3)–H Activation

Weakly coordinating amide auxiliaries are not the only directing groups that synergize with ligands on the palladium center to promote a variety of C(sp^3)–H activation reactions — the monodentate amine substrates are also reactive under ligand-accelerated conditions. In early 2014, our group reported the discovery of a MPAA ligand that enabled Pd(II)-catalyzed cross-coupling of γ-C(sp^3)–H bonds in triflyl-protected amines with arylboron reagents (Scheme 71).[231] The D-enantiomer of the ligand was applied to obtain high yields of L-amino acid substrates **236**, indicating that the spatial interaction between MPAA ligands and chiral amines on the Pd(II) center has noticeable influence on catalytic reactivity. Based on this observation, we envisioned that the bidentate MPAA ligand is capable of exerting chiral control in the C(sp^3)–H cleavage step through diastereoselection. Through a Pd(II)/Pd(IV) catalytic system, we developed highly enantioselective arylation of cyclopropyl C–H bonds with aryl iodides, providing a new route for the preparation of chiral *cis*-aryl-cyclopropylmethylamines **239** (Scheme 71).[232]

The observed significant ligand acceleration in the β-C(sp^3)–H olefination of alanine-derived amide **216**[221] as well as γ-C(sp^3)–H olefination of carboxylic acid derivatives[229] prompted us to investigate the feasibility of γ-C(sp^3)–H olefination of alkyl amines through the development of pyridine- and quinoline-based ligands. The newly identified 3-phenylquinoline (**Ligand 19**) was found to enable the olefination of Tf-protected simple alkyl amines **240** (Scheme 72).[233] The initially formed C(sp^3)–H olefinated product underwent Pd-catalyzed intramolecular aza-Wacker oxidative cyclization to give pyrrolidine derivative **241**. The electron-deficient pyridine-based ligand (**Ligand 20**) enabled the olefination of amino acid-derived substrate **242**. The simple styrene could also serve as the effective coupling partner, which has not been observed in other Pd-catalyzed C(sp^3)–H olefination reactions.[194,195,216,221,229] To improve the practicality of this reaction, we also developed conditions to accommodate the use of a common protecting group 4-nitrobenzenesulfonyl (Ns) instead of Tf. Phenanthrine (**Ligand 21**) was proven to be the optimal ligand for this practical directing group. Ns-protected L-*tert*-leucine substrate **244** was olefinated with acrylates and styrenes to give valuable pyrrolidines. With vinyl ketone and acrylonitrile coupling partners, the newly installed double bonds reacted with the Ns-protected amines via diastereoselective conjugate addition to afford the saturated pyrrolidines **245** (Scheme 72).[233]

Using bulky secondary amines as the directing group, Gaunt and co-workers realized several C(sp^3)–H activation reactions that proceed through a four-membered-ring cyclopalladation pathway (Scheme 73).[234–236] Oxidative addition of palladacycle intermediates from Pd(II) to Pd(IV) by $PhI(OAc)_2$ promotes C(sp^3)–N reductive elimination, affording aziridine products **247** from aminolactones.[234] Adding 20 equivalents of acetic acid and 2 equivalents of acetic anhydride could further improve the yield.[235] Simple aliphatic amines were functionalized to give β-acetoxylated products rather than aziridines under the same reaction conditions. Treating secondary amines with CO in the presence of $Pd(OAc)_2$ and $Cu(OAc)_2$ led to the formation of β-lactams **249** via a Pd(II)/Pd(0) catalytic cycle.[234] Under the conditions similar to triflamide-directed C(sp^3)–H cross-coupling,[231] *N*-Ac-protected amino acid ligands enabled Pd-catalyzed C–C bond formation of aliphatic amines **250** with arylboronic esters.[236] In 2015, the same group achieved γ-C(sp^3)–H activation reactions of the sterically hindered secondary amine **252** via a five-membered palladacycle intermediate, streamlining the synthesis of various amino alcohol derivatives (Scheme 74).[237] Steric repulsion between the substrates destabilized the bis(amine) Pd(II) complex, thereby promoting the C(sp^3)–H cleavage through the mono-ligated species.

6. CONCLUSIONS AND OUTLOOK

Over the past decade, substantial progress has been made in the field of Pd-catalyzed alkyl C–H bond activation through various coordination strategies. Early examples of oxidative addition of carbon–halogen bonds to Pd(0) species paved the way for the development of intramolecular C(sp^3)–H functionalizations of organohalides, allowing rapid assembly of heterocycle cores that can be realized in an enantioselective fashion by using chiral phosphine and NHC ligands. The introduction of strongly coordinating bidentate auxiliaries, including aminoquinoline and picolinic acid derivatives, demonstrated their effectiveness as directing groups in Pd-catalyzed C(sp^3)–H activation, especially in Pd(II)/Pd(IV) catalysis. These robust, highly efficient, and functional group-tolerant transformations soon found extensive applications in total synthesis. Thereafter, the discovery that weakly coordinating directing groups are compatible with external ligands encouraged us to develop a number of C(sp^3)–H activation/C–C and C–heteroatom bond forming reactions. Not only does the incorporation of ligand engender new reactivity in the C(sp^3)–H functionalization step, but also helps control the selectivity in the C(sp^3)–H cleavage step. γ-C(sp^3)–H activation of carboxylic acid derivatives as well as enantioselective C–H functionalization reactions of cycloalkanes have been achieved with suitable ligands.

Despite the myriad recent advances, there are many challenges that remain to be addressed to improve the practicality and versatility of C(sp^3)–H activation reactions. For instance, it will be of great importance to develop more effective ligands that enable Pd-catalyzed C(sp^3)–H activation of free carboxylic acids, amines, and alcohols without the installation of directing groups. The development of chiral ligands that can promote enantioselective methylene C(sp^3)–H activation as well as desymmetrization of *gem*-dimethyl substrates will also be highly desirable. Immobilizing palladium complexes on polymer or mesoporous silica supports would afford easy, scalable, and recyclable setups for ligand-promoted C(sp^3)–H activation, which is a key step towards the goal of developing sustainable chemical

processes. Taken together, pivotal to the future success in this field is the design of suitable ligands that match the coordination of substrates and accelerate C(sp^3)–H activation.

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Biographies

Jian He received his B.Sc. degree in Chemistry with highest honors from Zhejiang University where he conducted research in allene chemistry under the direction of Prof. Shengming Ma. In 2011, he moved to the Scripps Research Institute to begin his graduate studies under the supervision of Prof. Jin-Quan Yu, with a focus on ligand-promoted C(sp^3)–H activation using palladium catalysts.

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Kelvin S. L. Chan obtained his doctorate in Organic Chemistry from the Scripps Research Institute under the tutelage of Prof. Jin-Quan Yu. He received his B.A.(Hons) in Chemistry at the University of Cambridge and was a recipient of the prestigious A*STAR Singapore

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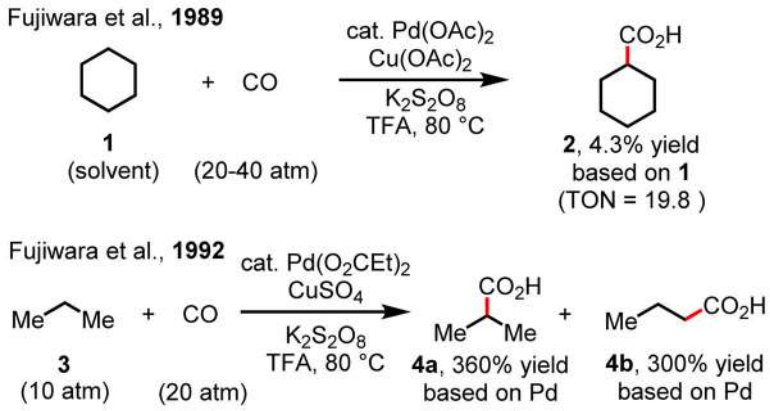
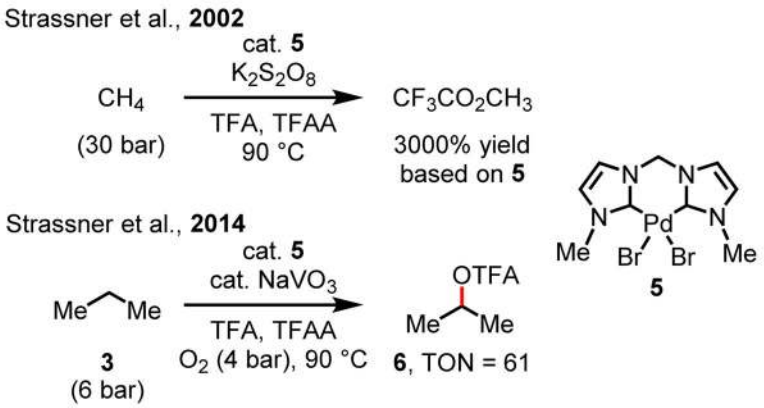
Qian Shao received her B.Sc. in Pharmaceutics from Ocean University of China in 2009. In the same year, she moved to Peking University, where she received her Ph.D. in Organic Chemistry under the direction of Prof. Yong Huang, focusing on developing novel asymmetric synthetic methods to introduce chiral carbon centers using organocatalysis. She is currently a postdoctoral fellow in the lab of Prof. Jin-Quan Yu at the Scripps Research Institute, for research into ligand-accelerated Pd-catalyzed C(sp^3)–H activation reactions.

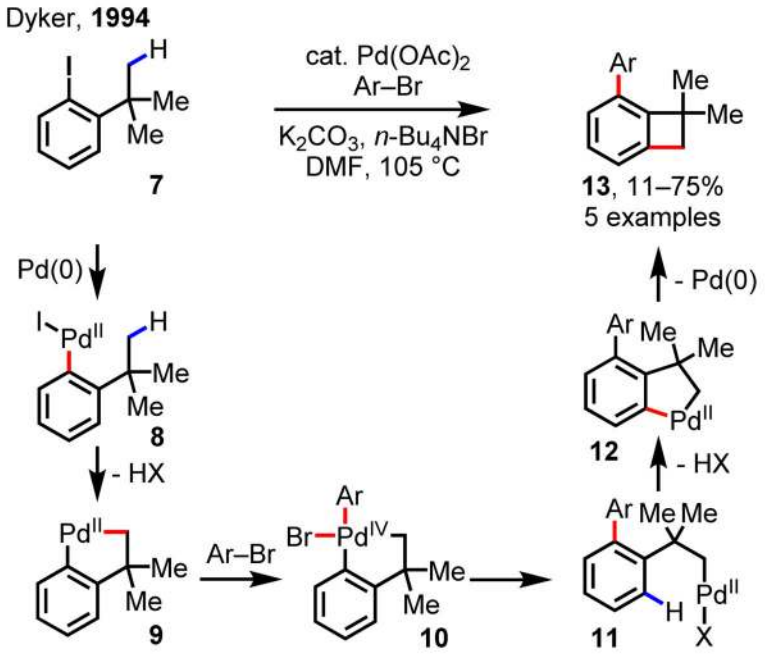
Jin-Quan Yu received his B.Sc. degree in Chemistry from East China Normal University and his M.Sc. degree from the Guangzhou Institute of Chemistry. In 2000, he obtained his Ph.D. degree at the University of Cambridge with Prof. Jonathan B. Spencer. After some time as a Junior Research Fellow at Cambridge, he joined the laboratory of Prof. E. J. Corey at Harvard University as a postdoctoral fellow. He then began his independent career at Cambridge (2003–2004), before moving to Brandeis University (2004–2007), and finally The Scripps Research Institute, where he is currently the Frank and Bertha Hupp Professor of Chemistry. His group studies transition-metal-catalyzed C–H activation.



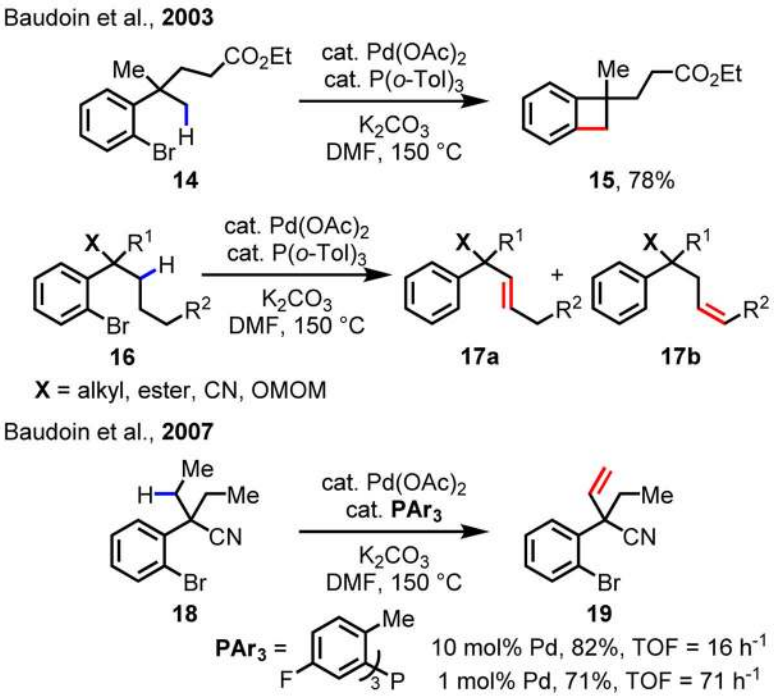
Scheme 1.
Pd(II)-Catalyzed Carbonylation of Alkanes



