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Review

Transition-Metal-Catalyzed, Coordination-Assisted Functionalization of Nonactivated C(sp^3)−H Bonds

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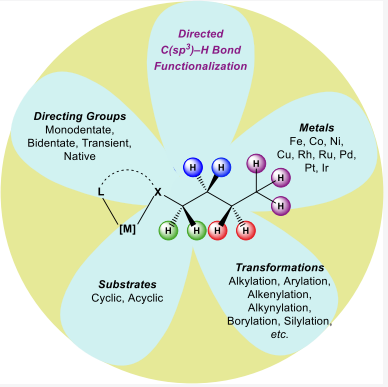
ABSTRACT: Transition-metal-catalyzed, coordination-assisted C(sp^3)−H functionalization has revolutionized synthetic planning over the past few decades as the use of these directing groups has allowed for increased access to many strategic positions in organic molecules. Nonetheless, several challenges remain preeminent, such as the requirement for high temperatures, the difficulty in removing or converting directing groups, and, although many metals provide some reactivity, the difficulty in employing metals outside of palladium. This review aims to give a comprehensive overview of coordination-assisted, transition-metal-catalyzed, direct functionalization of nonactivated C(sp^3)−H bonds by covering the literature since 2004 in order to demonstrate the current state-of-the-art methods as well as the current limitations. For clarity, this review has been divided into nine sections by the transition metal catalyst with subdivisions by the type of bond formation. Synthetic applications and reaction mechanism are discussed where appropriate.



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1. INTRODUCTION

In recent years, tremendous progress has been made in building carbon−carbon and carbon−heteroatom linkages directly from carbon−hydrogen bonds.[1−35] Furthermore, materials science and the pharmaceutical industry have benefited from the development of metal-catalyzed C−H bond activation and functionalization.[36−44] Because sp^2 and sp^3 carbon−hydrogen (C−H) bonds are ubiquitous in organic compounds, differentiating among the various C−H bonds in a complex substrate is extremely difficult. In recent years, significant advances have been made to overcome this challenge. Directing groups (DGs)

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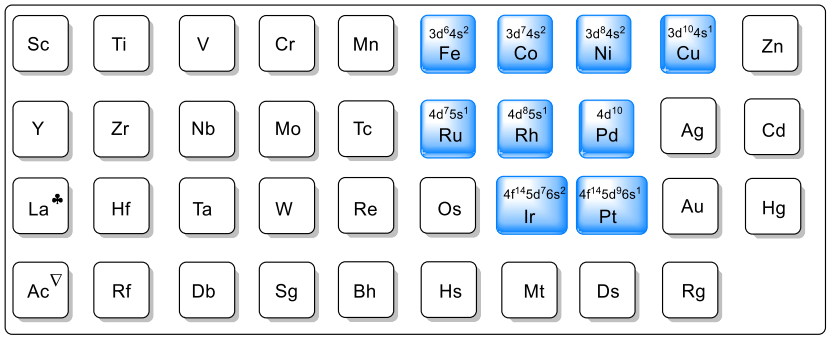

Figure 1. Transition metals in the periodic table used in coordination-assisted C(sp^3)−H activation and covered in this review.

have featured prominently to enable reaction sequences that involve site-selective C−H activation and functionalization. Several pioneering examples of this strategy have been reported since the 1950s,[45−48] such as cobalt-catalyzed *ortho*-carbonylation of aldimine by Murahashi,[45] palladium-catalyzed *ortho*-halogenation of azobenzene by Fahey,[46] *ortho*-C−H alkylation of phenol catalyzed by a cyclometalated ruthenium complex by Lewis and Smith,[47] and ruthenium-catalyzed *ortho*-selective alkylation of aromatic ketones with olefins reported by Murai and co-workers.[48]

A multitude of functional groups, including amides, imines, azaheterocycles, amines, carboxylic acids, esters, ketones, oximes, aldehydes, and hydroxyl groups have been employed as DGs for catalytic C−H bond functionalizations. In addition, functional groups that contain sulfur, phosphorus, and silicon as well as those that demonstrate π-coordination have been developed as directing groups.

Compared to the significant progress in C(sp^2)−H bond activation and functionalization, catalytic functionalization of C(sp^3)−H bonds remains an enormous challenge due to the low acidity and the comparatively weak nature of the corresponding metal−alkyl bonds.[49] Furthermore, compared to primary C(sp^3)−H bonds, methylene C(sp^3)−H bonds are more difficult to functionalize due to steric hindrance during the C−H metalation step.

Although earlier reviews have dealt with certain aspects of C(sp^3)−H functionalization reactions, including the transition-metal-catalyzed arylation of unactivated C(sp^3)−H bonds,[8] alkyl C−H activation catalyzed by palladium,[34] reactions assisted by specific directing groups (e.g., exo-type DGs[22] or amines[30]), and the cross-dehydrogenative coupling of C(sp^3)−H bonds,[50] a comprehensive overview of this cutting-edge area has not been summarized, and numerous new advances have been made in the past several years. We reasoned that a review on coordination-assisted, nonactivated C(sp^3)−H functionalization reactions that covers the full breadth of transition metal catalysts would be a useful addition to the literature (Figure 1).

This review will focus on transition-metal-catalyzed, coordination-assisted functionalization reactions of nonactivated C(sp^3)−H bonds, covering the literature published through March 2020, with any omissions being unintentional. Intramolecular C(sp^3)−H functionalization methods that involve an initial oxidative addition event, for example, with the metal adding into Ar−X[51−58] or Si−H[59−66] bonds are outside of the scope of this review and will not be discussed except when illustrative of other key points. For clarity, this review has been divided into nine sections by metal type, in which the discussion of C(sp^3)−H bond functionalization is arranged according to the types of bonds that are formed. Moreover, both synthetic applications and mechanism are discussed where appropriate. It is worth noting that this is the first comprehensive review that encompasses the large body of work in this field over the past 16 years (2004−March 2020) (Figure 2). We hope that this review will inspire new developments in coordination-assisted, transition-metal-catalyzed, nonactivated C(sp^3)−H functionalization to overcome existing challenges and stimulate additional uses of these methods in the synthesis of natural products, pharmaceuticals, and other functionally significant molecules.

2. PALLADIUM-CATALYZED, COORDINATION-ASSISTED C(sp^3)−H FUNCTIONALIZATION

Palladium-catalyzed C−H functionalization reactions have been extensively investigated. These reactions can be subdivided based on the change of the oxidation state of the palladium catalyst during the catalytic cycle (Scheme 1).[5,51−58,67−70] For example, the Pd(0)/Pd(II) catalytic cycle, which is well-known in classical cross-coupling, is also applicable in numerous C−H functionalization reactions,[51−58] that will not be covered in this review. These reactions can also proceed through Pd(II)/Pd(0) and Pd(II)/Pd(IV) catalytic cycles.[4,67,71] Bimetallic Pd(III)−Pd(III) intermediates have been proposed as the active palladium species in C−H functionalization reactions by the Sanford and Ritter groups.[68,69] C−H functionalization reactions can also proceed through a Pd(II)/Pd(II) catalytic cycle, in which the Pd−C bond is cleaved via direct electrophilic substitution without a change in oxidation state at the metal center.

2.1. Palladium-Catalyzed C(sp^3)−H Functionalization Using Monodentate Directing Groups

Most C(sp^3)−H activation methods employ heteroatom-containing functional groups that coordinate to the metal and direct the metal's insertion into the C−H bonds. In the past decade, a variety of monodentate DGs, including pyridines, oxazolines, oximes, amides, and amines, have been developed for C(sp^3)−H activation (Figure 3).

2.1.1. Carbon−Carbon Bond Formation. *2.1.1.1. Arylation.* Three pathways for the directed arylation of unactivated C(sp^3)−H bonds with monodentate DGs are summarized in Scheme 2. Usually, cyclopalladated intermediate **B** is generated after C(sp^3)−H activation. Subsequently, Pd(II)/Pd(0) or Pd(II)/Pd(IV) redox couples can operate. In the Pd(II)/Pd(0) pathway, Pd(II) intermediate **C** is produced by transmetalation with a nucleophilic coupling partner. Intermediate **C** then undergoes reductive elimination to afford the arylated product and Pd(0). In the Pd(II)/Pd(IV) pathway, after oxidative addition with an electrophilic coupling partner, a Pd(IV)

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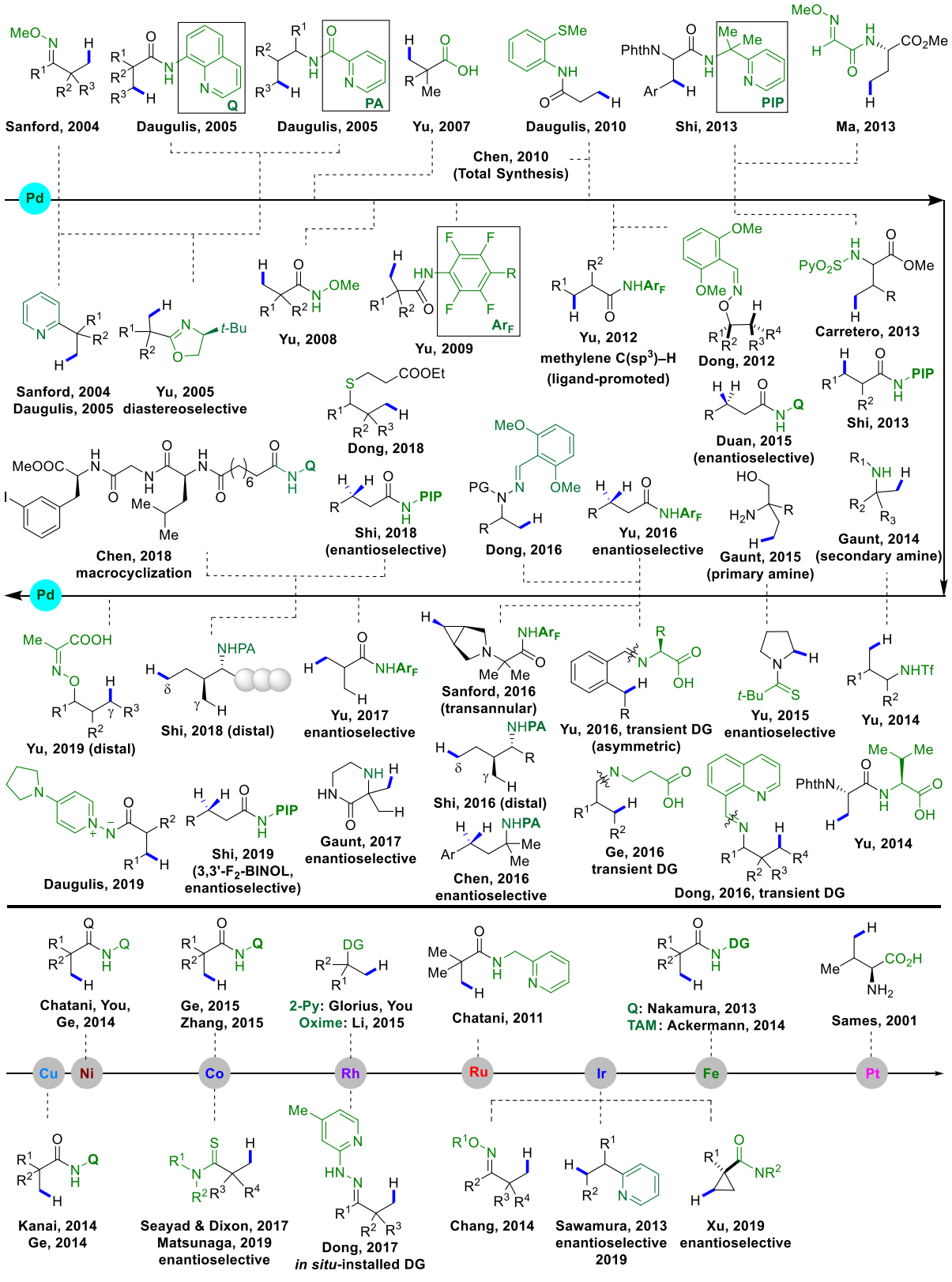

Figure 2. Timeline of the representative discovery and development of coordination-assisted transition-metal-catalyzed C(sp^3)–H functionalization reactions.

intermediate **E** or **G** is generated. Pd(IV) intermediate **E** then undergoes reductive elimination to afford the arylated product and Pd(II). Alternatively, Pd(IV) intermediate **G** is converted to Pd(IV) intermediate **H** via C(sp^2)–H palladation followed by reductive elimination to afford the arylated product and Pd(II).