Scheme 2.
Pd(II)-Catalyzed Trifluoroacetoxylation of Alkanes

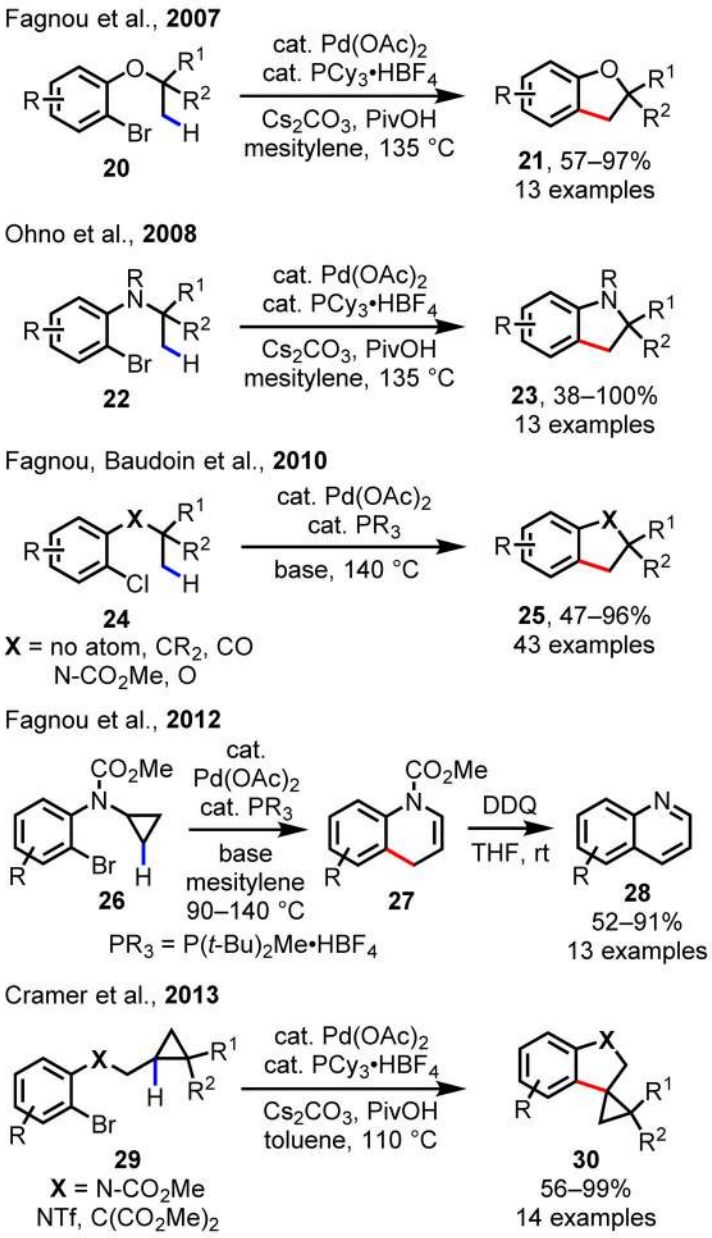


Scheme 3.
Dyker's Synthesis of 1,2-Dihydrocyclobutabenzene

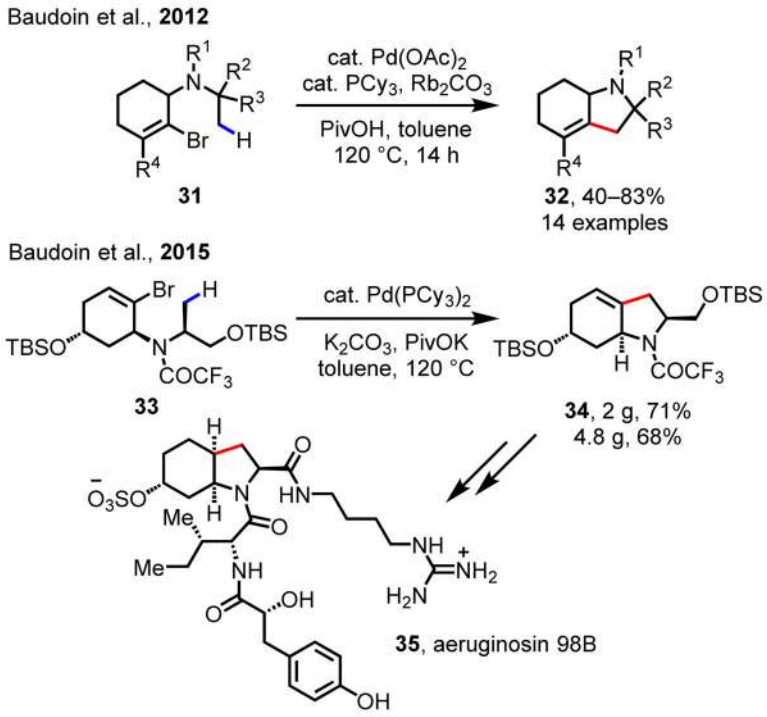


Scheme 4.

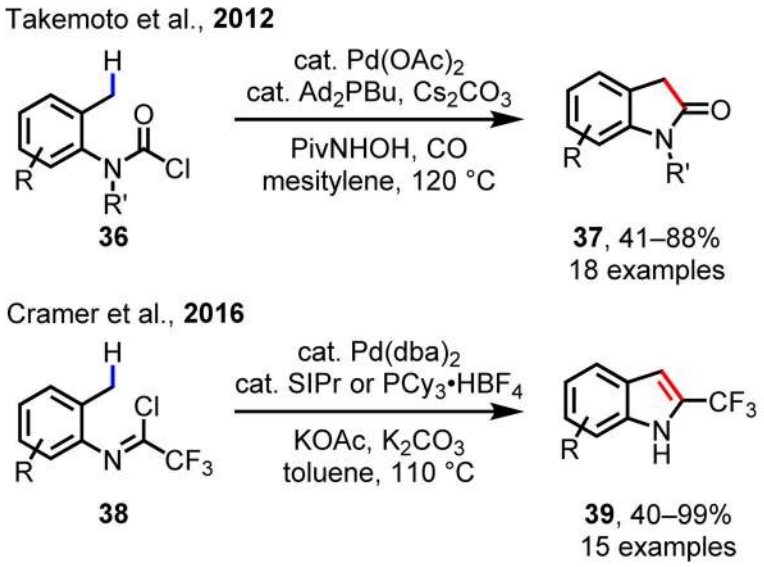
Pd(0)/PAr_3-Catalyzed Intramolecular C(sp^3)–H Activation



Scheme 5.
Pd(0)-Catalyzed Intramolecular C(sp^3)–H Arylation

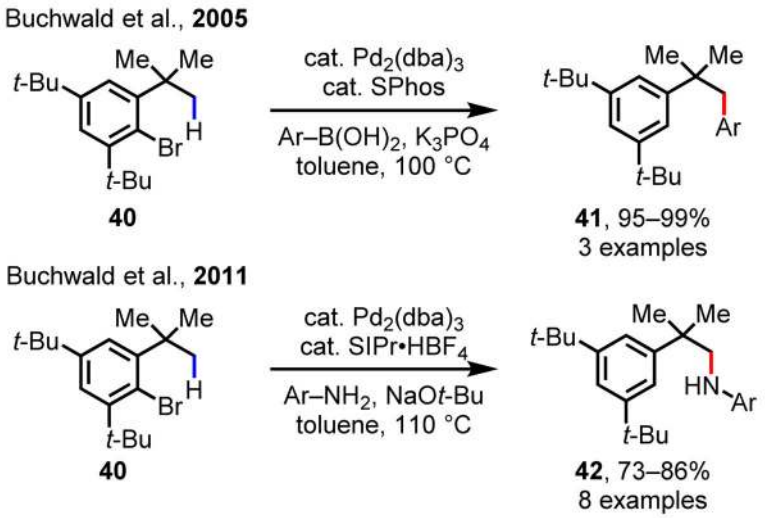


Scheme 6.
Pd(0)-Catalyzed Intramolecular C(sp^3)–H Alkenylation



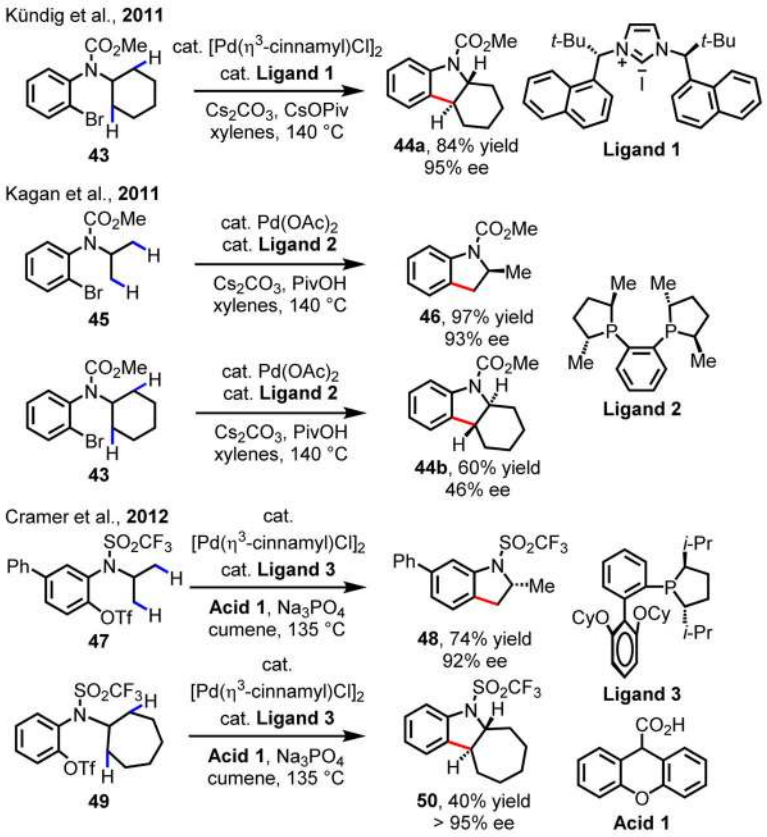
Scheme 7.

Pd(0)-Catalyzed Intramolecular Cyclization of Benzylic C(sp^3)–H Bonds



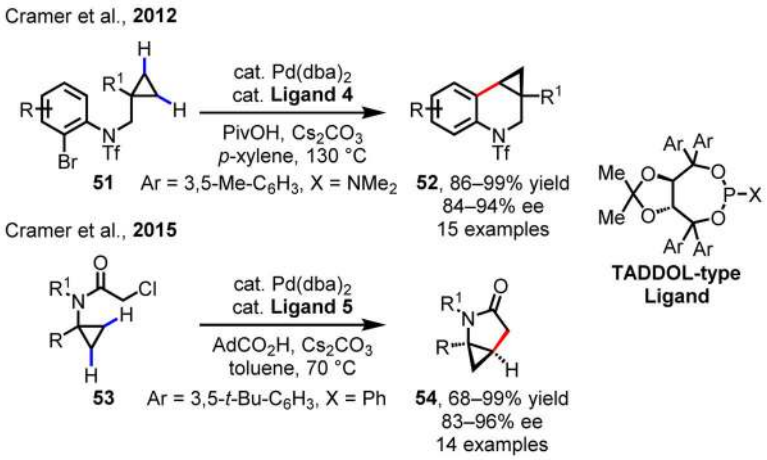
Scheme 8.

Pd(0)-Catalyzed Intermolecular C(sp^3)–H Functionalizations



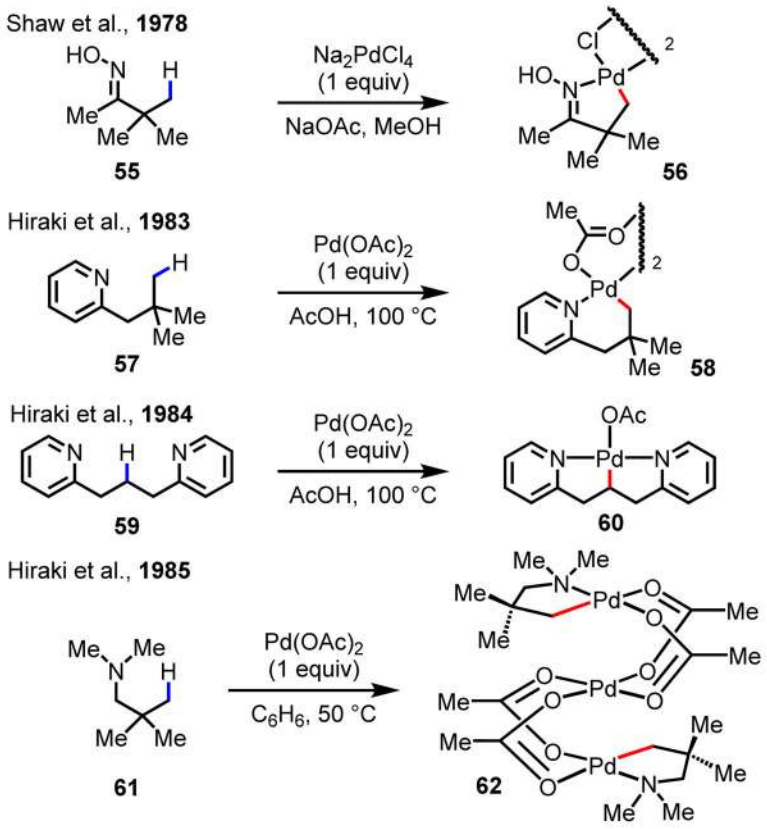
Scheme 9.

Pd(0)-Catalyzed Enantioselective Intramolecular C(sp^3)–H Arylation

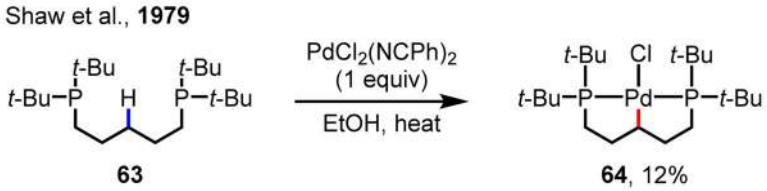


Scheme 10.

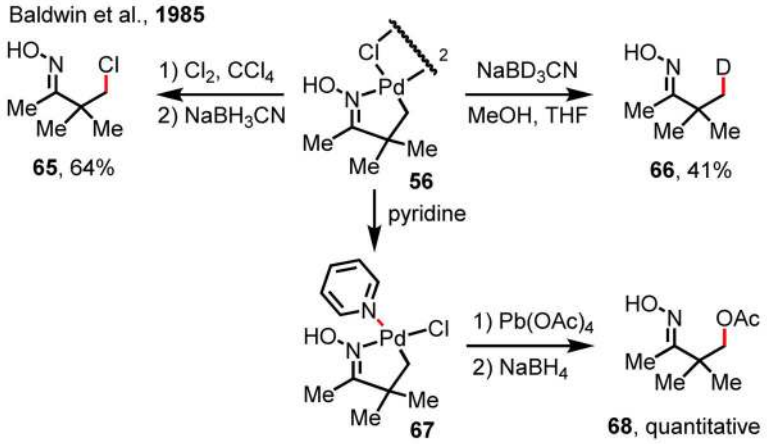
Pd(0)-Catalyzed Enantioselective Intramolecular C(sp^3)–H Activation of Cyclopropanes



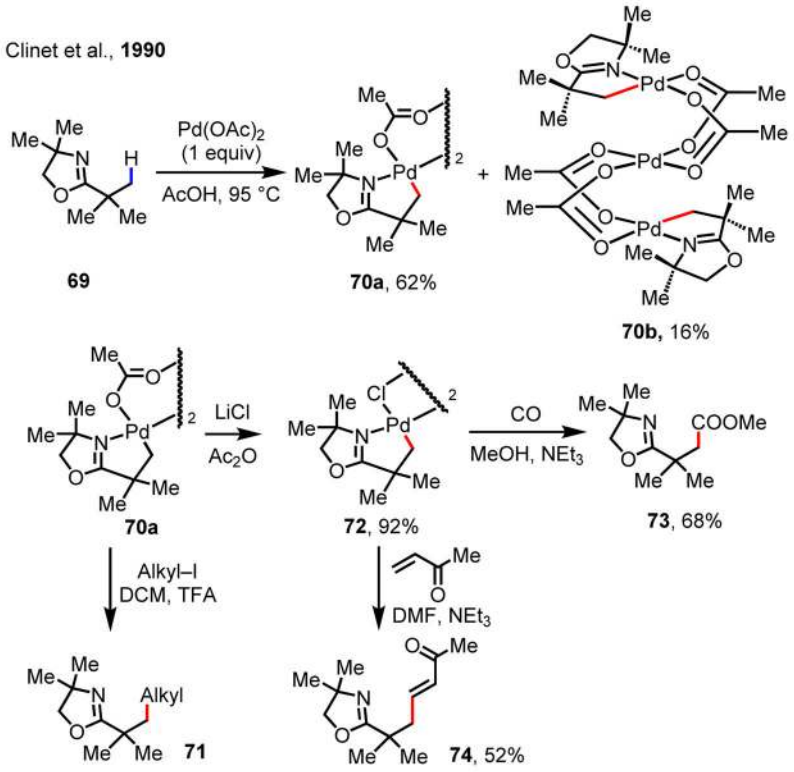
Scheme 11.
Cyclopalladation Using Nitrogenous Directing Groups



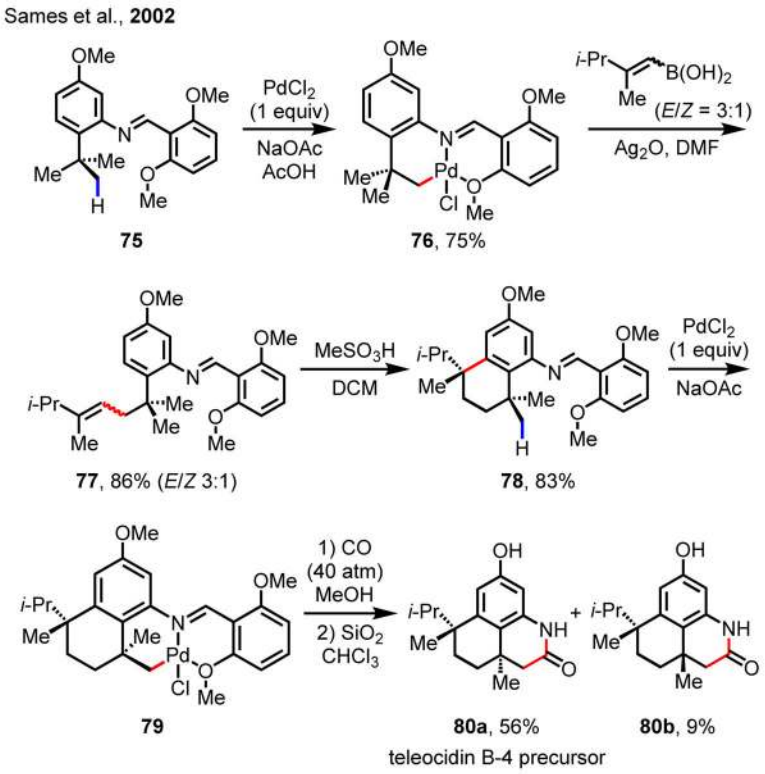
Scheme 12.
Pd(II)-Insertion into Methylene C(sp^3)–H Bond



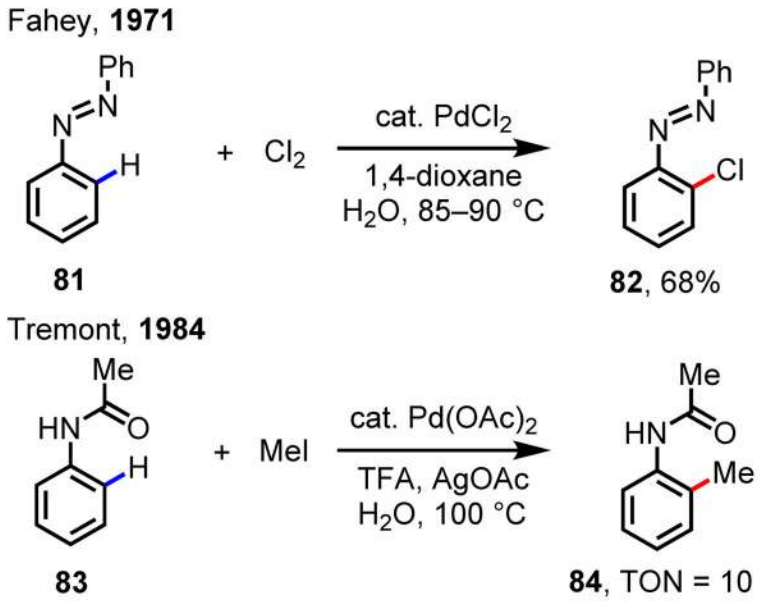
Scheme 13.
Reactions of Oxime-Derived Palladacycles



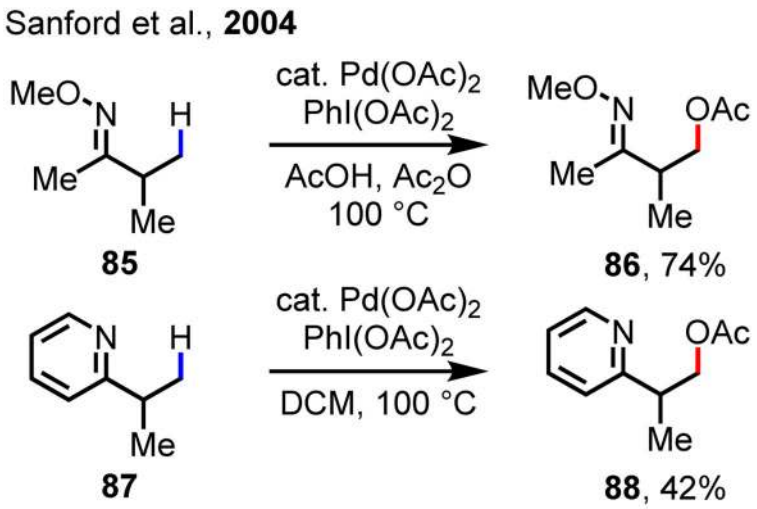
Scheme 14.
Reactions of Oxazoline-Derived Palladacycles



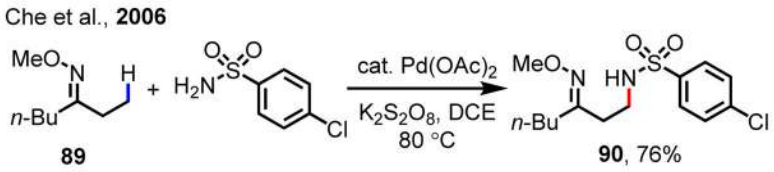
Scheme 15.
Synthesis of Teleocidin B-4 Core



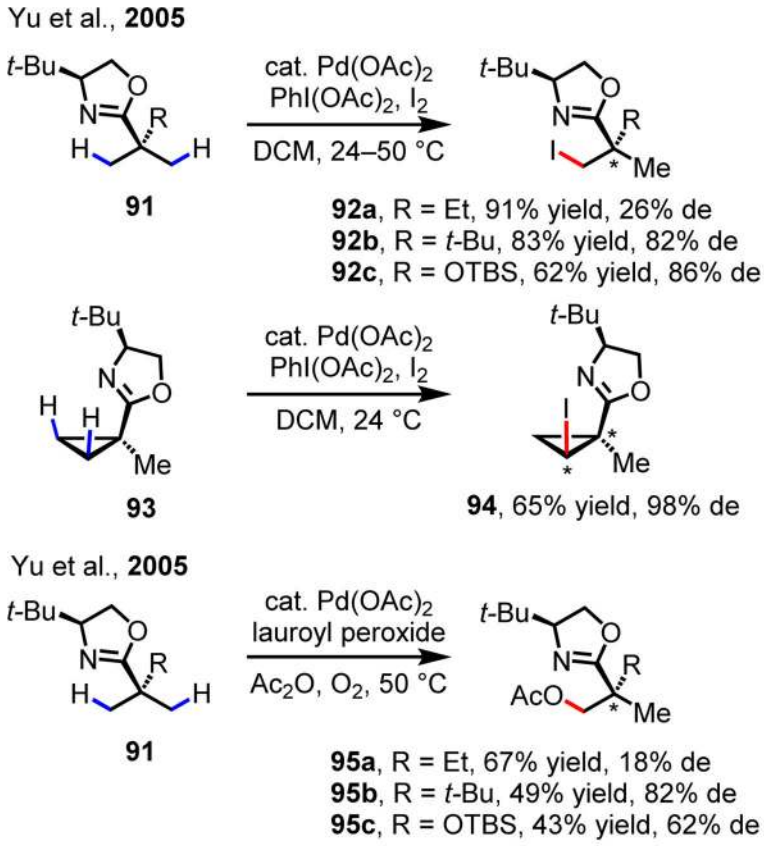
Scheme 16.
Pd(II)-Catalyzed C(sp^2)–H Functionalizations



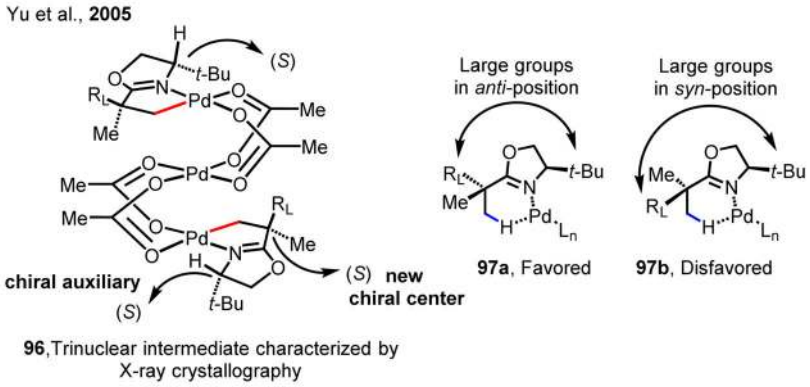
Scheme 17.
Pd(II)-Catalyzed C(sp^3)–H Acetoxylation



Scheme 18.
Pd(II)-Catalyzed C(sp^3)–H Amidation

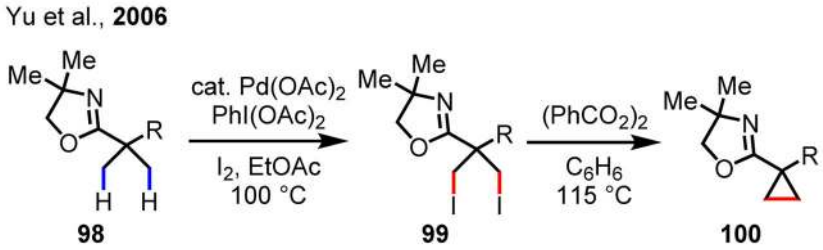


Scheme 19.
Diastereoselective C(sp^3)–H Functionalizations

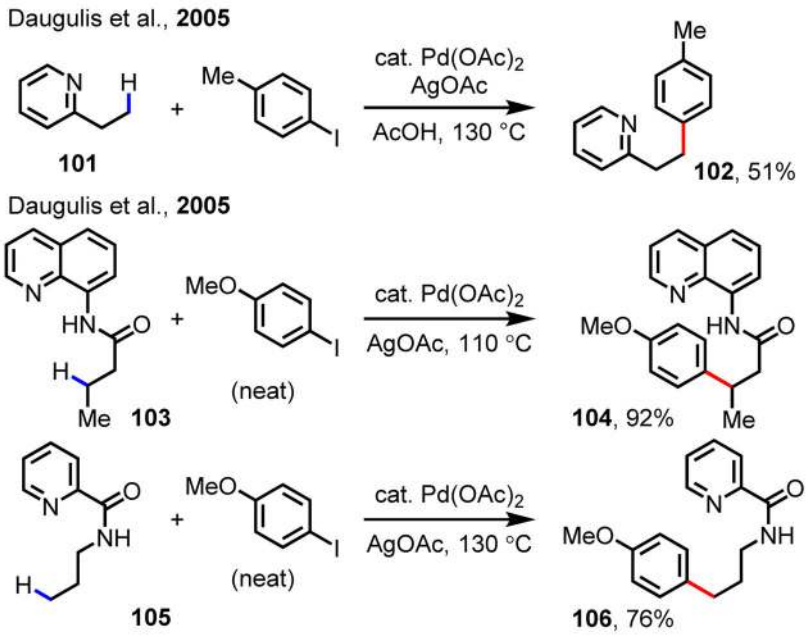


Scheme 20.