2.1.1.1.1. Monodentate Directing Group Assisted C(sp^3)–H Arylation via Pd(II)/Pd(IV) Catalysis. Monodentate nitrogen-

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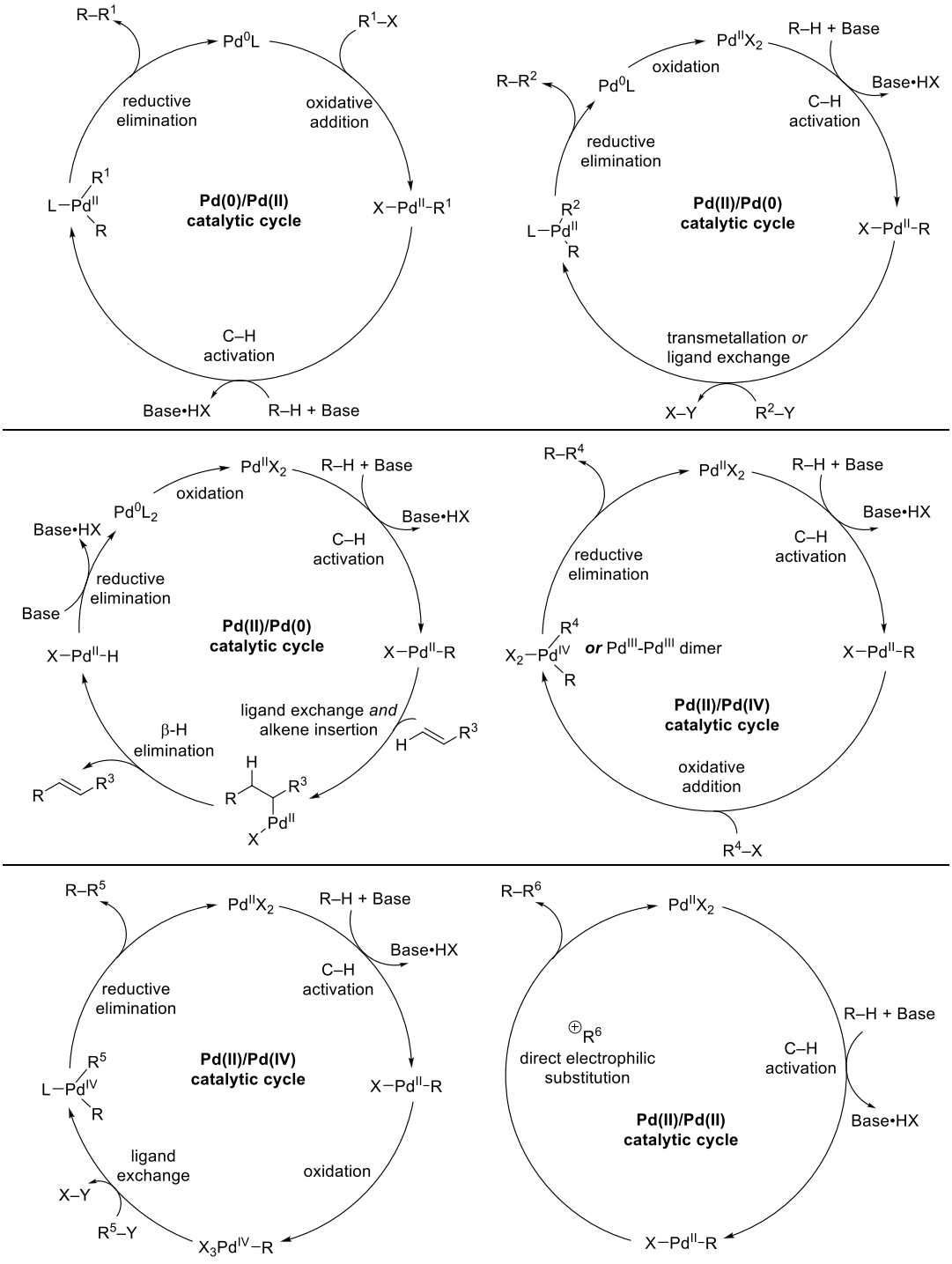
Scheme 1. Overview of Proposed Catalytic Cycles of Palladium-Catalyzed C−H Functionalization Reactions



based DGs have been recognized as one of the most efficient DG classes for transition-metal-catalyzed C−H functionalization since the pioneering investigations into stoichiometric cyclopalladation processes in the 1970s and 1980s.[72−75] In 2005, palladium-catalyzed, pyridine-directed C(sp^3)−H bond arylation with 1-iodo-4-methylbenzene **2** was reported by the Daugulis group.[76] Despite the high reaction temperature, long reaction times, and excess of aryl iodides that were required in this reaction, the report is an early demonstration of C(sp^3)−H arylation via a Pd(II)/Pd(IV) catalytic cycle (Scheme 3).

In 2015, Yu, Stamos, and co-workers developed a cascade process involving pyrazole-directed C(sp^3)−H bond arylation with aryl iodides followed by CONHAr$_F$-directed (Ar$_F$ = (4-CF$_3$)-C$_6$F$_4$) pyrazole C(sp^2)−H bond and *ortho*-phenyl C−H bond activation and cyclization (Scheme 4a).[77] Surprisingly, pyrazole directed the arylation of the C(sp^3)−H bond. Pd(OTf)$_2$(MeCN)$_4$ proved to be the most active palladium catalyst for this transformation. The catalytic system for this orchestrated cascade triple C−H activation tolerates a variety of functional groups with excellent selectivity and shortens the synthetic route to medicinally important benzo[*e*]indazole

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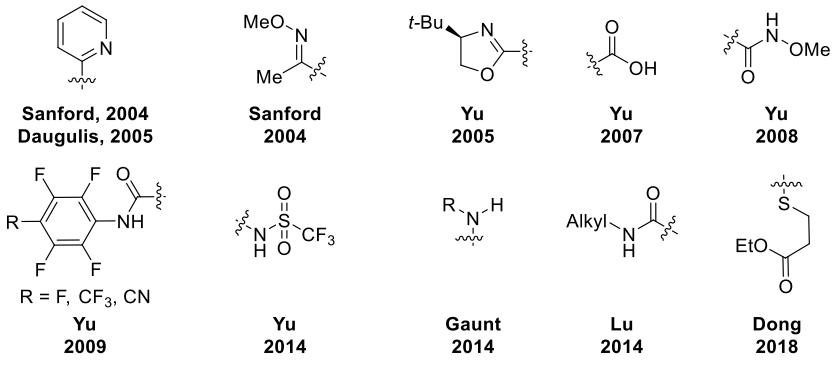
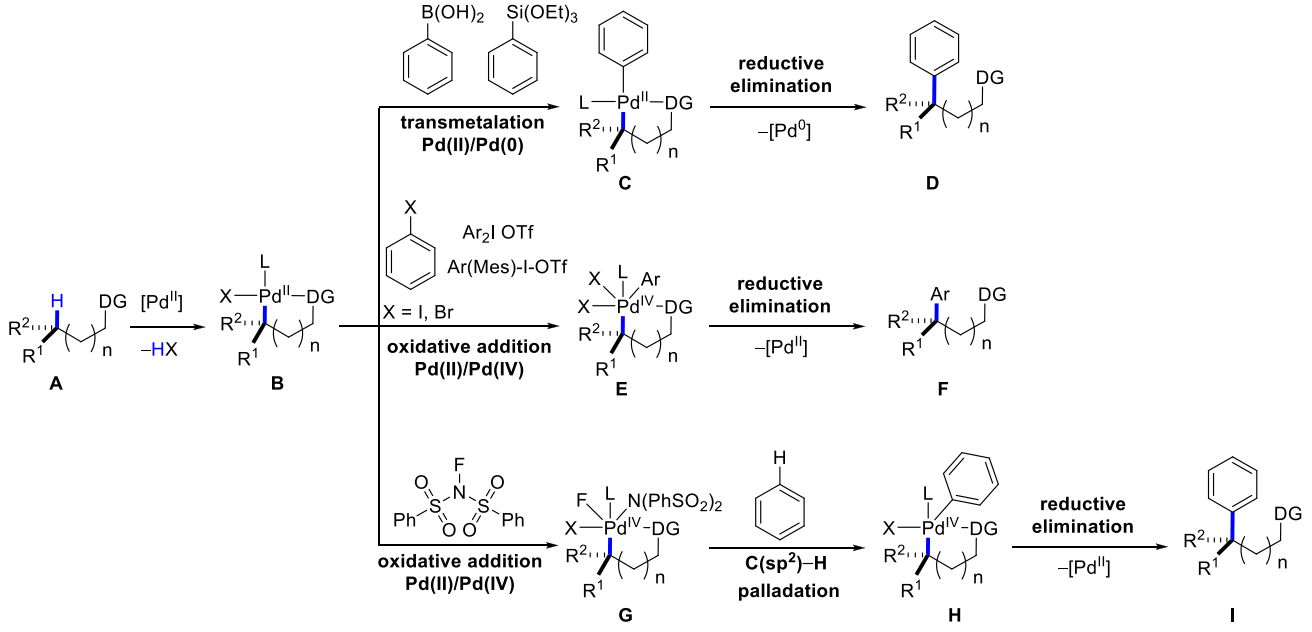
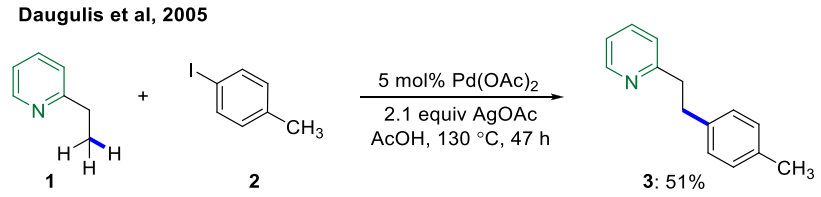


Figure 3. Representative monodentate DGs for C(sp^3)−H activation.

Scheme 2. Overview of Monodentate DG-Assisted C(sp^3)−H Bond Arylation



Scheme 3. Pyridine-Directed C(sp^3)−H Bond Arylation Reported by Shabashov and Daugulis[76]



derivatives. In 2017, Gulia and Daugulis also demonstrated a pyrazole-directed C(sp^3)−H bond arylation reaction, which was catalyzed by $Pd(OAc)_2$ and employed silver(I) oxide as a halide scavenger and base precursor (Scheme 4b).[78] The pyrazole moiety in the product can be removed by ozonolysis to afford *β*-phenethylamines.

Inspired by the cyclometalation of 1-aminopyridine ylides with various transition metals (Pd, Rh, Pt), Daugulis and co-workers coupled a number of 1-aminopyridines onto aliphatic carboxylic acids to investigate C(sp^3)−H bond functionalization with this family of directing groups (Scheme 5).[79] The NaOTf additive was found to increase the yield of arylated product significantly when using hexafluoroisopropanol (HFIP) as the solvent at 90 °C. Secondary C(sp^3)−H arylation was achieved using *N*-acetyl-L-phenylalanine (**L1**) as ligand. The discovery of 1-aminopyridine ylides expanded the arsenal of removable monodentate DGs for challenging C(sp^3)−H activation reactions.

Through the electronic and steric modification of amine groups, Gaunt and co-workers developed a palladium-catalyzed C(sp^3)−H arylation reaction of protected 1,2-amino alcohols (Scheme 6a).[80] The reported reaction conditions include $Pd(OAc)_2$ (15 mol %) with Ph_2IOTf in the presence of sodium acetate in 1,2-dichloroethane at 70 °C. They succeeded in using both electron-rich and electron-deficient aryl iodide reagents, and various functional groups, such as bromo and fluoro, were tolerated. In 2019, Gaunt and co-workers observed that 2-halobenzoic acids could promote oxidative addition to a less hindered alkylamine-derived palladacycle (Scheme 6b). When 2-iodobenzoic acid (2 equiv) and AgOAc (1 equiv) were added

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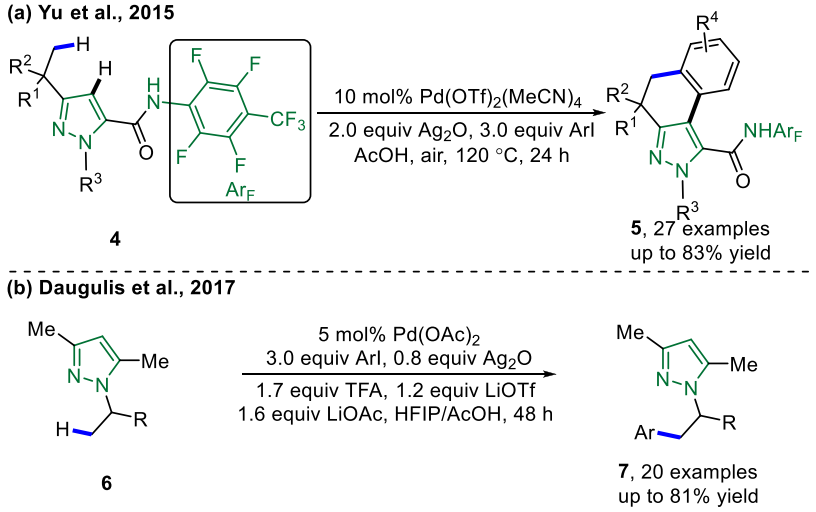
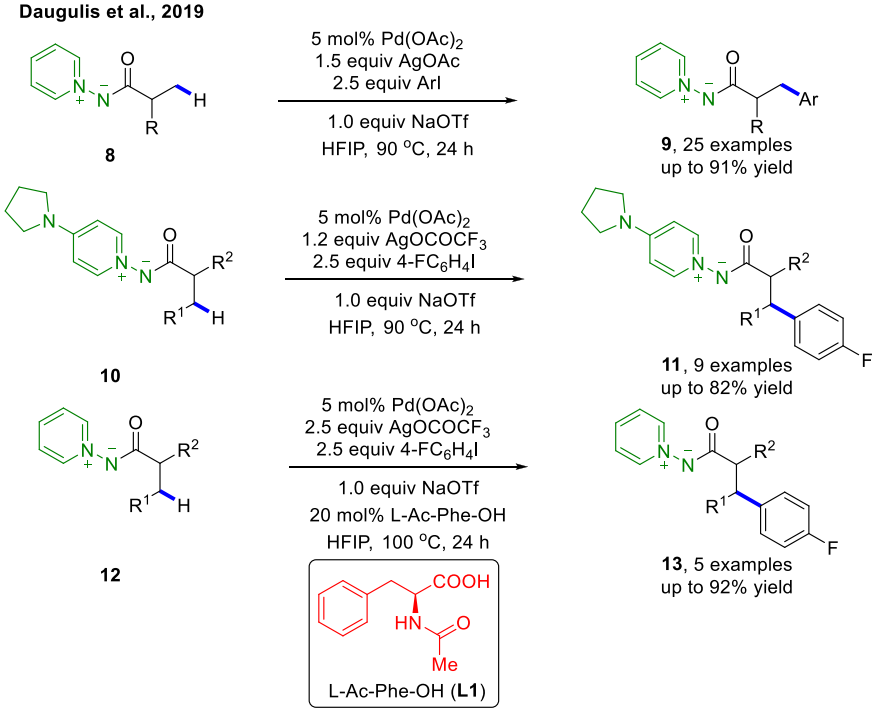
Scheme 4. (a) Pyrazole-Directed C(sp^3)−H Bond Arylation Reported by Yu et al.[77] and (b) Pyrazole-Directed C(sp^3)−H Bond Arylation Reported by Gulia and Daugulis[78]



Scheme 5. 1-Aminopyridinium-Ylide-Directed β-C(sp^3)−H Arylation[79]



to the solution of palladacycle **18** in $CHCl_3$, a palladacycle **20** was identified.[81] The authors propose that this seven-membered palladacycle forms through a concerted 1,2-arylpalladium migration and reductive elimination process triggered by decarboxylation. Free primary aliphatic amine-directed arylation of unactivated C(sp^3)−H bonds with an acid additive has also been reported (Scheme 7).[82,83]

Other strongly coordinating monodentate DGs have also been developed. In 2016, Chen and co-workers reported an oxime-ether-directed, Pd(II)-catalyzed arylation of β-C(sp^3)−H bonds using diaryliodonium salts as arylating reagents (Scheme 8).[84] This technique allows the preparation of useful β-arylated oximes from ketones and aldehydes. After investigation of different solvents, HFIP was found to accelerate the reaction.

In 2018, the Dong group reported a thioether-directed, palladium-catalyzed γ-C(sp^3)−H arylation reaction.[85] The authors protected the free thiol through a Michael addition between the thiol substrate and ethyl acrylate, which maintained the ability of sulfur to coordinate to the Pd catalyst (Scheme 9). A variety of protecting groups have been tested under the standard reaction conditions. No desired product was obtained when thiols were protected as Michael adducts bearing pendant carboxylic acid or amide groups. Moreover, the corresponding *tert*-butyl ester was unstable under acidic conditions, and the methyl ester furnished the desired product in only low yield.

The Yu group established the first example of Pd(II)-catalyzed, carboxyl-directed arylation of β-C(sp^3)−H bonds in simple aliphatic acids.[86] However, this reaction suffered from low yields and a narrow substrate scope (Scheme 10). This

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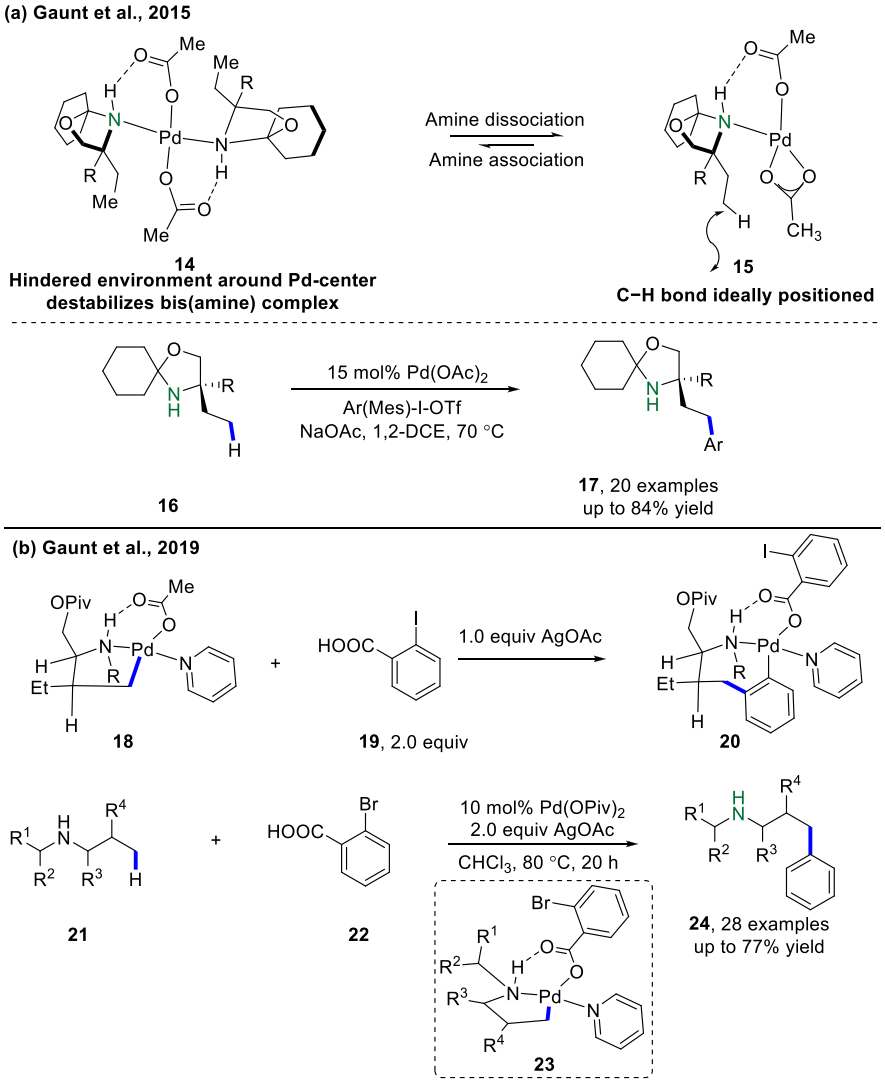
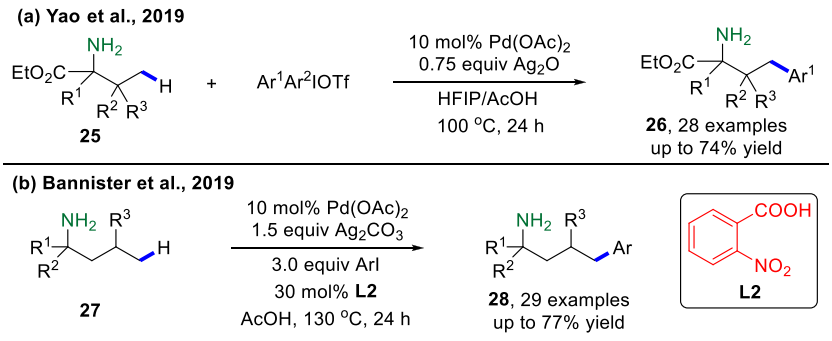
Scheme 6. (a) C(sp^3)−H Arylation of Amino Alcohol Derivatives[80] and (b) C(sp^3)−H Arylation of Alkylamines[81]



Scheme 7. (a) Free Amine-Directed, γ-C(sp^3)−H Arylation of α-Amino Esters[82] and (b) Free Amine-Directed δ-C(sp^3)−H Arylation[83]



reactivity of carboxylic acids was significantly promoted by sodium counterions. Subsequent studies support the proposal that the countercation binds to the carboxylate group in a κ^2 coordination mode, which induces Pd(II) to coordinate with the unhindered oxygen lone pair in a κ^1 fashion (**39**).[87] C−H activation was triggered through a process analogous to the complex induced proximity effect (CIPE).[88]

Due to the low yields in the first version of this Pd(II)-catalyzed, carboxylate-directed β-C(sp^3)−H functionalization, the Yu group was motivated to develop a robust monodentate carboxamide DG that would demonstrate high reactivity, selectivity, and scope. In 2009, Yu and co-workers successfully introduced the CONHAr$_F$ (Ar$_F$ = C$_6$F$_5$) DG, which allowed the desired β-methyl C−H arylation reaction to proceed efficiently with Buchwald's cyclohexyl-JohnPhos ligand (**L3**) and CsF as the base (Scheme 11a).[89] Various α-methylated amides were arylated in good to excellent yield. The authors observed that an acidic N−H bond in the DG is essential for reactivity. Although

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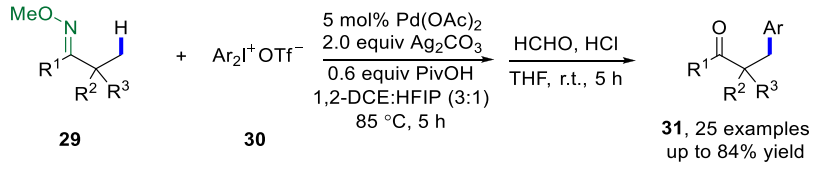
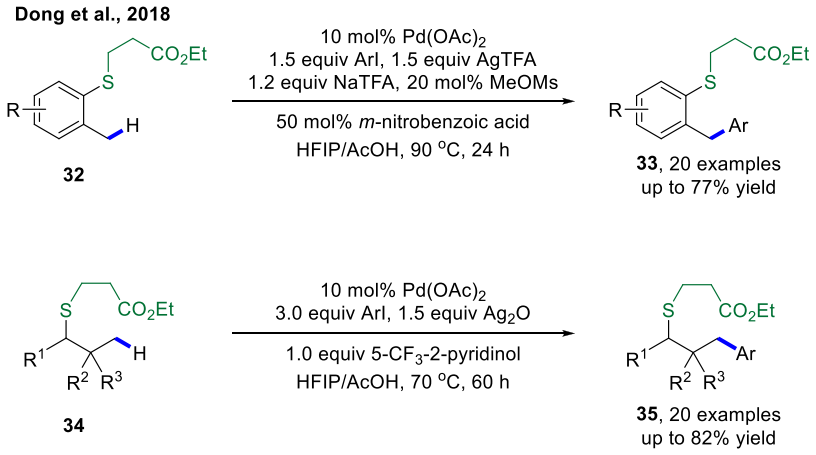
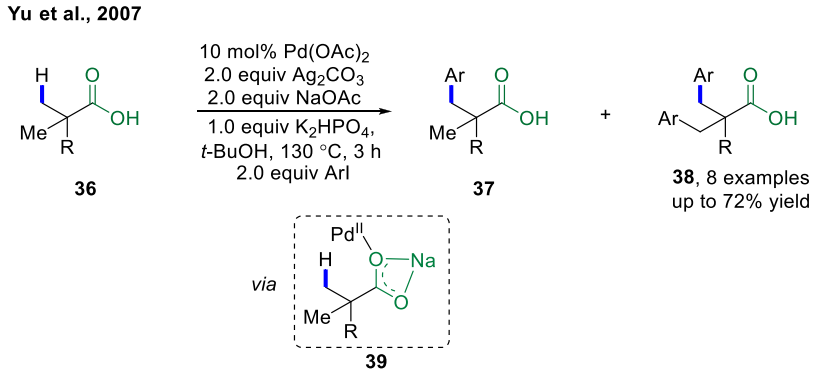
Scheme 8. Oxime-Directed β-Arylation of Oxime Ethers Using Diaryliodonium Salts[84]