Asymmetric Induction Model and Characterized Intermediate Structure

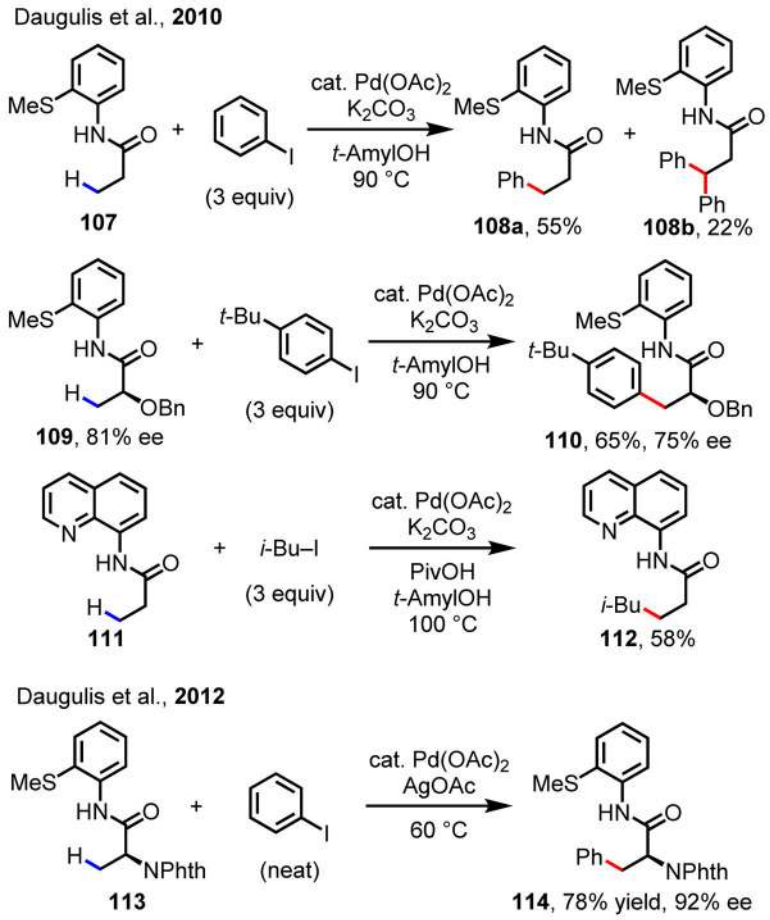


Scheme 21.
Conversion of *gem*-Dimethyl Groups into Cyclopropanes



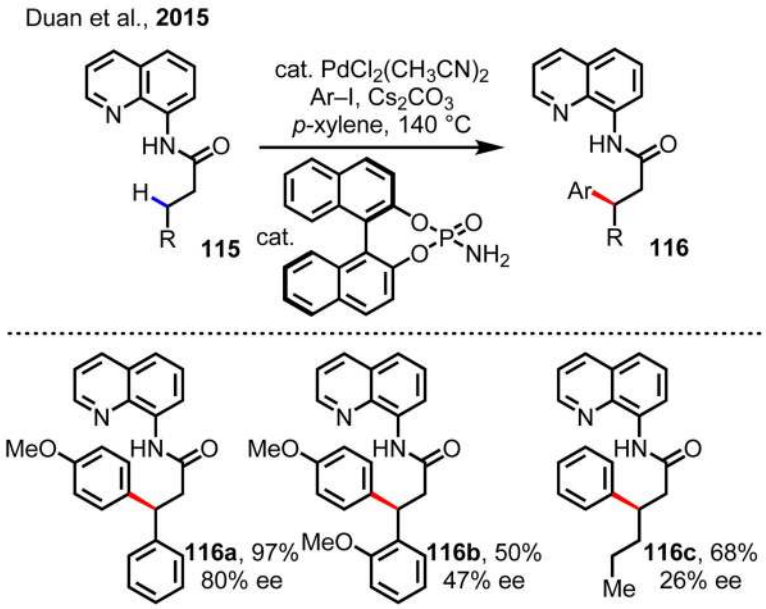
Scheme 22.

Pd(II)-Catalyzed C(sp^3)–H Arylation with Aryl Halides

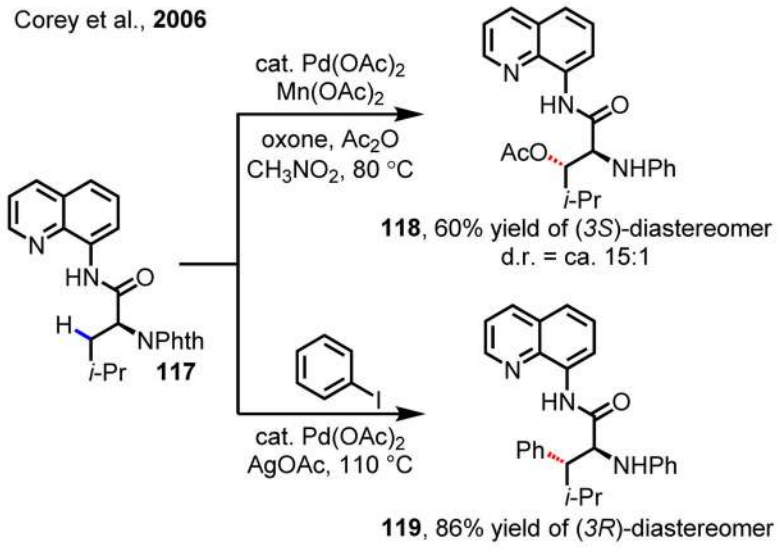


Scheme 23.

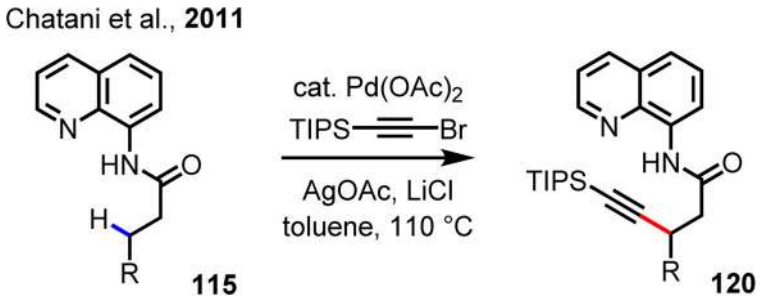
C(sp^3)–H Activation Facilitated by Bidentate Directing Groups



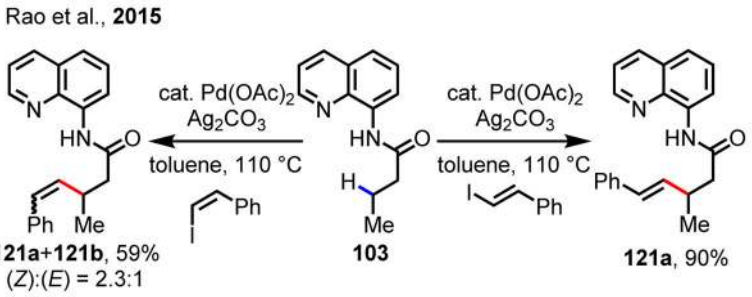
Scheme 24.
Asymmetric C(sp^3)–H Arylation Induced by Chiral Phosphoramides



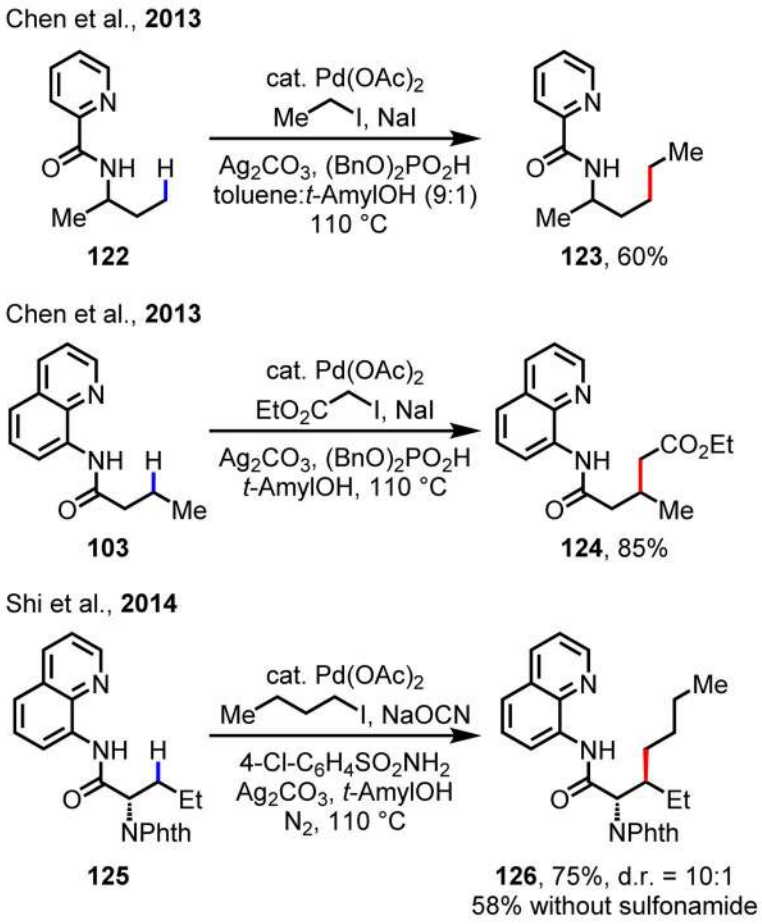
Scheme 25.
Functionalizations of α-Amino Acid Derivatives



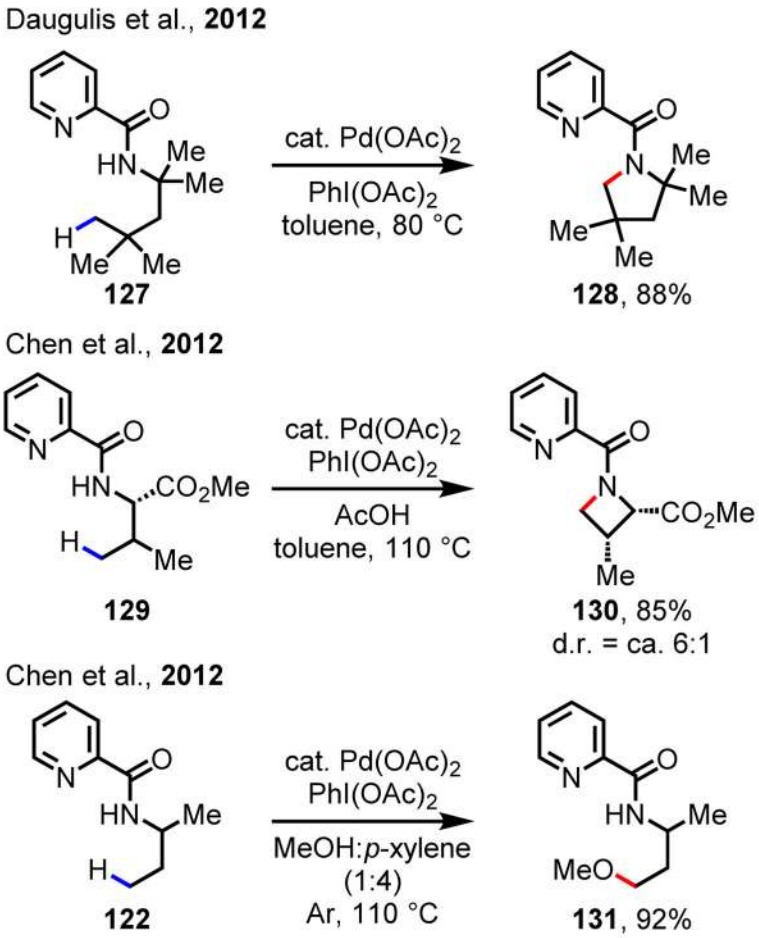
Scheme 26.
Pd(II)-Catalyzed C(sp^3)–H Alkynylation



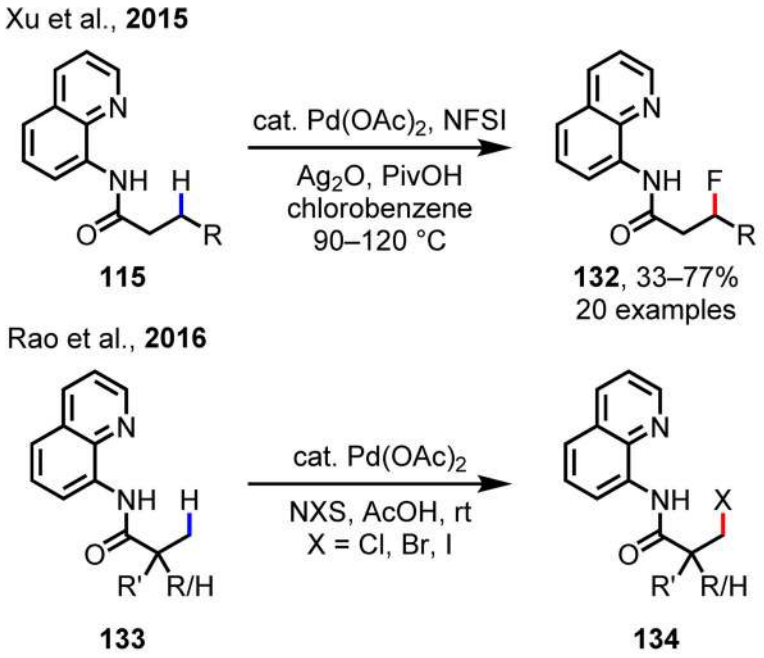
Scheme 27.
Pd(II)-Catalyzed C(sp^3)–H Alkenylation



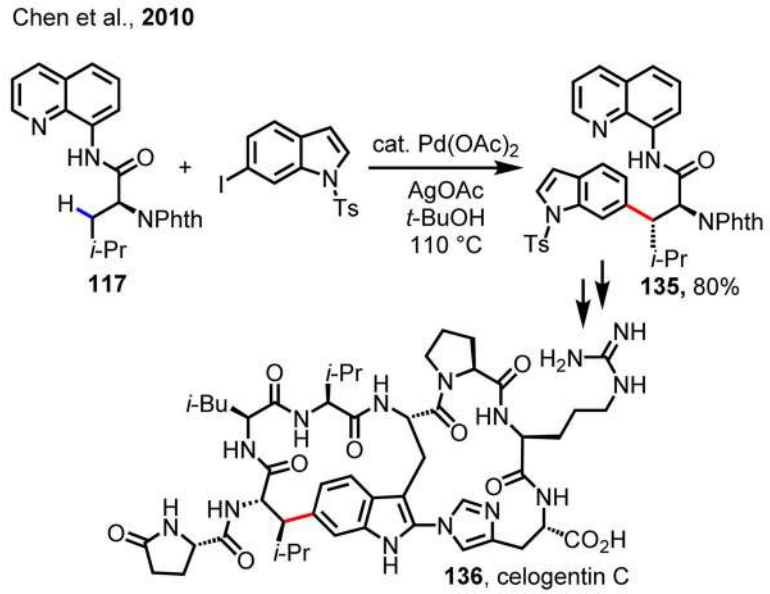
Scheme 28.
Pd(II)-Catalyzed C(sp^3)–H Alkylation