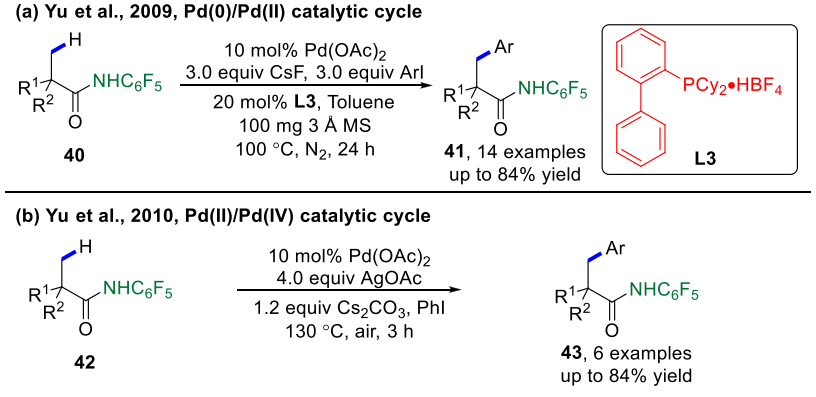
Scheme 9. Thioether-Directed γ-C(sp^3)−H Arylation[85]



Scheme 10. Carboxyl-Directed, Pd(II)-Catalyzed Arylation of β-C(sp^3)−H Bonds[86]



Scheme 11. First Example of CONHAr$_F$ (Ar$_F$ = C_6F_5)-Directed Arylation of β-Methyl C(sp^3)−H Bonds via (a) Pd(0)/Pd(II)[89] **or (b) Pd(II)/Pd(IV)**[90] **Catalytic Cycle**



this protocol is believed to proceed through a Pd(0)/Pd(II) catalytic cycle, it represents the first introduction of the monodentate, weakly coordinating CONHAr$_F$ (Ar$_F$ = C_6F_5) DG for use in C(sp^3)−H activation. Shortly after, the Yu lab successfully applied the same CONHAr$_F$ DG in Pd(II)/Pd(IV) chemistry, which allowed the desired β-methyl C−H arylation

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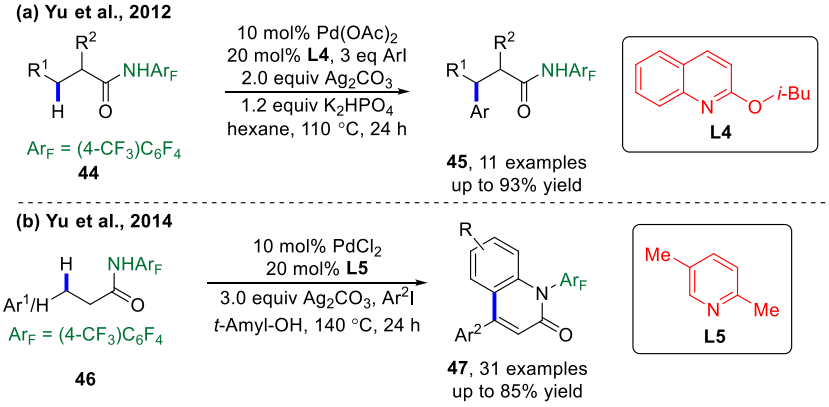
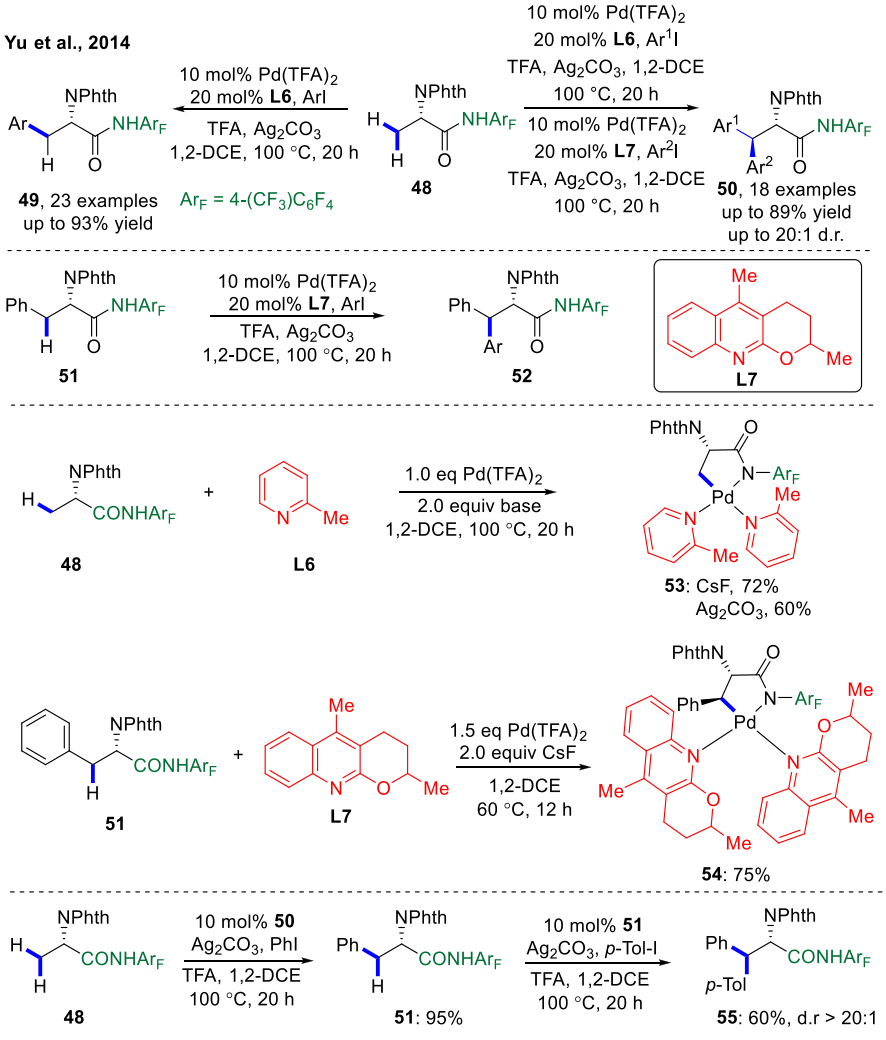
Scheme 12. (a) First Example of $CONHAr_F$ (Ar_F = *p*-$CF_3C_6F_4$)-Directed *β*-Methylene C(sp^3)−H Arylation[91] and (b) Ligand-Promoted $CONHAr_F$ (ArF = *p*-$CF_3C_6F_4$)-Directed Triple C−H Activation Reactions[92]



Scheme 13. Ligand-Promoted $CONHAr_F$ (Ar_F = *p*-$CF_3C_6F_4$)-Directed Arylation of Alanine- and Phenylalanine-Derived Substrates[93]



reaction to proceed efficiently with $Pd(OAc)_2$ as the catalyst, AgOAc as the additive, and Cs_2CO_3 as the base. Several carboxylic acid derivatives were arylated in moderate to good yields that were comparable to those obtained via the Pd(0)/Pd(II) catalytic cycle (Scheme 11b).[90]

In 2012, the Yu laboratory described the first example of $CONHAr_F$-directed (Ar_F = *p*-$CF_3C_6F_4$), Pd(II)-catalyzed arylation of acyclic and cyclic *β*-methylene C(sp^3)−H bonds, which was achieved through systematic screening of mutually repulsive 2,6-dialkoxypyridine and 2-alkoxyquinoline ligands.[91] The reported reaction conditions are as follows: $Pd(TFA)_2$(10 mol %), **L4** (20 mol %), ArI (3.0 equiv), Ag_2CO_3 (2.0 equiv) as the additive, K_2HPO_4 (1.2 equiv) as the base, hexane, 110 °C, 24 h (Scheme 12a). In this system, the methylene C−H

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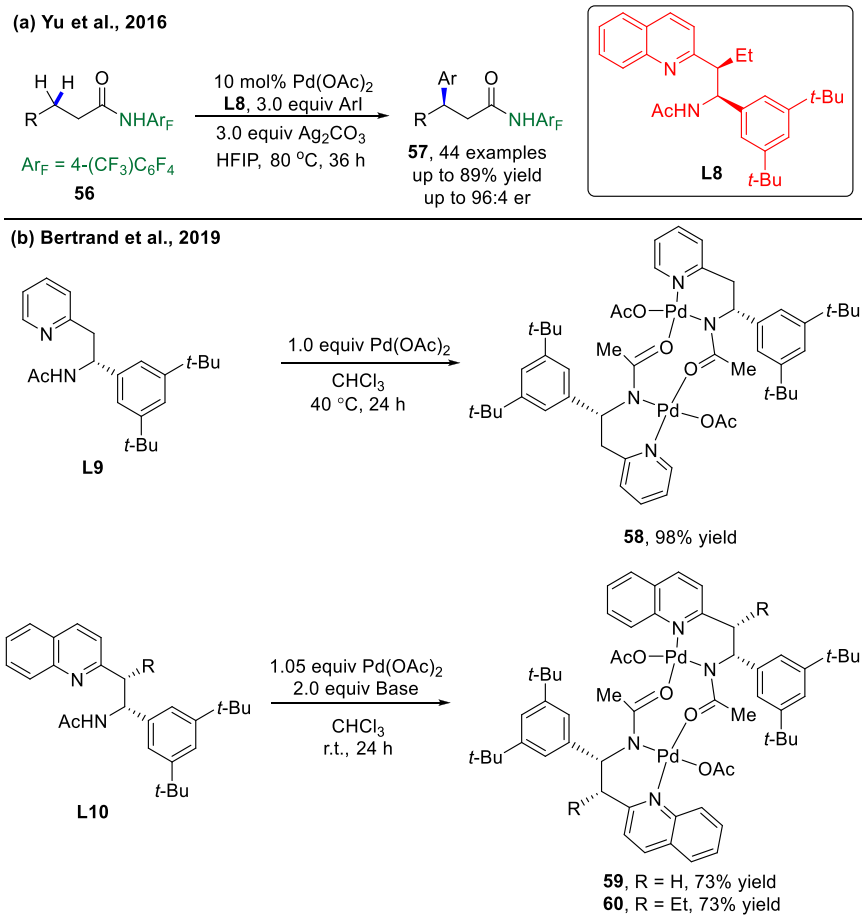
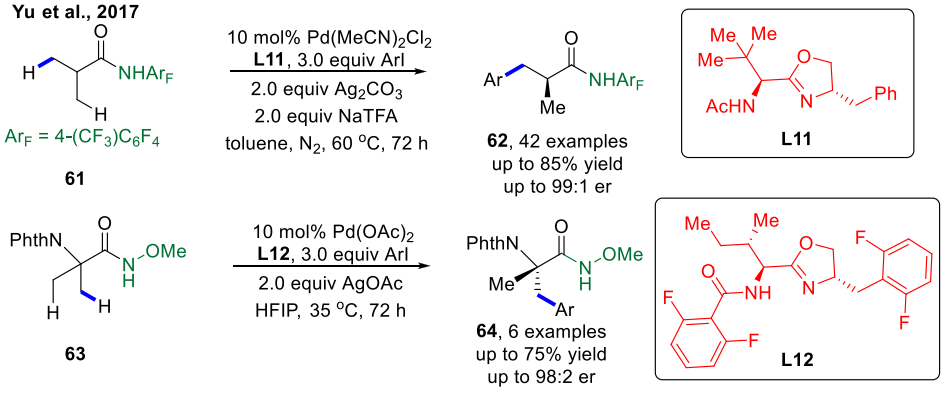
Scheme 14. Ligand-Accelerated Enantioselective Methylene C(sp^3)−H Bond Arylation[97,100]



Scheme 15. Asymmetric β-C(sp^3)−H Arylation Providing Access to α-Chiral Centers[101]



arylation of alicyclic substrates was also possible. In 2014, Yu and co-workers developed a one-pot synthesis of 4-aryl-2-quinolinones via ligand-promoted triple sequential C−H activation from the propionamide (Scheme 12b).[92] The mechanism involves C(sp^3)−H arylation, dehydrogenation, Heck-type addition of another aryl halide partner, and intramolecular C(sp^2)−H amidation. After extensive screening, the optimized reaction conditions were reported to be $PdCl_2$ (10 mol %) using Ag_2CO_3 (3.0 equiv) as the additive and 2,5-lutidine **L5** (20 mol %) as the ligand at 140 °C in *t*-Amyl-OH for 24 h. A wide variety of functional groups on the aryl iodide were well tolerated in the reaction. The installation of two different aryl groups saw the intramolecular amidation occur at the less hindered position.

Later, the Yu group demonstrated the first example of ligand-controlled C(sp^3)−H arylation of alanine derivatives that bear a *p*-$CF_3C_6F_4$ amide auxiliary (Scheme 13).[93] Monoarylation of the methyl C(sp^3)−H bond with aryl iodides was achieved when a pyridine-based ligand (**L6**) was used. When a quinoline-based ligand (**L7**) was used, the arylation of the resulting benzylic methylene C(sp^3)−H bond with different aryl iodides was enabled. Arylation of a phenylalanine derivative with aryl iodides promoted by quinoline-based ligand **L7** were also investigated. In this system, various functional groups are well tolerated. Palladacycles **53** and **54** were synthesized via primary and

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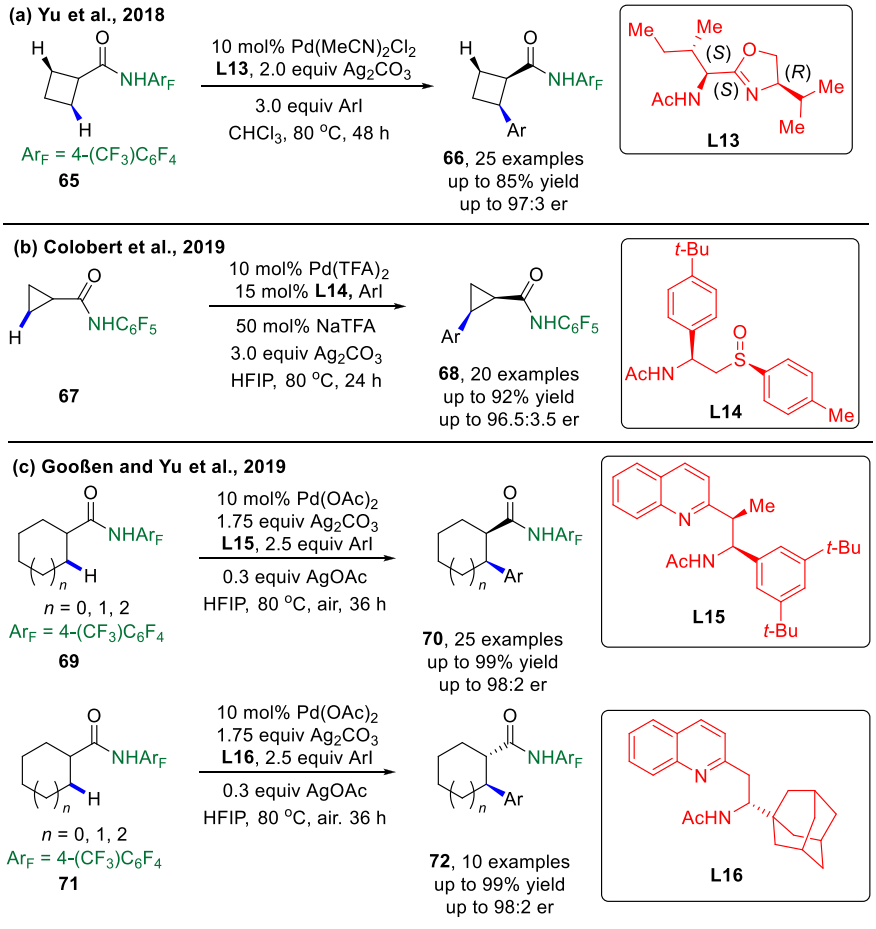
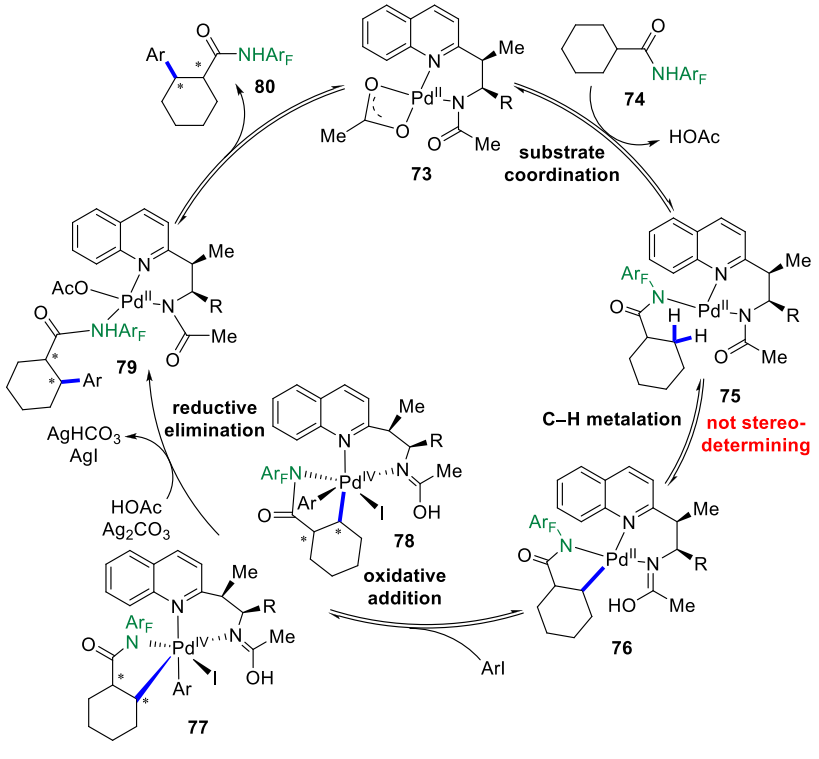
Scheme 16. (a) Enantioselective C(sp^3)−H Arylation of Cyclobutyl Carboxylic Amides,[102] (b) Enantioselective C(sp^3)−H Arylation of Cyclpropyl Carboxylic Amides,[103] and (c) Enantioselective C(sp^3)−H Arylation Cycloalkyl Carboxylic Amides[104]



Scheme 17. Proposed Mechanism of Enantioselective C(sp^3)−H Arylation Cycloalkyl Carboxylic Amides[104]



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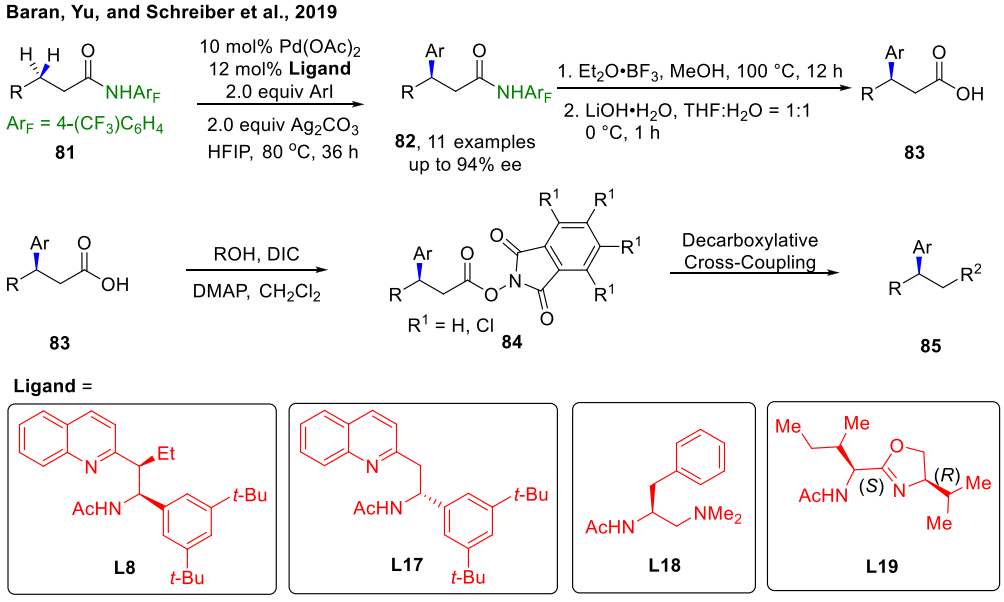
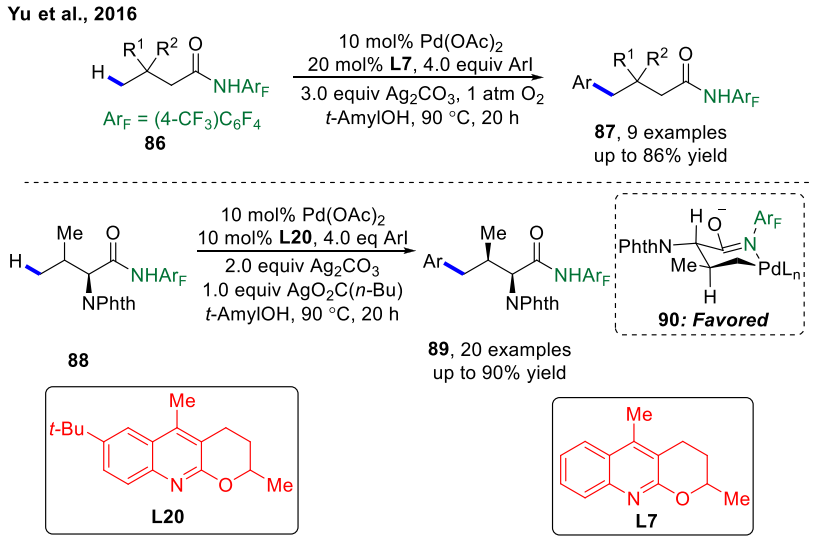
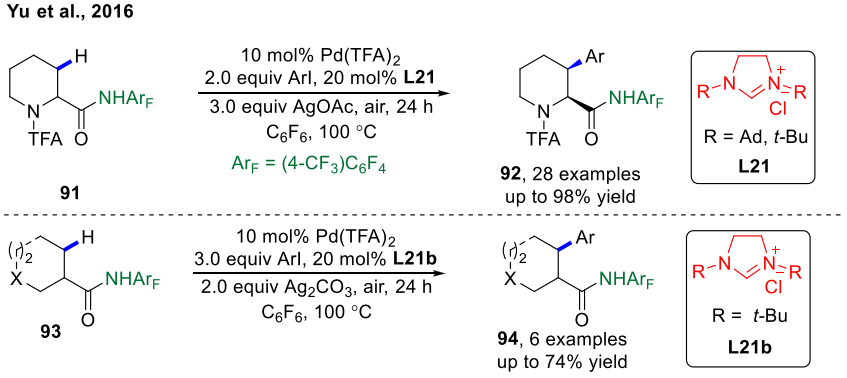
Scheme 18. Ligand-Accelerated Enantioselective Methylene C(sp^3)−H bond Arylation Followed by Decarboxylative Cross-Coupling[105]



Scheme 19. Ligand-Promoted CONHAr$_F$ (Ar$_F$ = *p*-CF$_3$C$_6$F$_4$)-Directed Arylation of *γ*-C(sp^3)−H Bonds[106]



Scheme 20. *N*-Heterocyclic Carbene Ligand-Enabled CONHAr$_F$ (Ar$_F$ = *p*-CF$_3$C$_6$F$_4$)-Directed C(sp^3)−H Arylation[107]



secondary C(sp^3)−H activation, respectively. Characterization of these complexes sheds light on the underlying mechanism of these transformations, offering a platform for further computational and kinetic studies. Palladacycles **53** and **54** were found to