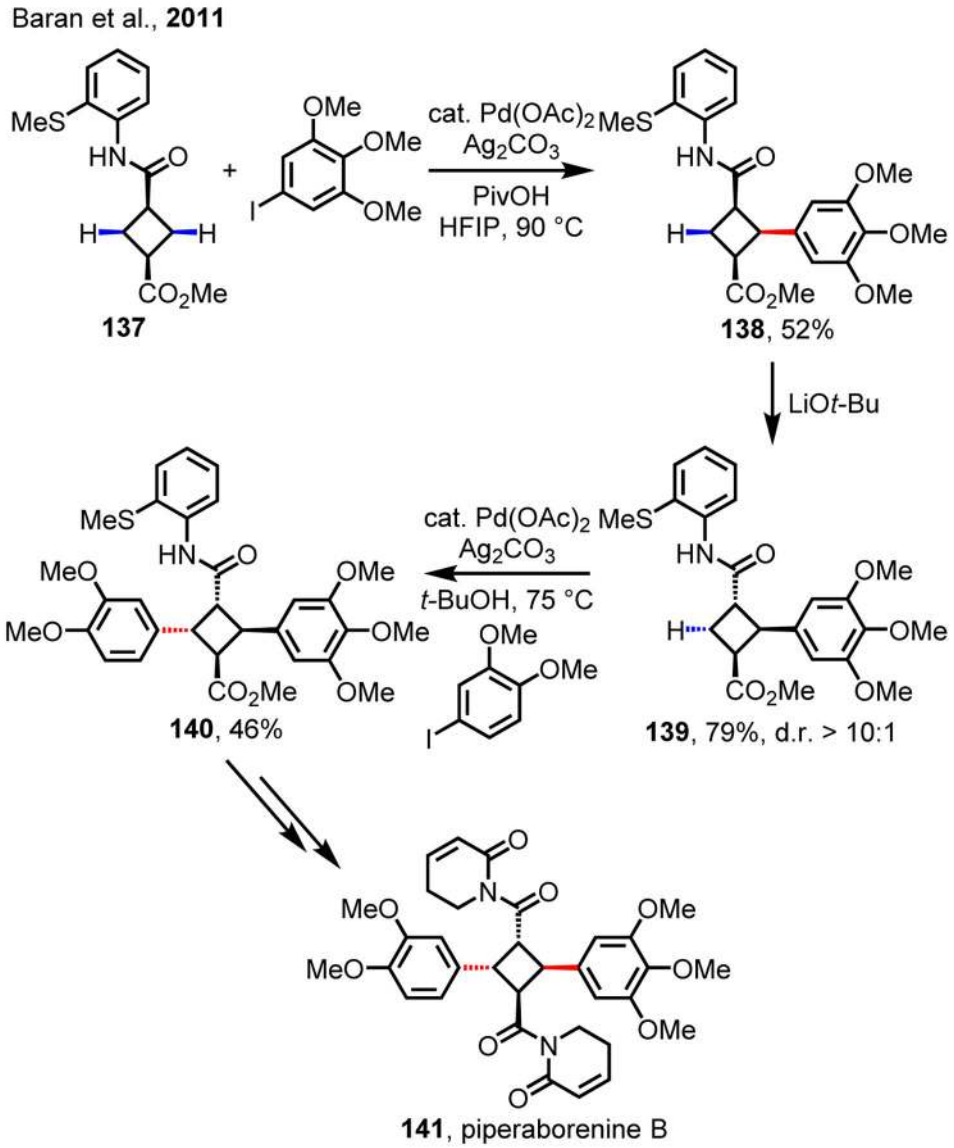
Scheme 29.
Formations of C(sp^3)–Heteroatom Bonds



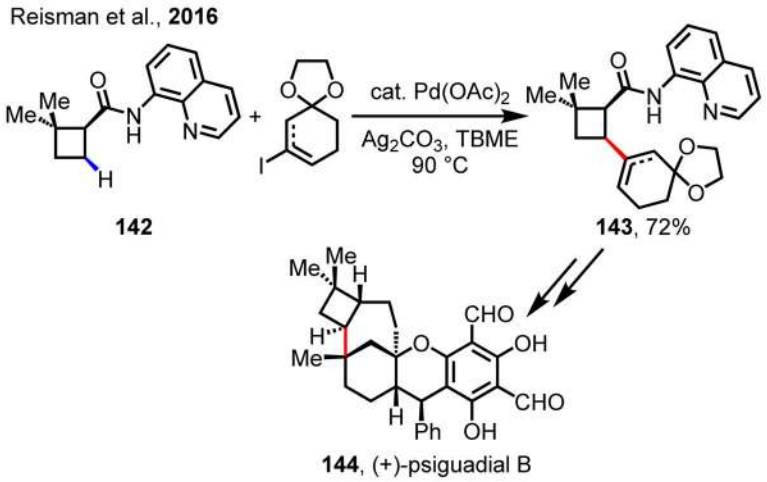
Scheme 30.
Pd(II)-Catalyzed C(sp^3)–H Halogenation



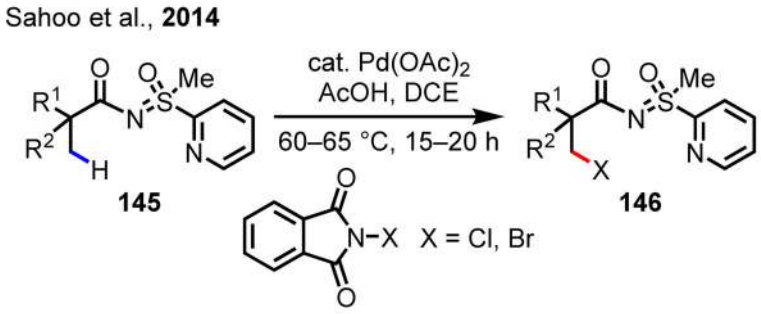
Scheme 31.
Synthesis of Celogentin C



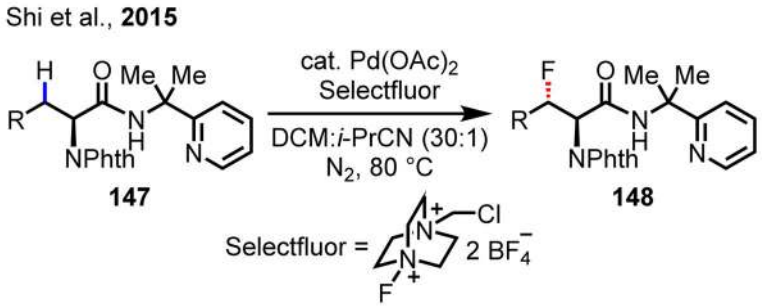
Scheme 32.
Synthesis of Piperaborenine B



Scheme 33.
Enantioselective Synthesis of (+)-Psiguadial B

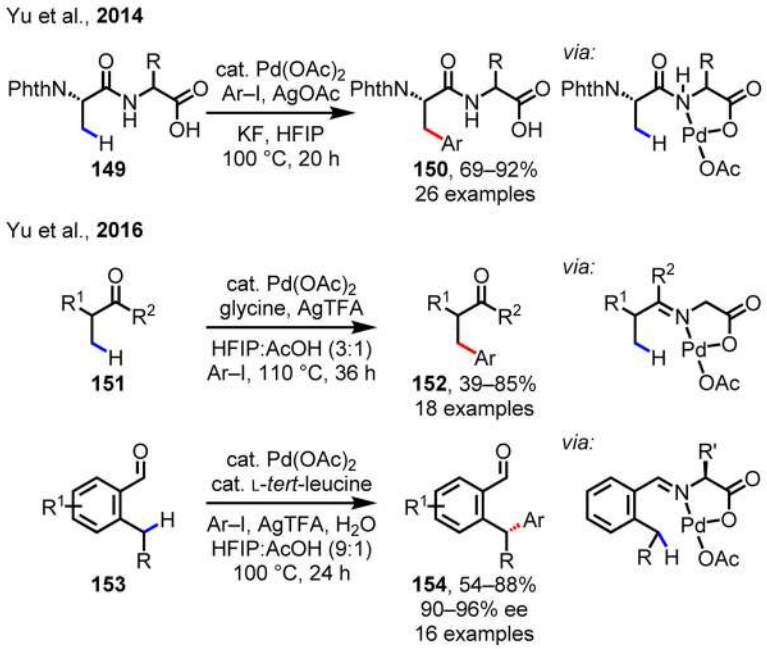


Scheme 34.
Sulfoximine-Assisted Halogenation of β-C(sp^3)–H Bonds of Amides

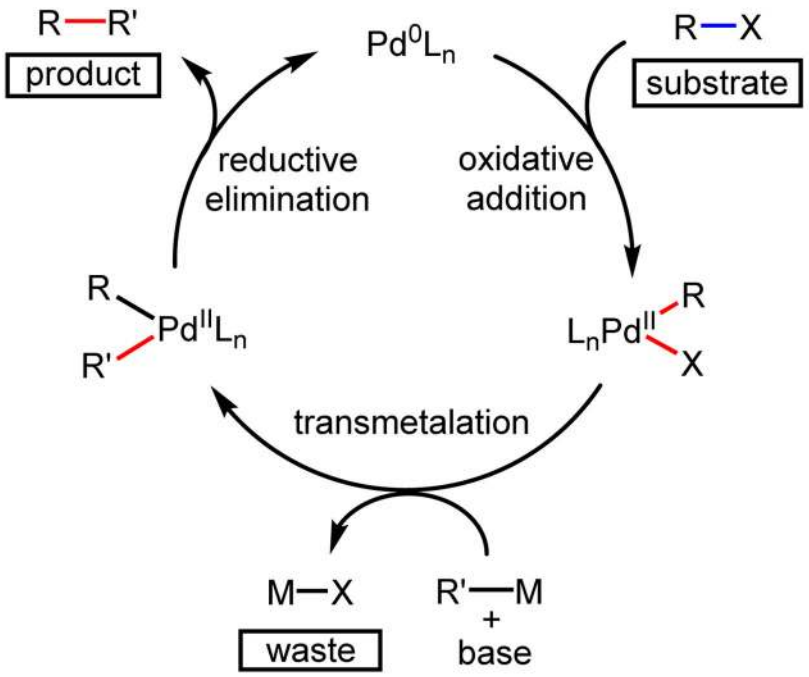


Scheme 35.

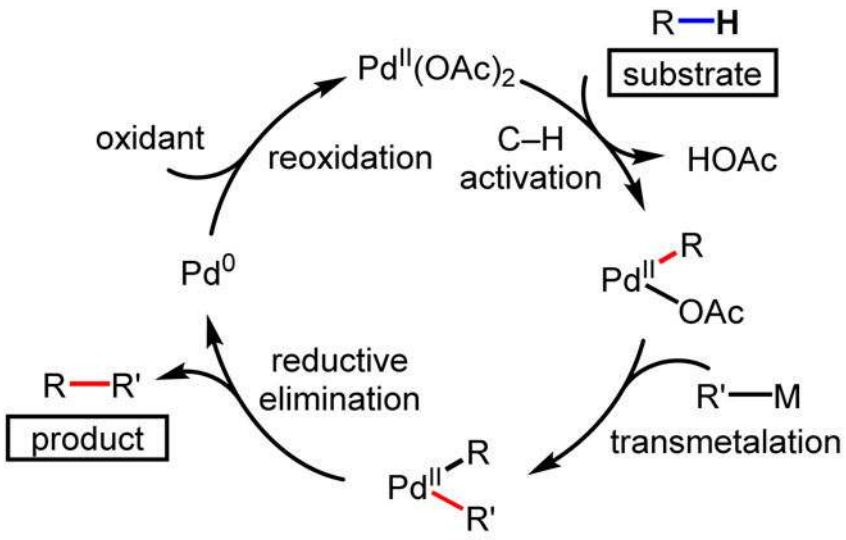
β-Methylene C(sp^3)–H Fluorination of α-Amino Acid Derivatives



Scheme 36.
Amino Acid-Directed C(sp^3)–H Arylation

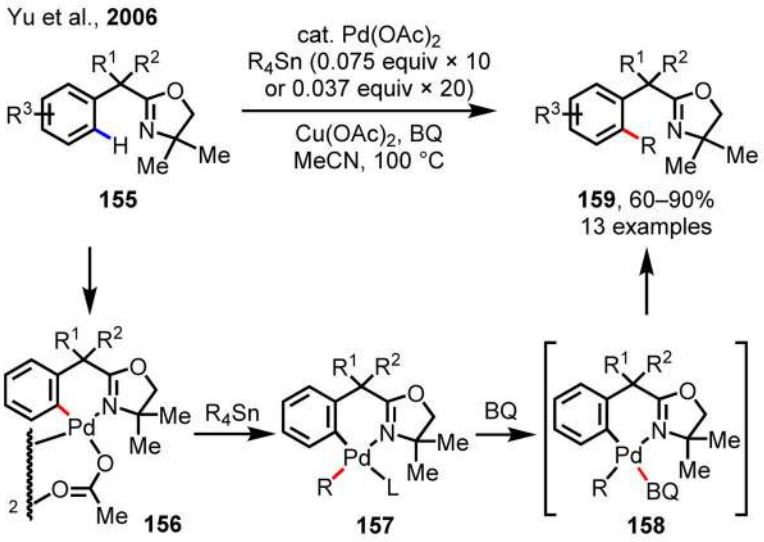


Scheme 37.
A Simplified Catalytic Cycle for Pd(0)-Catalyzed Cross-Coupling Reactions

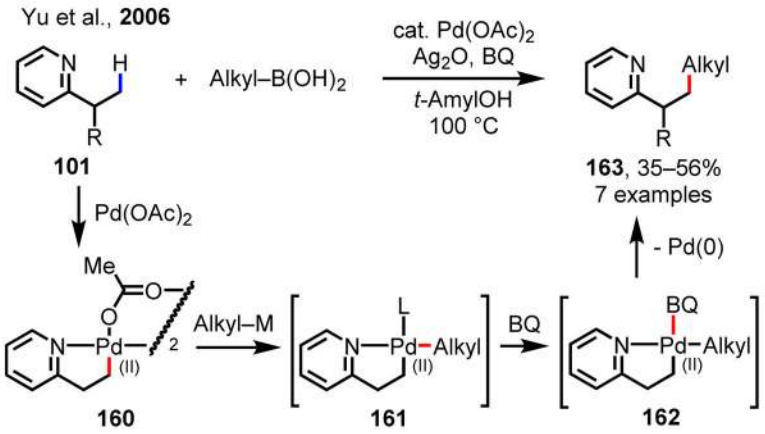


Scheme 38.

Proposed Catalytic Cycle for Pd(II)-Catalyzed C–H Activation/C–C Cross-Coupling Reactions

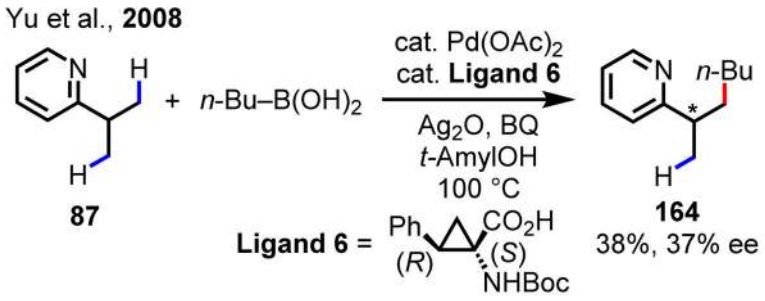


Scheme 39.
C(sp^2)–H Activation/Alkyltin Cross-Coupling Reaction

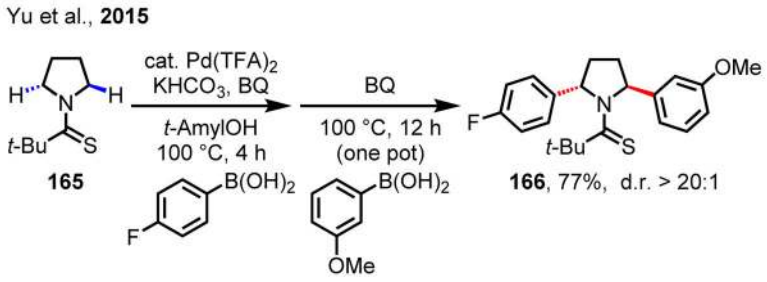


Scheme 40.