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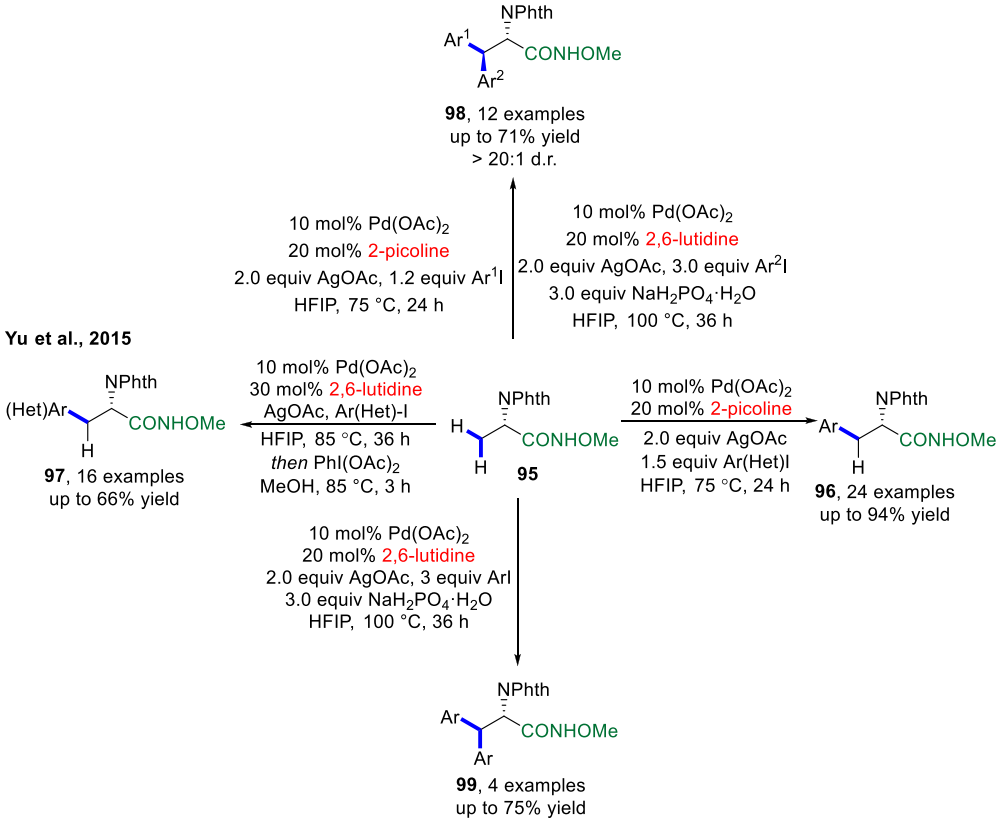
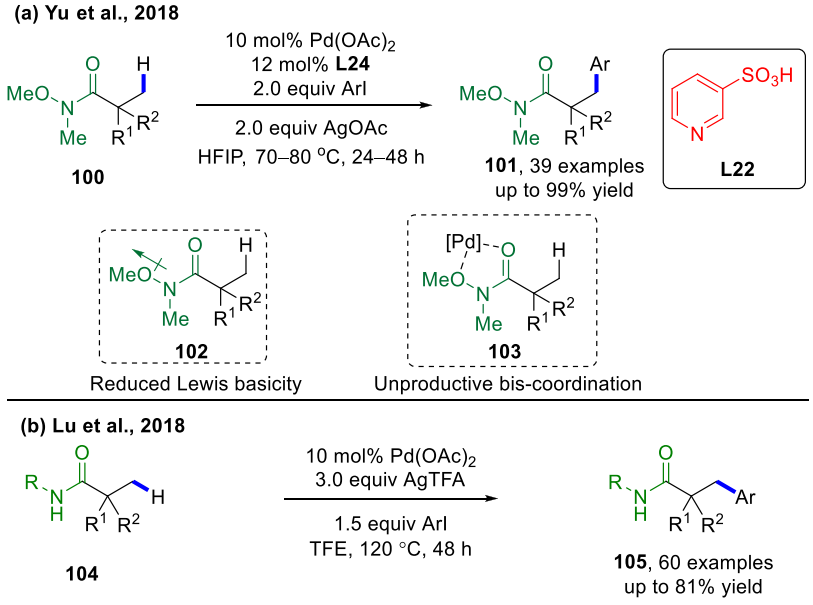
Scheme 21. Methoxyamide-Directed Arylation of Methyl β-C−H of α-Amino Acids[108]



Scheme 22. (a) Ligand-Enabled, Palladium-Catalyzed β-C(sp^3)−H Arylation of Weinreb Amides[109] **and (b) Simple Amide-Directed β-C(sp^3)−H Arylation**[110]



be viable precatalysts for primary and secondary C(sp^3)−H arylation, respectively, with the addition of TFA to facilitate the dissociation of one of the pyridine ligands. Computational studies revealed that the nonactivated precatalyst was activated by the deprotonation of the amide with CsF.[94] These studies also showed that the C(sp^3)−H bond cleavage is the rate-limiting step.[95] A reusable polymeric ligand platform was also designed to facilitate C(sp^3)−H arylations of alanine by the Jones group in 2016.[96]

Ligand-accelerated, enantioselective methylene C(sp^3)−H bond activation was discovered by the Yu group in 2016 (Scheme 14a).[97] The researchers observed that monodentate chiral ligands do not affect the stereochemistry of the palladium insertion step. Inspired by both quinoline-based ligands and chiral monoprotected amino acid (MPAA) ligands, chiral *N*-

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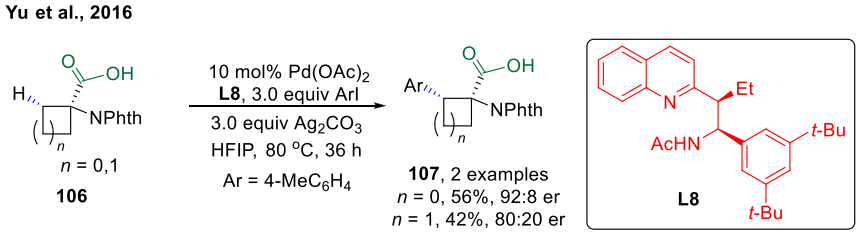
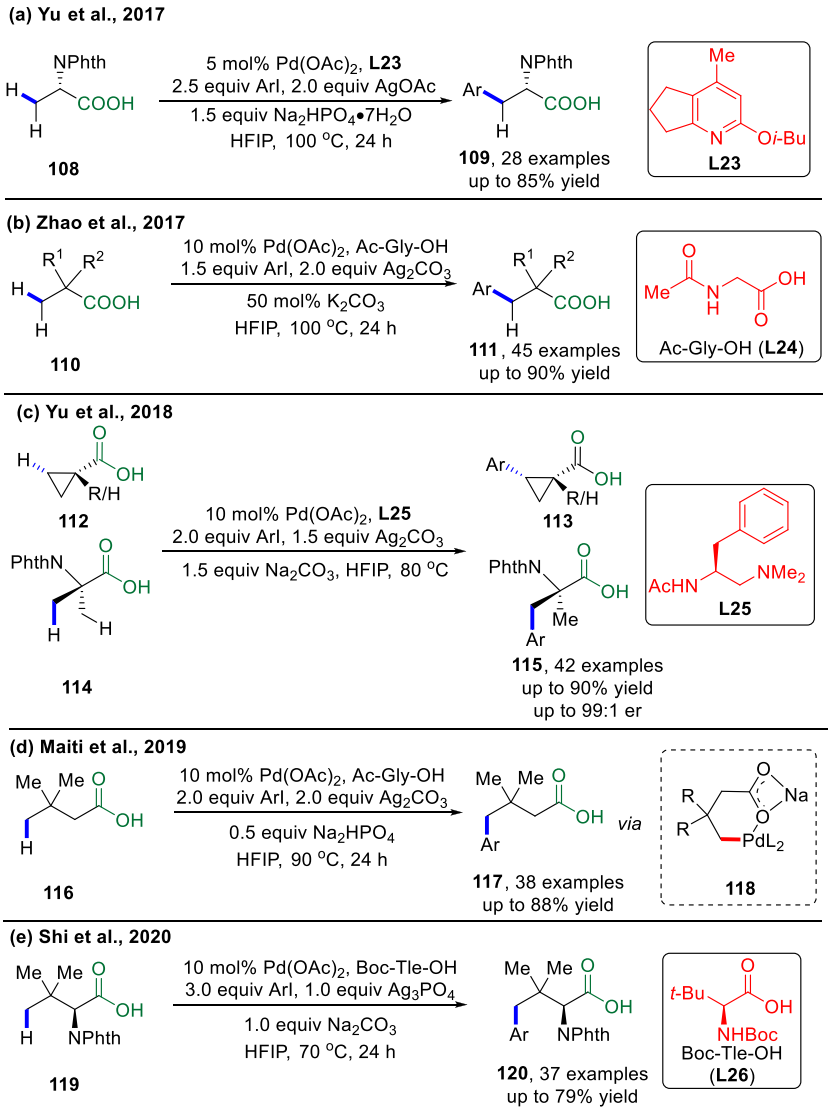
Scheme 23. Palladium-Catalyzed Asymmetric β-C(sp^3)−H Arylation of Free Carboxylic Acids[97]



Scheme 24. (a) Ligand-Enabled β-C−H Arylation of α-Amino Acids,[111] **(b) Ligand-Enabled β-C(sp^3)−H Arylation of Aliphatic Carboxylic Acids and α-Amino Acids,**[112] **(c) Enantioselective β-C(sp^3)−H Arylation of Substituted Cyclopropanecarboxylic Acids and 2-Aminoisobutyric Acid via Pd^{II}/Pd^{IV},**[113] **(d) Carboxyl-Directed, Pd(II)-Catalyzed γ-C(sp^3)−H Arylation,**[114] **and (e) Carboxyl-Directed γ-C(sp^3)−H arylation of *tert*-Leucine and Peptides**[115]



acetyl-protected aminoethyl quinoline (APAQ) ligands, which form six-membered chelates when bound to Pd, were found to enable Pd(II)-catalyzed enantioselective arylation of β-methylene C−H bonds of aliphatic amides with enantiomeric ratios reaching up to 96:4 and yields as high as 89%. Density functional theory (DFT) evidence suggests that the six-membered chelate can alleviate the steric repulsion between the quinoline group of the ligand and the Ar_F group of the substrate.[98] A dimeric palladium species, which was further investigated by the Blackmond group, was proposed as the resting state but not as an active catalyst.[99] A subsequent computational study by Bertrand, Yu, and co-workers explored three unprecedented amide-bridged Pd(II) dimers (**58**−**60**) and demonstrated that the quinoline ring of the APAQ ligands promotes catalytic activity (Scheme 14b).[100] Dramatically reduced reactivity was observed when *N*-acetyl-protected aminoethylpyridine (APAPy) was used as a ligand, and Bertrand, Yu, and co-workers reasoned that the off-cycle Pd(II) dimer (**58**) with

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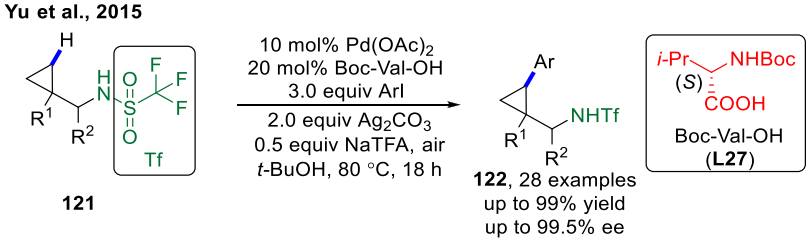
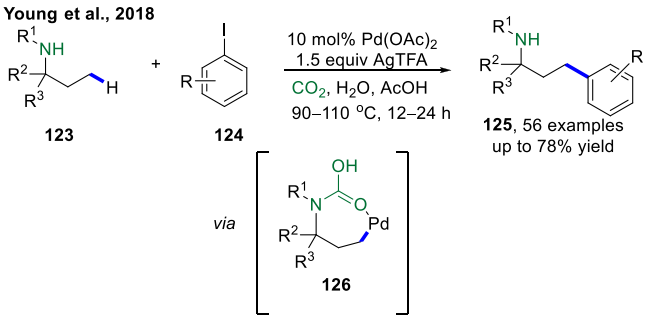
Scheme 25. Enantioselective C(sp^3)−H Arylation of Cyclopropyl Ethylamines via Pd(II)/Pd(IV) Catalytic Cycle[116]



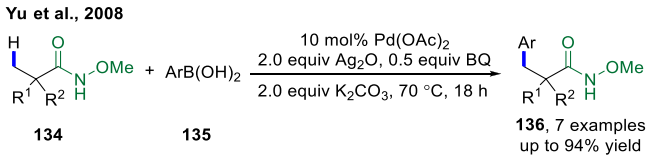
Scheme 26. Carbon Dioxide-Mediated C(sp^3)−H Arylation of Amine[117]



APAPy ligand is more stable, which slows the dissociation to the catalytically active species in solution.

In 2017, the Yu group devised a protocol for the desymmetrization of the *geminal* methyl groups in an isopropyl moiety using chiral mono-*N*-protected aminomethyl oxazoline (MPAO) ligands (Scheme 15).[101] Two challenging aspects of this desymmetrization include (1) the differentiation between the α hydrogen atom and the α-methyl substituent and (2) the long distance between the prochiral carbon and the ligated transition metal center. A bidentate, chiral APAQ ligand was investigated first but gave almost no enantioselectivity, reflecting the different nature of the transition states for enantioselective methylene C−H activation and isopropyl desymmetrization.