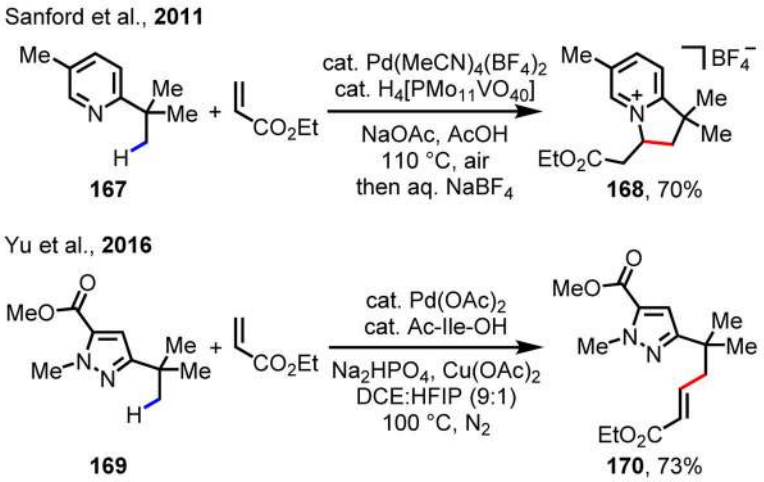
C(sp^3)–H Activation/Organoboron Cross-Coupling Reaction



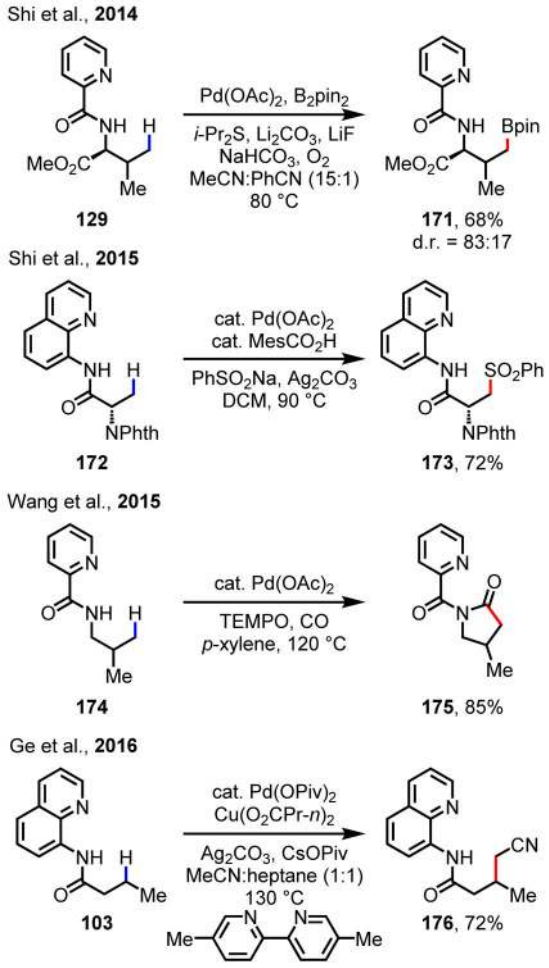
Scheme 41.
Enantioselective Pd(II)-Catalyzed C(sp^3)–H Alkylation



Scheme 42.
Thioamide-Directed C(sp^3)–H Cross-Coupling of Pyrrolidines

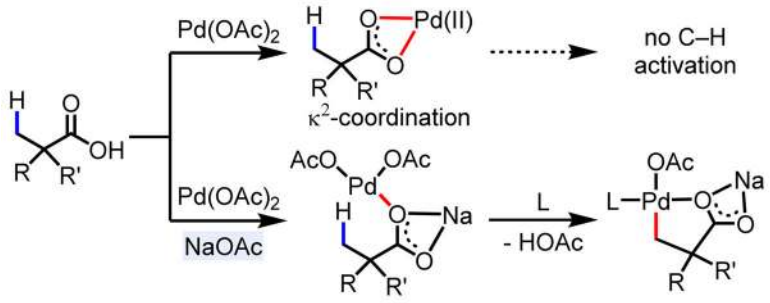


Scheme 43.
Heterocycle-Directed C(sp^3)–H Olefination

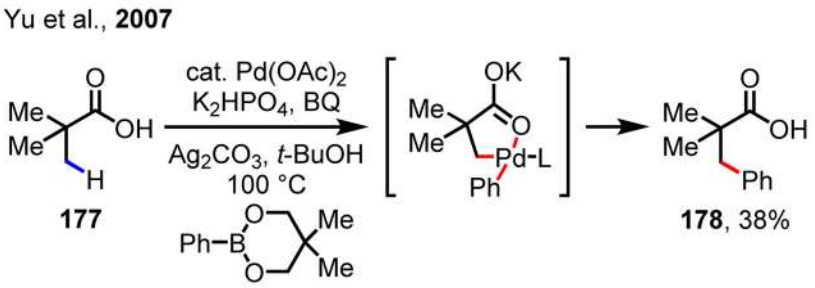


Scheme 44.

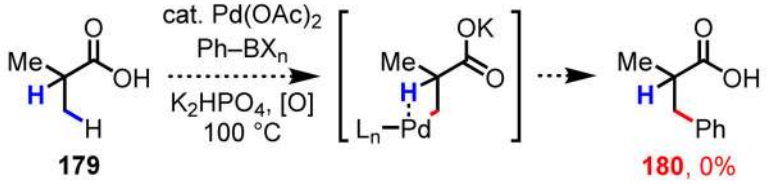
Bidentate Auxiliary-Assisted C(sp^3)–H Activation via Pd(II)/Pd(0) Catalysis



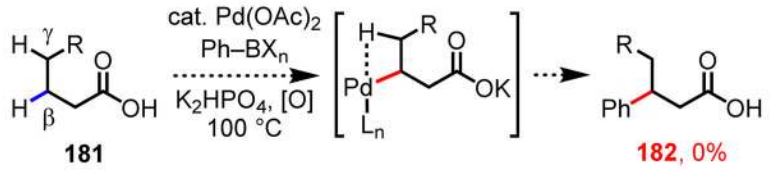
Scheme 45.
Countercation-Enabled Carboxylate-Directed C(sp^3)–H Activation



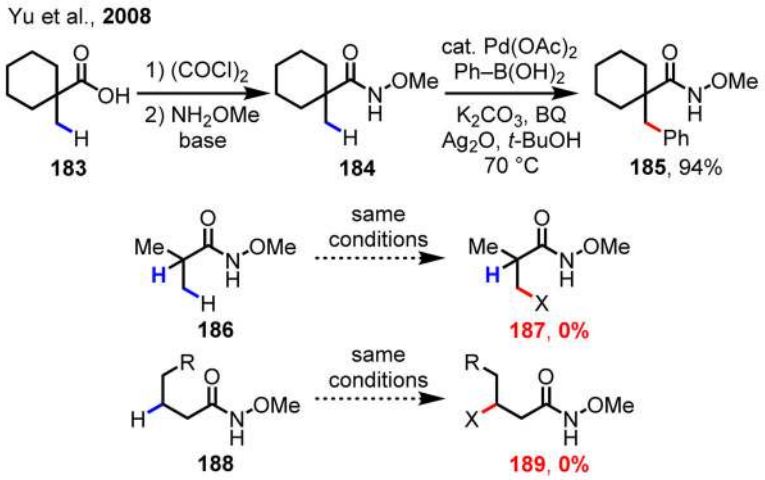
Scheme 46.
Pd(II)-Catalyzed C(sp^3)–H Activation/Cross-Coupling



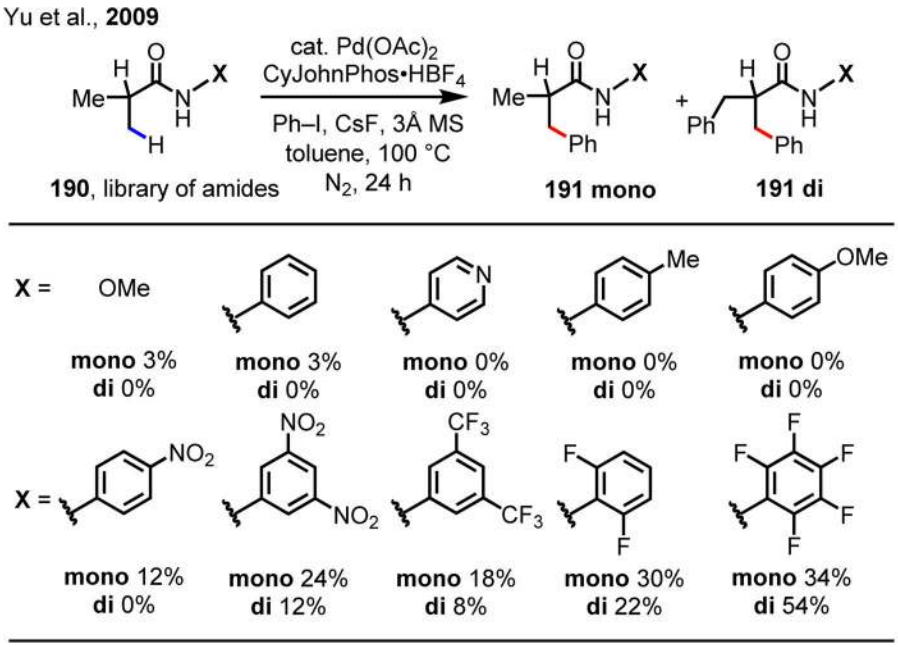
Scheme 47.
Reaction with Substrates Containing α-Hydrogen Atoms



Scheme 48.
Reaction with Methylene C(sp^3)–H Bonds

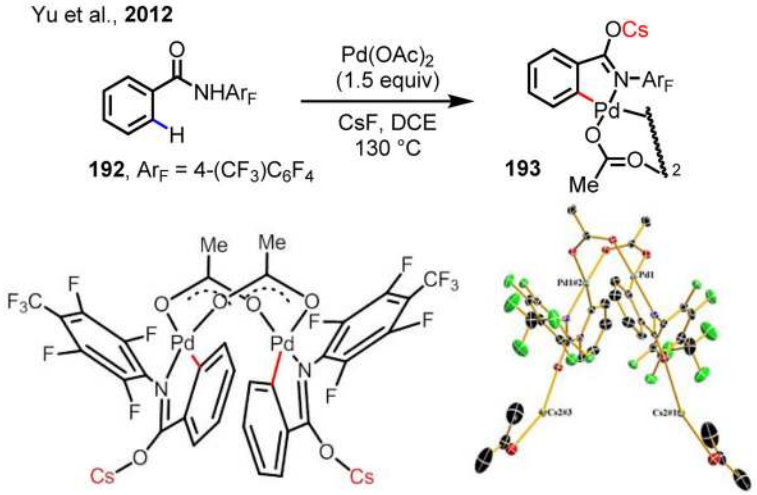


Scheme 49.
Hydroxamic Acid-Directed C(sp^3)–H Activation

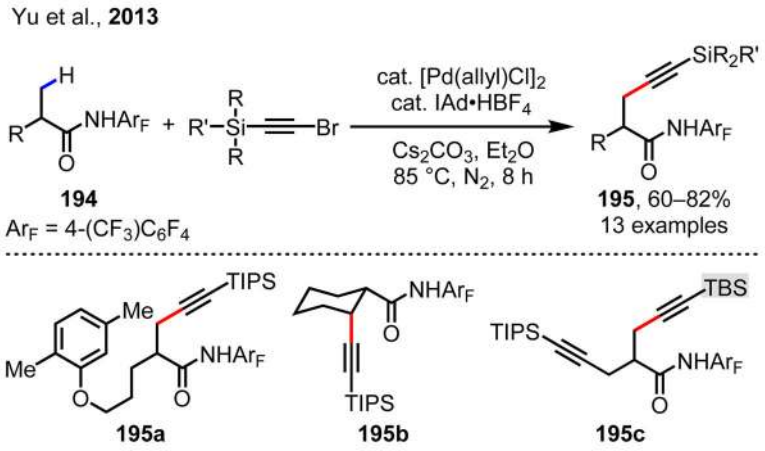


Scheme 50.

Optimization of Arylamide Auxiliaries in Intermolecular C(sp^3)–H Arylation

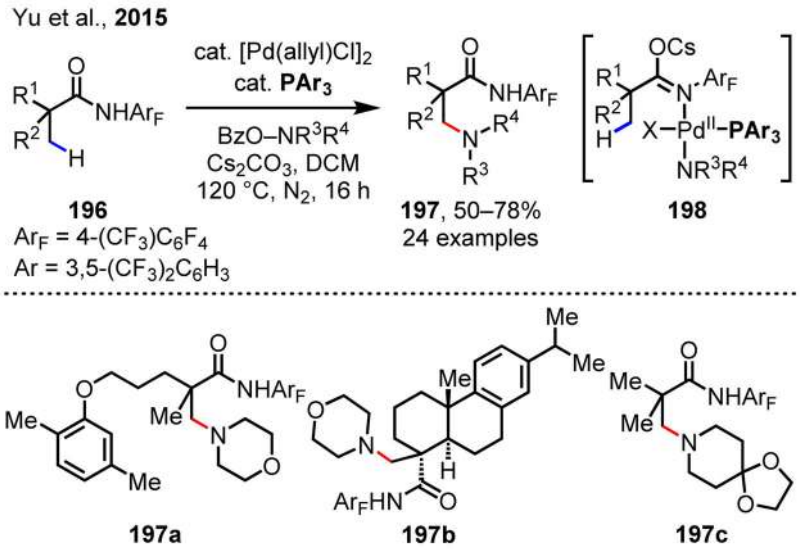


Scheme 51.
Coordination of *N*-Arylamides to Pd Catalysts



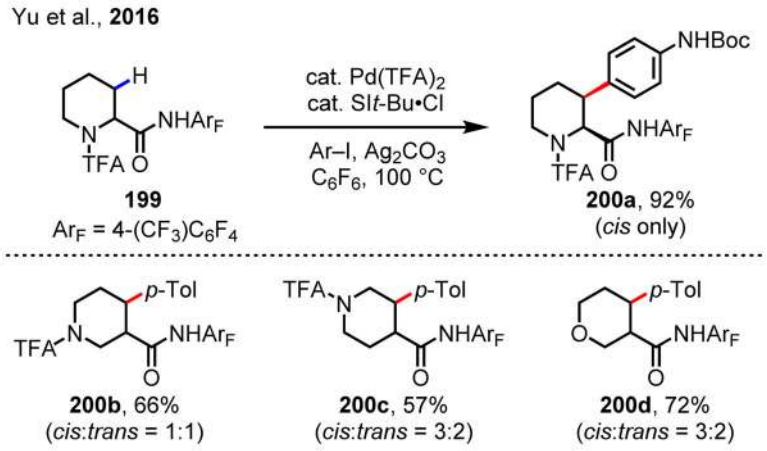
Scheme 52.