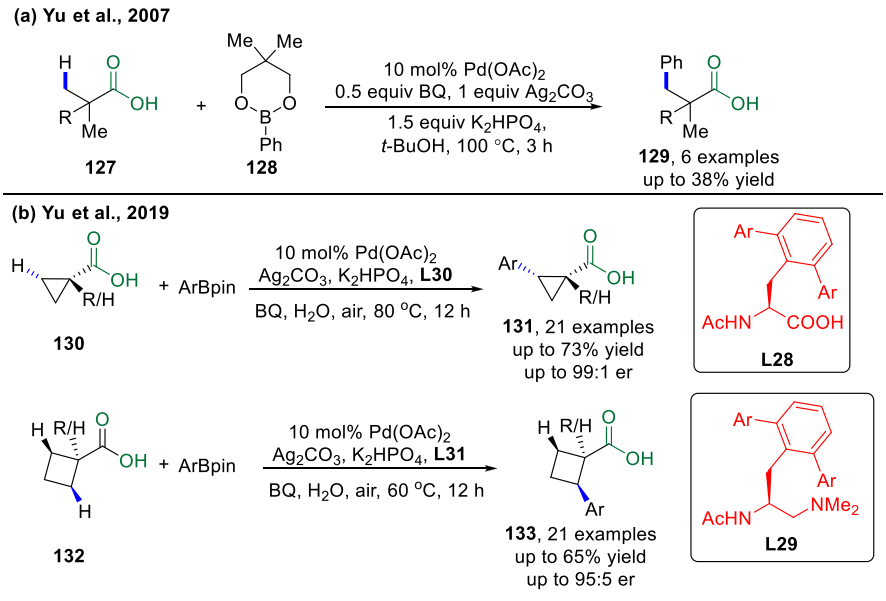
Scheme 28. Methoxyamide-Directed Arylation of C(sp^3)−H Bond with Arylboronic Acids[119]



After extensive screening and ligand modification, chiral MPAO ligands were found to effect enantioselective C(sp^3)−H activation of isopropyl groups. A wide range of aryl iodide compounds that contain electron-donating or electron-withdrawing groups are tolerated, producing desired products with enantiomeric ratios up to 98:2 using **L11** as chiral ligand. By using an *N*-methoxyamide auxiliary as a directing group and replacing the *N*-acetyl moiety with an *ortho*-difluorobenzoyl group to make **L12**, Yu and co-workers maintained high enantioselectivity while improving the yield of **64**, α,α-disubstituted α-amino acids containing chiral α-quaternary centers.

In 2018, Yu and co-workers prepared various chiral cyclobutanes via a Pd(II)-catalyzed enantioselective arylation of cyclobutyl carboxylic amides that bear α-hydrogen atoms using a chiral MPAO ligand (Scheme 16a, **L13**).[102] A variety of aryl iodide compounds that contain electron-donating or electron-withdrawing functional groups afford the corresponding products in moderate to good yields and excellent

Scheme 27. (a) Carboxyl-Directed, Pd(II)-Catalyzed Arylation of β-C(sp^3)−H Bonds[86] and (b) Enantioselective C(sp^3)−H Activation/Cross-Coupling Reactions of Free Carboxylic Acids via Pd^{II}/Pd^{0}[118]



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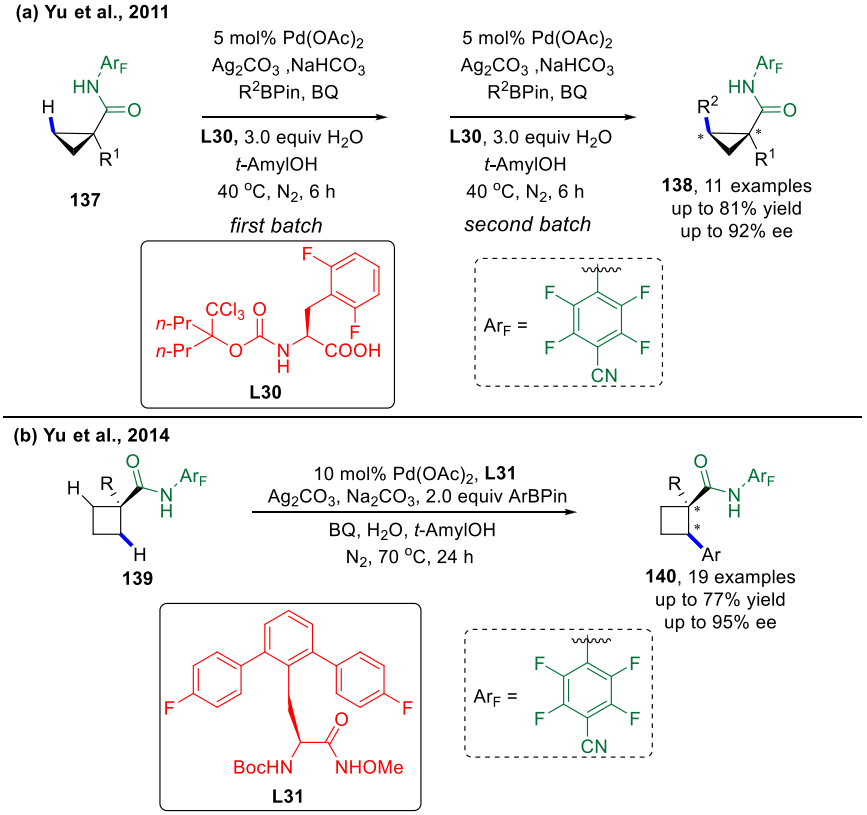
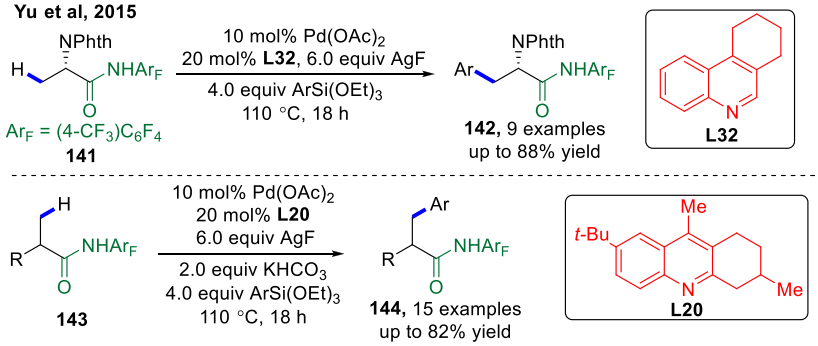
Scheme 29. (a) Palladium-Catalyzed, CONHAr$_F$ (Ar$_F$ = *p*-CNC$_6$F$_4$)-Directed Asymmetric Cyclopropane C−H Arylation[120] and (b) Palladium-Catalyzed, CONHAr$_F$ (Ar$_F$ = *p*-CNC$_6$F$_4$)-Directed Asymmetric Cyclobutane C−H Arylation[121]



Scheme 30. Ligand-Enabled C(sp^3)−H Cross-Coupling with Arylsilanes[122]



enantioselectivities. In 2019, asymmetric C(sp^3)−H arylation of cyclopropanes enabled by an *N*-protected aminosulfoxide ligand (**L14**) was reported by Colobert and co-workers. Stacking of π bonds between the ligand and the substrate leads to a nearly barrierless C−H activation process (Scheme 16b).[103] Enantio- and diastereoselective C(sp^3)−H arylation of cyclopentane, cyclohexane, and cycloheptane carboxylic acid derivatives directed by CONHAr$_F$ (Ar$_F$ = *p*-CF$_3$C$_6$F$_4$) was further studied by Yu and co-workers (Scheme 16c).[104] The proposed mechanism is shown in Scheme 17. C−H activation was ruled out as the stereodetermining step because the extent of stereoinduction was significantly influenced by substitution pattern of the aryl iodide. This observation is consistent with oxidative addition or reductive elimination being the stereo-determining step, given that oxidative addition potentially generates two diastereomeric Pd(IV) intermediates (**77**, **78**).

The combination of asymmetric C(sp^3)−H arylation with decarboxylative cross-coupling was developed by Baran and co-workers in 2019 (Scheme 18).[105] A variety of enantiopure, *trans*-1,2-disubstituted building blocks were synthesized in this fashion.

Cyclopalladation pathways that require six-membered alkyl palladacycles are generally both kinetically and thermodynamically disfavored when compared to analogous pathways that rely on the formation of five-membered alkyl palladacycles. As a result, reactions that require the formation of six-membered alkyl palladacycles remain underdeveloped. Inspired by their early research on ligand-enabled γ-olefination of amide derivatives, in 2016, Yu and co-workers designed a palladium-catalyzed, ligand-enabled, and CONHAr$_F$ (Ar$_F$ = *p*-CF$_3$C$_6$F$_4$)-directed, γ-C(sp^3)−H arylation of primary C−H bonds that are attached to quaternary carbon centers of aliphatic acid derivatives (Scheme 19).[106] An extensive screening of various

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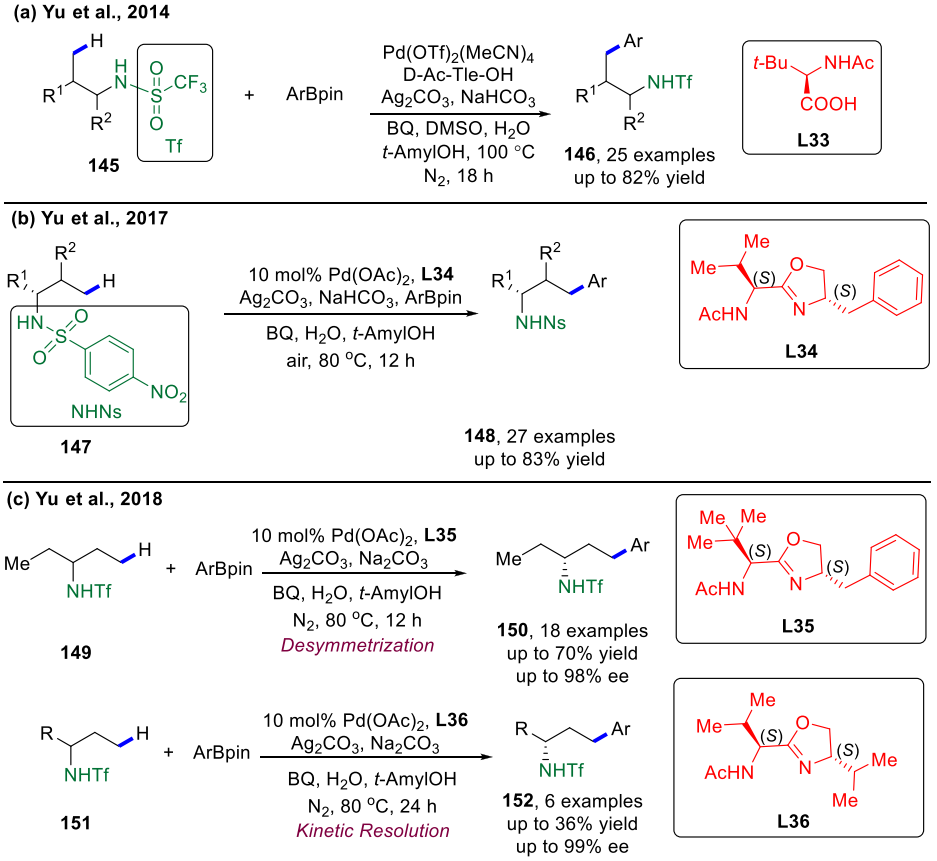
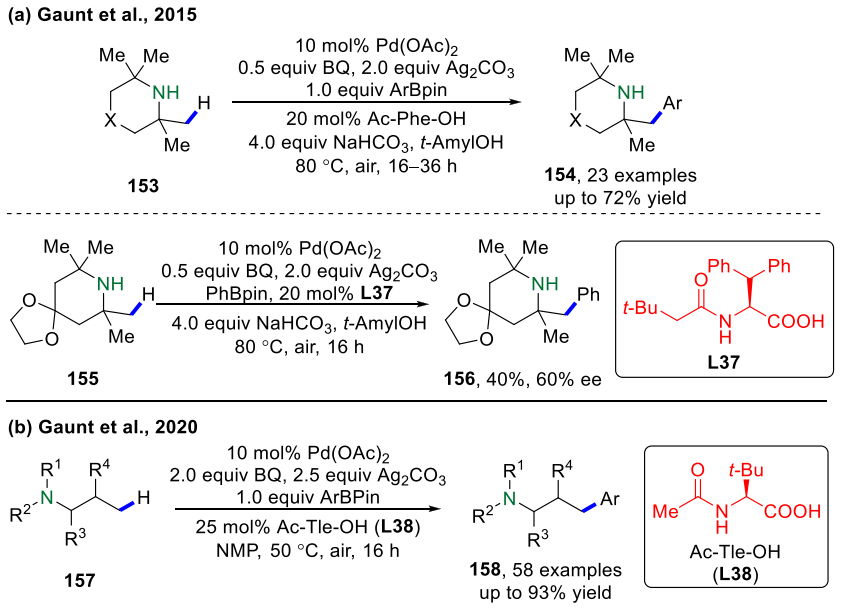
Scheme 31. (a) Triflamide-Directed γ-C(sp³)−H Bond Arylation,[123] (b) Ligand-Enabled γ-C(sp³)−H Arylation of Nosyl-Protected Amines,[124] and (c) Enantioselective γ-C(sp³)−H Activation of Alkyl Amines via Pd(II)/Pd(0) Catalysis[125]



Scheme 32. (a) Palladium-Catalyzed β-C(sp³)−H Arylation of Secondary Amines[126] and (b) Palladium-Catalyzed γ-C(sp³)−H Arylation of Tertiary Alkylamines[127]



ligands was conducted, and tricyclic quinolines were found to be the most effective. Under standard conditions, this reaction can involve aryl or heteroaryl iodides that contain a range of functional groups and steric and electronic properties. The high diastereoselectivity (dr > 20:1) was attributed to steric interactions between the methyl and the phthalimide groups in the six-membered palladacycle in which the *trans*-conformation is favored over the *cis*-conformation. Furthermore, carbamate formation followed by nucleophilic addition of LiSEt or $LiOH/H_2O_2$ can efficiently transform the amide auxiliary into the corresponding thioester or carboxylic acid, respectively.