Palladium(0)-Catalyzed Alkynylation of C(sp^3)–H Bonds



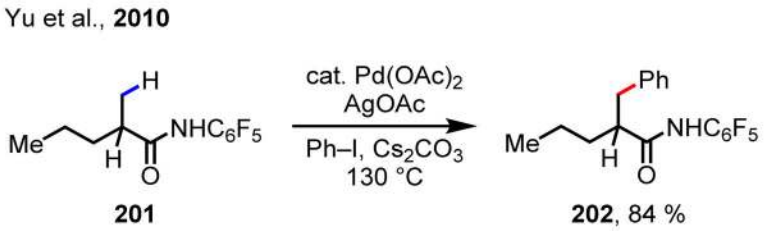
Scheme 53.

Pd(0)/PAr_3-Catalyzed Intermolecular Amination of C(sp^3)–H Bonds

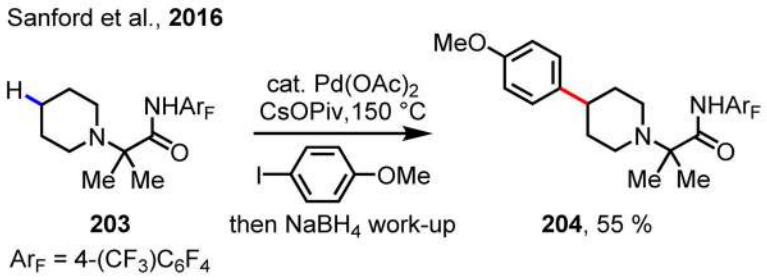


Scheme 54.

NHC Ligand-Enabled C(sp^3)–H Arylation of Saturated Heterocycles

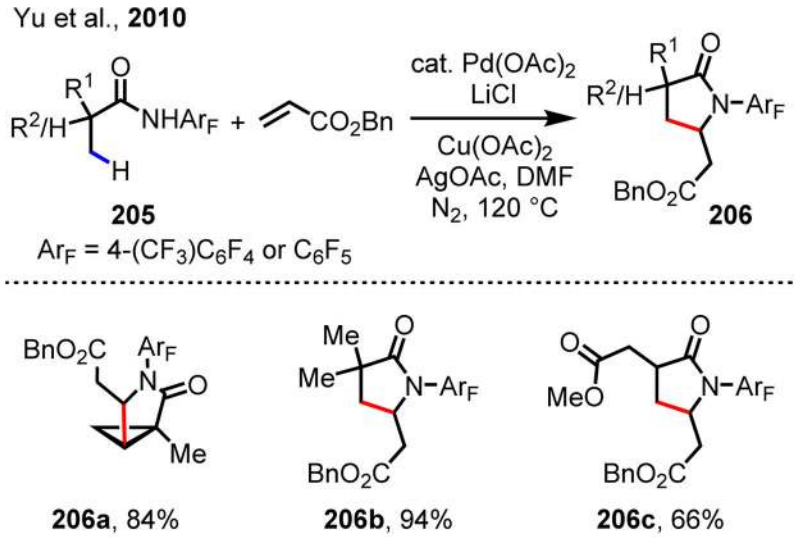


Scheme 55.
β-C(sp^3)–H Arylation of *N*-Arylamides

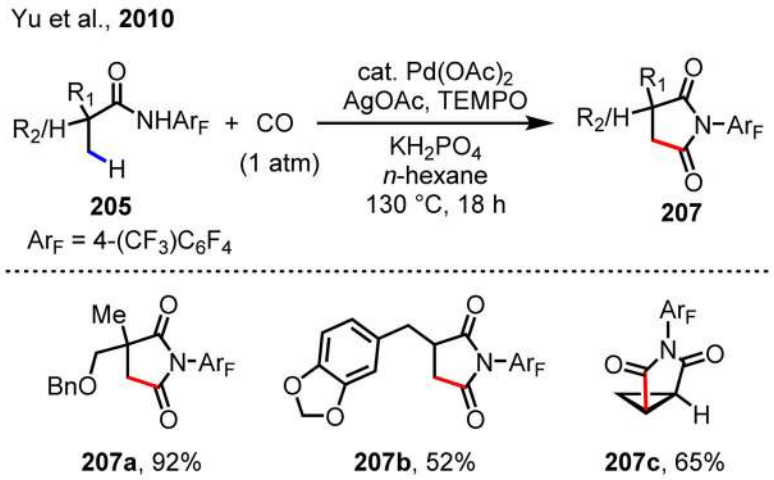


Scheme 56.

Pd(II)-Catalyzed Transannular C(sp^3)–H Arylation of Alicyclic Amines

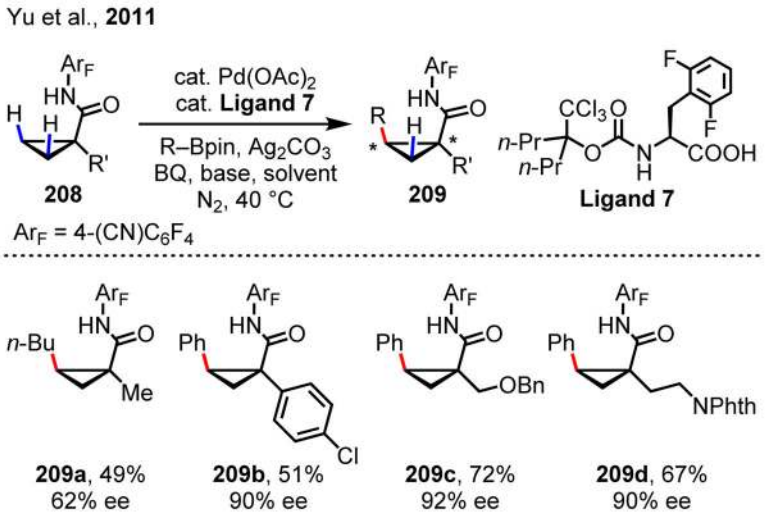


Scheme 57.
Amide-Directed Olefination of C(sp^3)–H Bonds



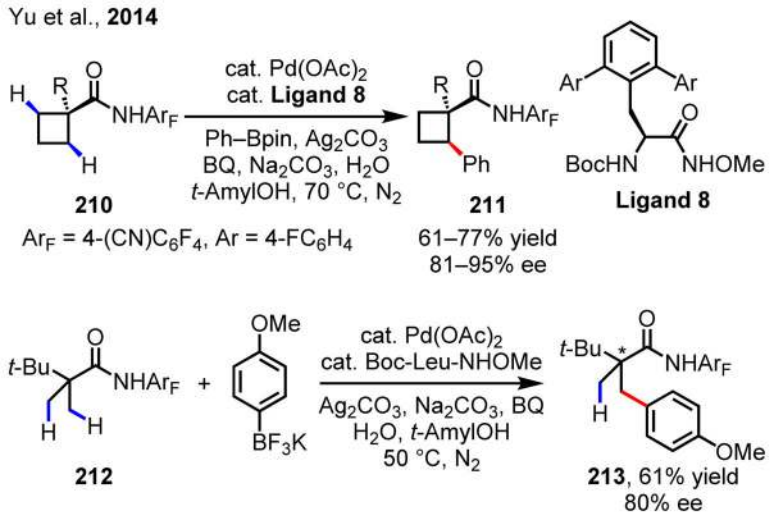
Scheme 58.

Amide-Directed Carbonylation of C(sp^3)–H Bonds



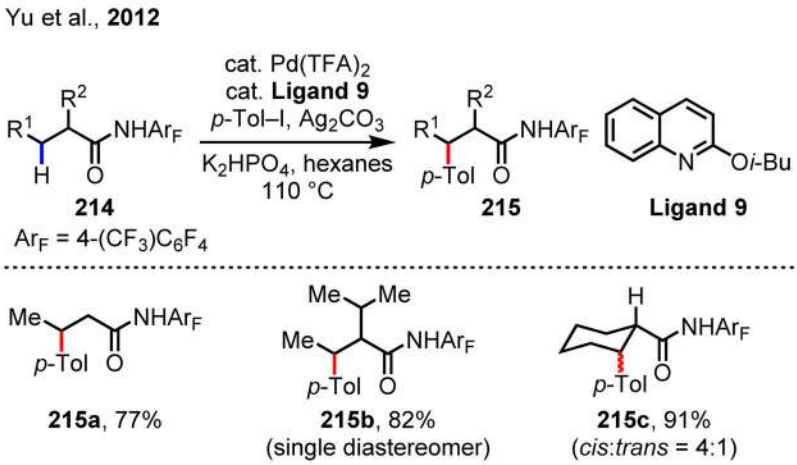
Scheme 59.

Enantioselective C(sp^3)–H Cross-Coupling using MPAA Ligands

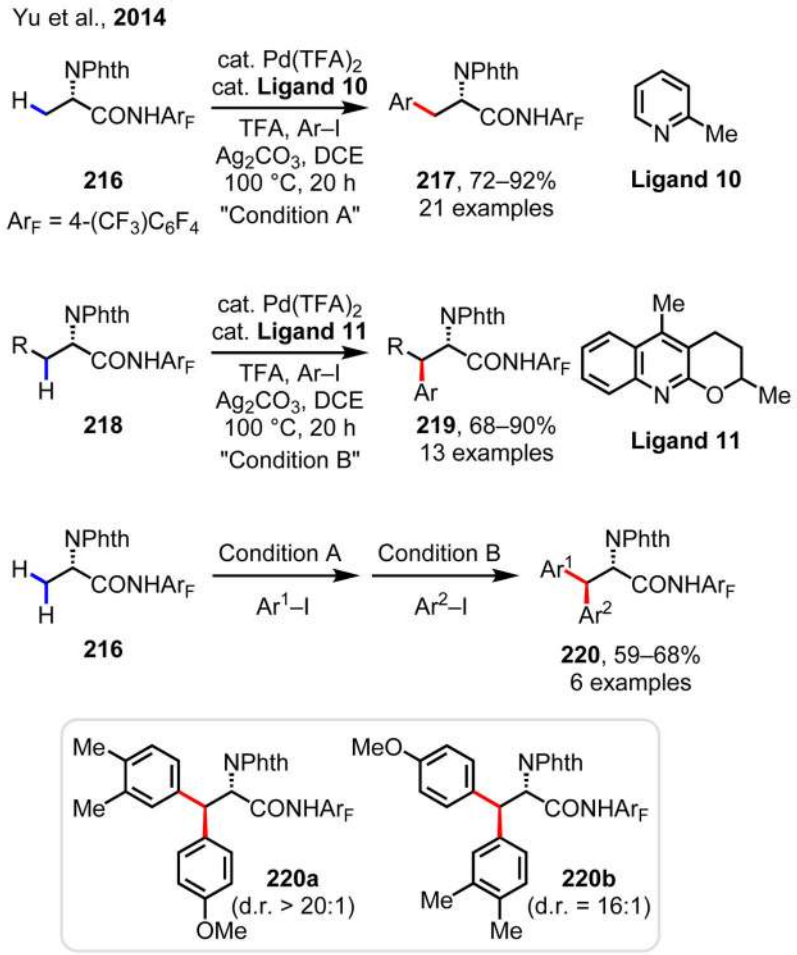


Scheme 60.

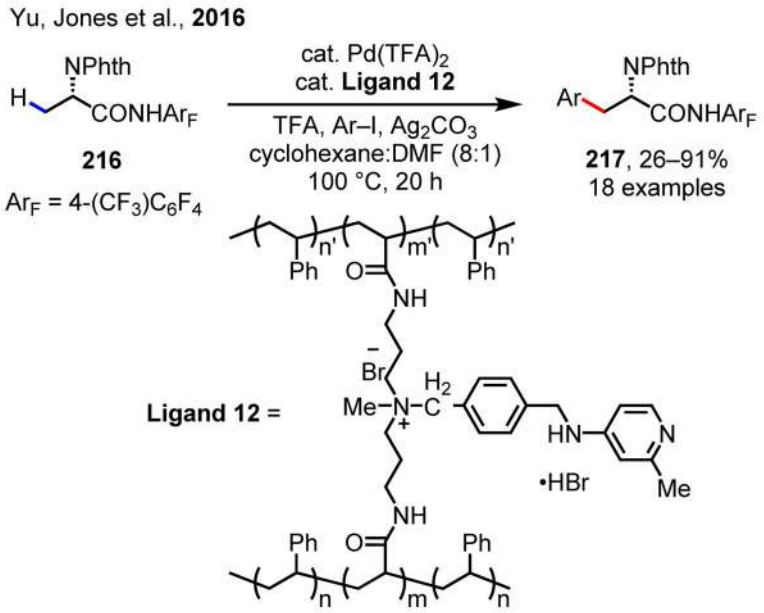
Enantioselective C(sp^3)–H Cross-Coupling using MPAHA Ligands



Scheme 61.
Ligand-Enabled Methylene C(sp^3)–H Arylation

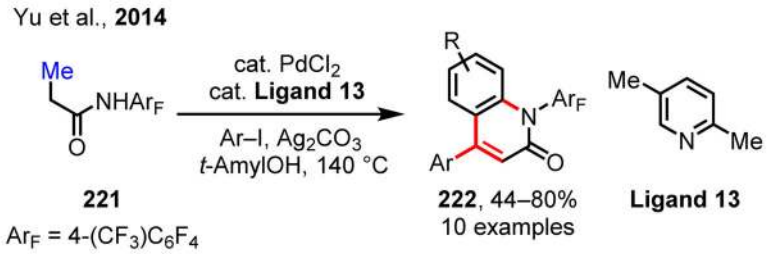


Scheme 62.
Catalyst-Controlled C(sp^3)–H Arylation

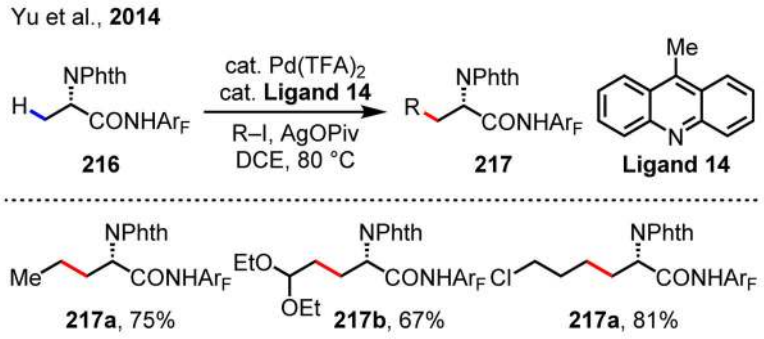


Scheme 63.

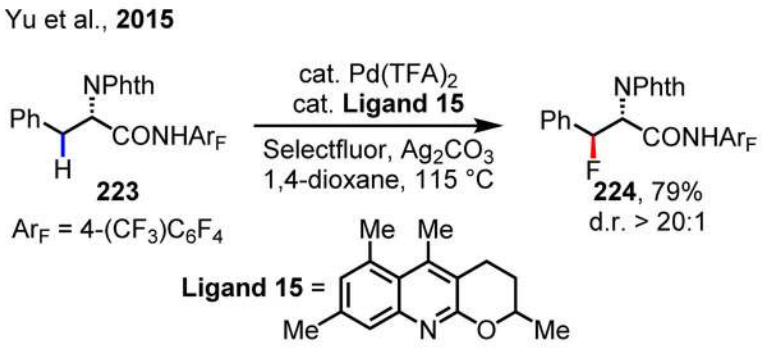
Polymer-Supported Pyridine Ligands for Pd(II)-Catalyzed C(sp^3)–H Arylation



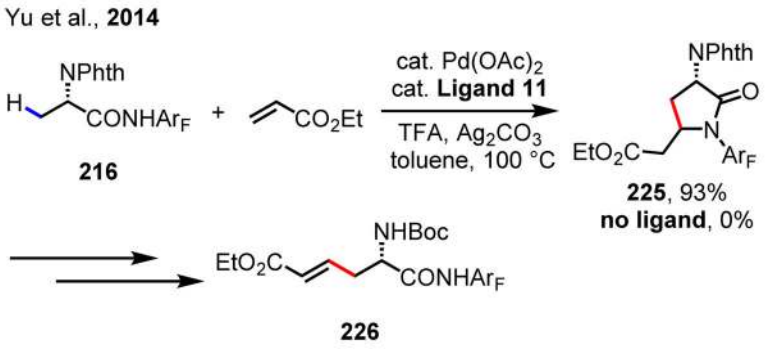
Scheme 64.
Ligand-Enabled Cascade C–H Activation



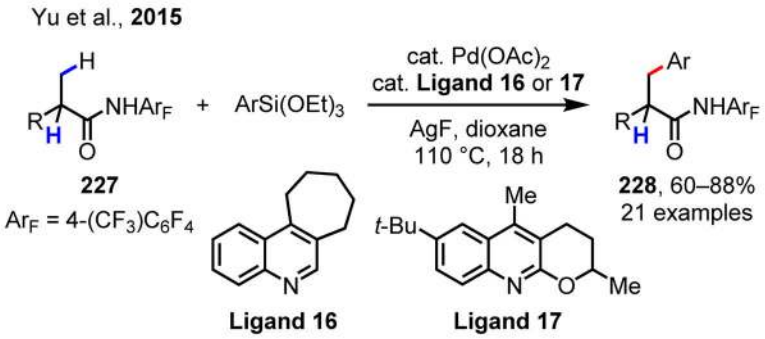
Scheme 65.
Ligand-Promoted Alkylation of C(sp^3)–H Bonds



Scheme 66.
Ligand-Enabled Fluorination of C(sp^3)–H Bonds

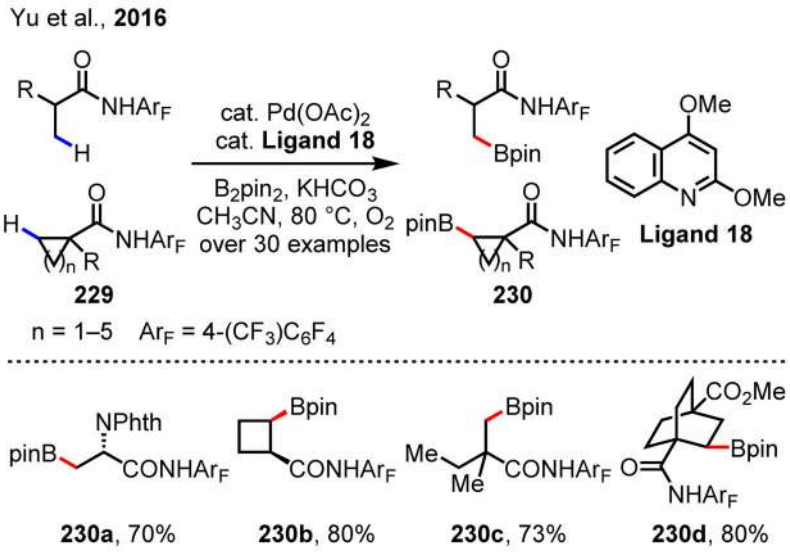


Scheme 67.
Ligand-Enabled C(sp^3)–H Olefination of Alanine Substrates



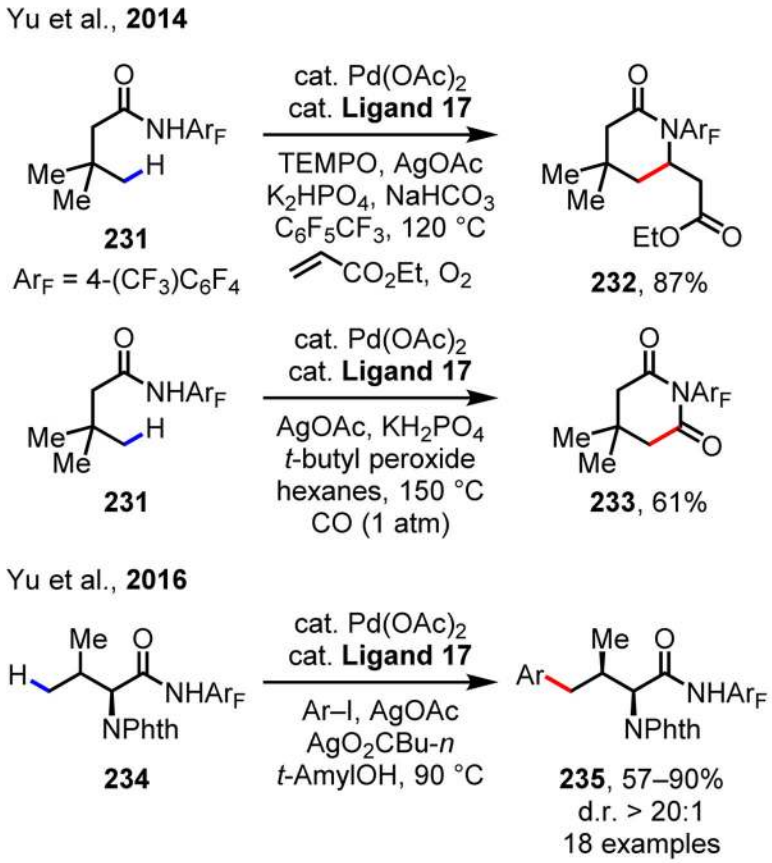
Scheme 68.

Ligand-Enabled Cross-Coupling of C(sp^3)–H Bonds with Arylsilanes



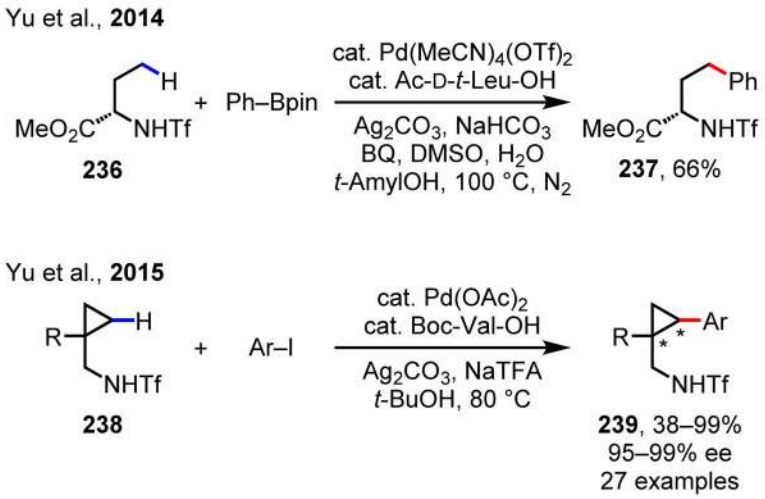
Scheme 69.

Ligand-Promoted Borylation of C(sp^3)–H Bonds



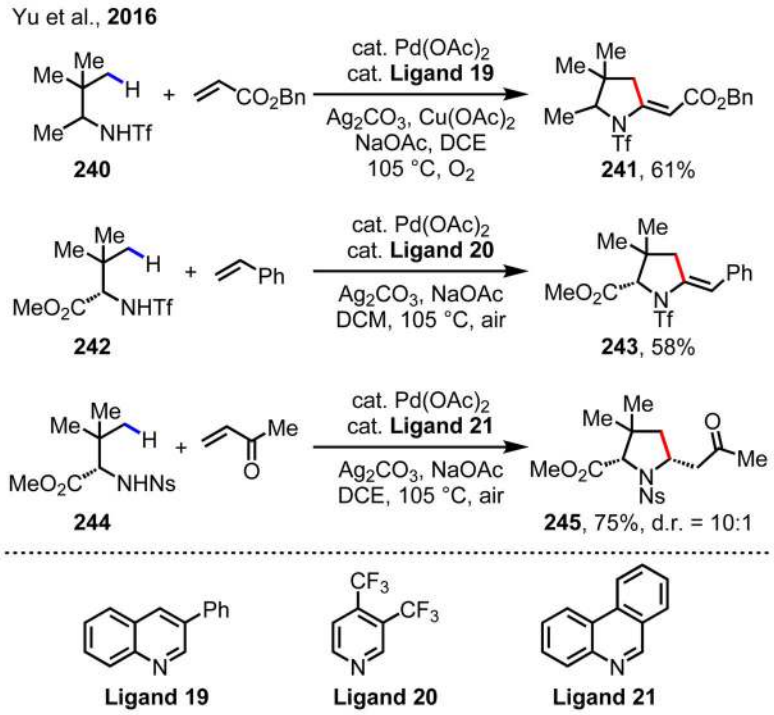
Scheme 70.

Ligand-Enabled γ-C(sp^3)–H Activation of Carboxylic Acid Derivatives



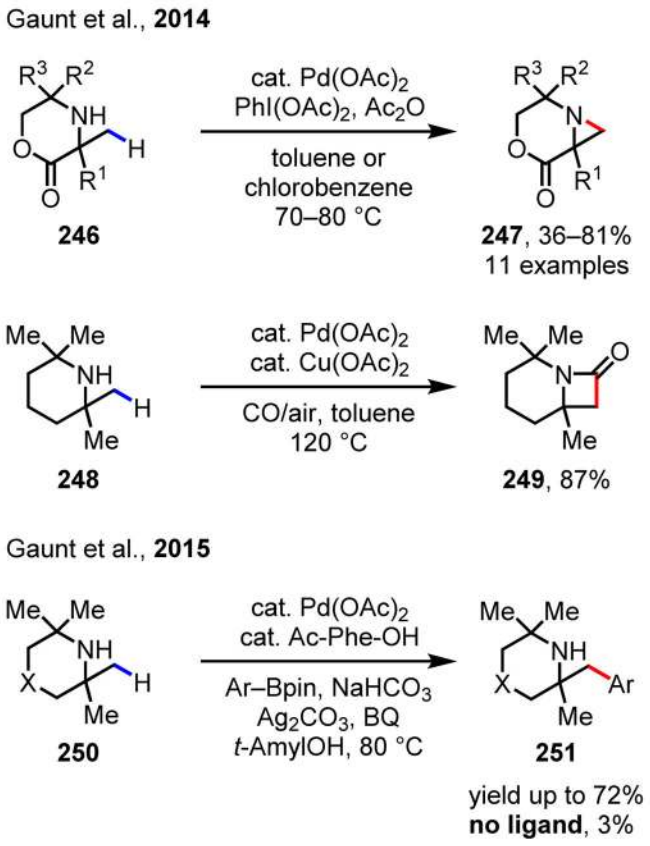
Scheme 71.

Pd-Catalyzed C(sp^3)–H Activation of Tf-Protected Amines Enabled by MPAA Ligands

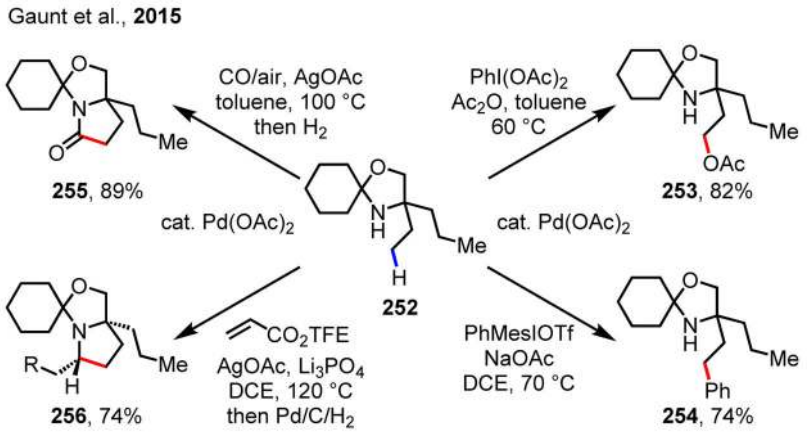


Scheme 72.

Ligand-Enabled γ-C(sp^3)–H Olefination of Amines



Scheme 73.
Pd(II)-Catalyzed β-C(sp^3)–H Activation of Secondary Amines



Scheme 74.

Pd(II)-Catalyzed γ-C(sp^3)–H Activation of Secondary Amines