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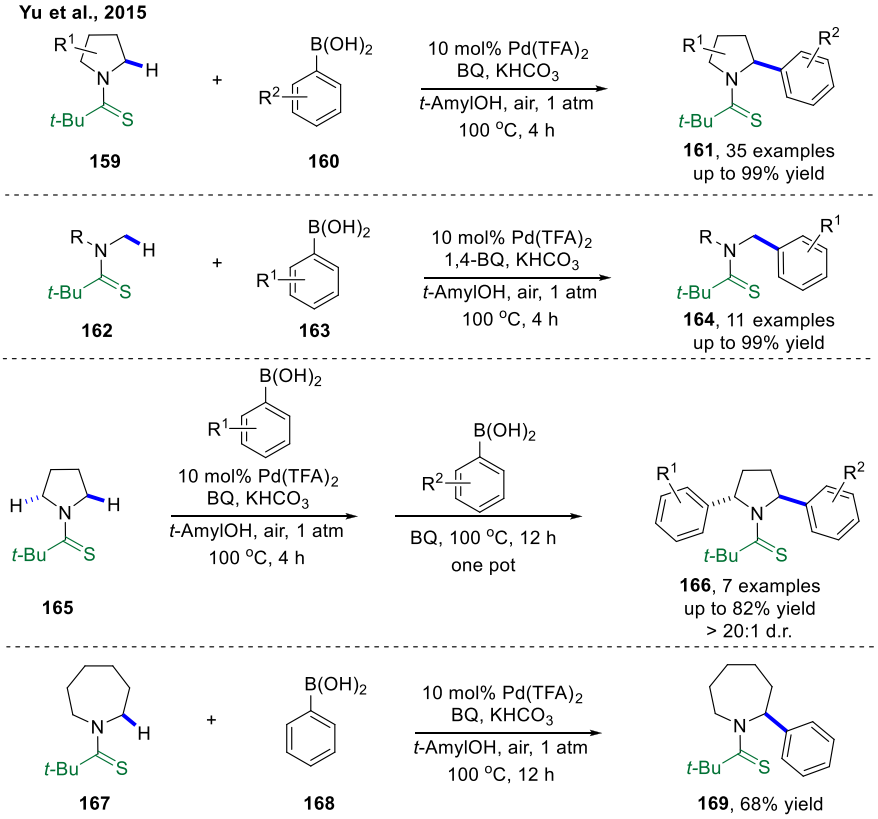
Scheme 33. Thioamide-Directed Amine α-Functionalization via Palladium(II)-Catalyzed C(sp^3)−H Arylation[128]



Palladium-catalyzed *N*-heterocyclic carbene (NHC) ligand-enabled C(sp^3)−H arylation of piperidine and tetrahydropyran derivatives was developed by Yu and co-workers in 2016 (Scheme 20).[107] Based on their earlier research showing that pyridine- and quinoline-type monodentate σ-donor ligands significantly accelerate C(sp^3)−H functionalization of amide substrates, they sought to examine another class of σ-donor ligands, NHCs. After systematic screening of ligands, 4,5-dihydroimidazolium with sterically bulky *N*-alkyl groups (**L21**) was found to be the best choice for this transformation. C−H arylation of both the C3 and C4 positions of piperidines and tetrahydropyrans were investigated. A wide range of functional groups such as halides, silyl ethers, and aldehydes were tolerated. The researchers proposed a mechanism whereby a Pd(II)/NHC species inserts into a C(sp^3)−H bond to form an alkylpalladium(II) species that subsequently reacts with the aryl iodide.

The readily installable and removable *N*-methoxyamide (CONHOMe) DG was used in Pd(II)/Pd(IV) catalysis by Yu and co-workers in 2015 (Scheme 21).[108] Arylation of both primary and secondary C(sp^3)−H bonds of amino acid scaffolds was accomplished. The monoarylation of primary C(sp^3)−H bonds was promoted by a 2-picoline ligand, with a 2,6-lutidine ligand enabling the subsequent arylation of the secondary C(sp^3)−H bonds in one pot. Notably, decomposition of the starting material was inhibited with acidic solvents such as 2,2,2-trifluoroethanol (TFE) or hexafluoro-2-propanol (HFIP). Under standard conditions, the reaction tolerates various substituted aryl iodide compounds that contain methyl, methoxy, and fluoro groups. Aryl iodide compounds that contain DGs such as acetamide, phosphonate, and hydroxyl groups were also tolerated reaction partners. Notably, aryl iodide compounds that contain dioxane and *N*-tosyl-protected indolyl also produce desired arylation product in moderate yields. Pyridyl and quinoline iodides afforded the desired product in lower yields, and 2,6-lutidine was identified as a more efficient ligand in these cases.

In 2018, Yu and co-workers developed a palladium-catalyzed, Weinreb-amide-directed β-methyl C(sp^3)−H arylation reaction, which was enabled by commercially available 3-pyridinesulfonic acid (**L22**) as the ligand (Scheme 22a).[109] Two challenges exist with this directing group compared to simple amides. First, the coordination of the carbonyl group on the DG with the Pd catalyst is weakened by the inductive effect of methoxy (**102**). Second, catalytic turnover can be decelerated by the unproductive bis-coordination of the catalyst to both the carbonyl group and methoxy (**103**). The ligand was computed to stabilize the substrate-bound Pd species, and this ligand effect was proposed to promote the dissociation of an acetate anion via electrostatic repulsion, which leads to the opening of a coordination site for C(sp^3)−H bond cleavage. Also in 2018, Lu and co-workers disclosed a palladium-catalyzed, simple amide-directed arylation of β-methyl C(sp^3)−H bonds, affording a wide range of β-aryl amides in good yields (Scheme 22b).[110]

Although monodentate amide DGs that were developed by the Yu group (CONHR, R = 4-(CF_3)C_6F_4, OMe) have demonstrated outstanding efficiency in directing C(sp^3)−H activation, their applications are limited by the requirement of their installation and removal. In 2016, the Yu group reported two isolated examples of ligand-accelerated, free carboxylic acid-directed reactions to allow enantioselective C(sp^3)−H arylation of strained methylene C−H bonds (e.g., cyclopropane and cyclobutane; Scheme 23), and an α-quaternary carbon center is necessary for the reactions to take place.[97] Inspired by their

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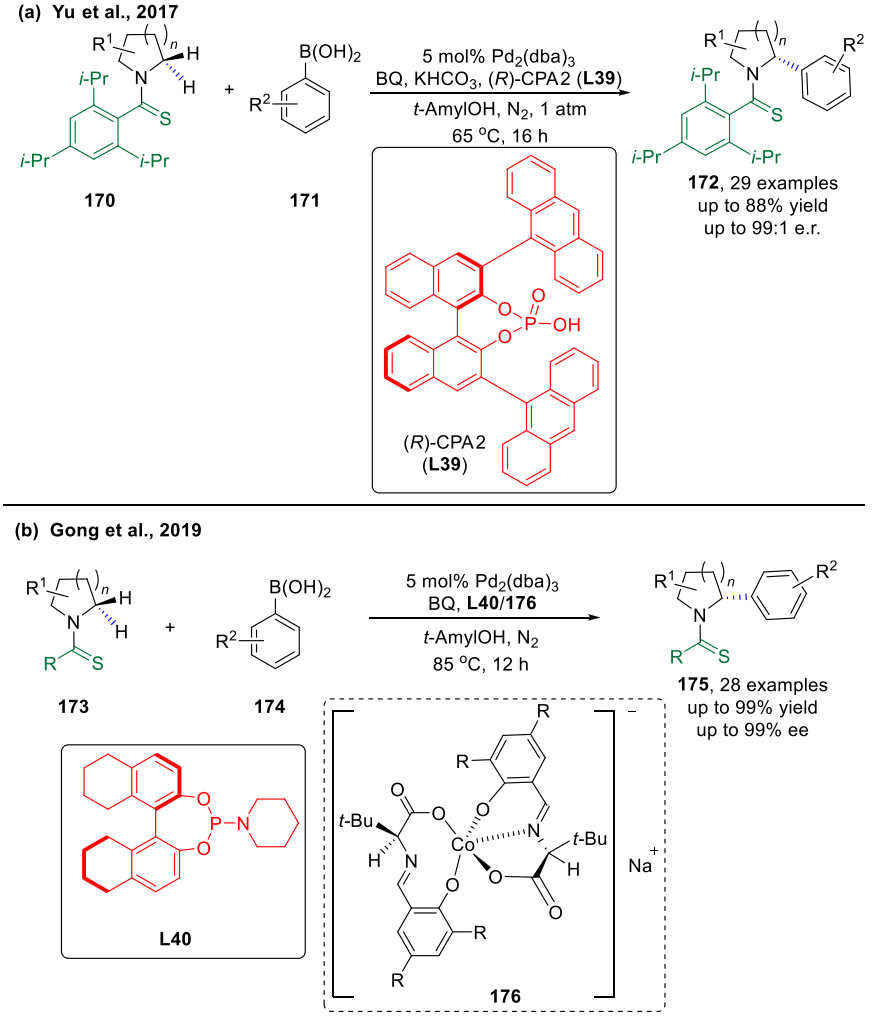
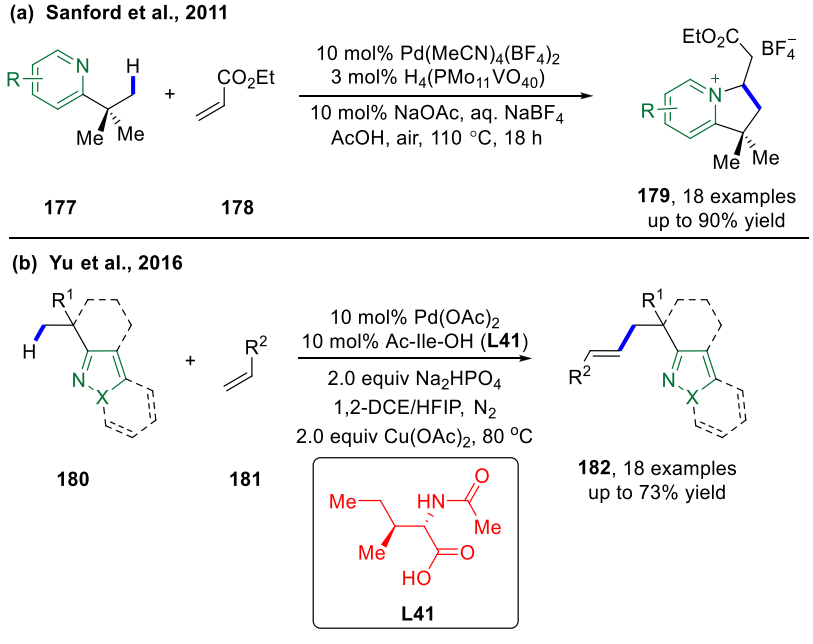
Scheme 34. Thioamide-Directed Enantioselective Amine α-Functionalization via Palladium(II)-Catalyzed C(sp^3)−H Arylation (a) by Yu et al.[129] and (b) by Gong et al.[130]



Scheme 35. (a) Pyridine-Directed C(sp^3)−H Alkenylation[131] and (b) Ligand-Promoted C(sp^3)−H Olefination Directed by Pyrazoles[132]



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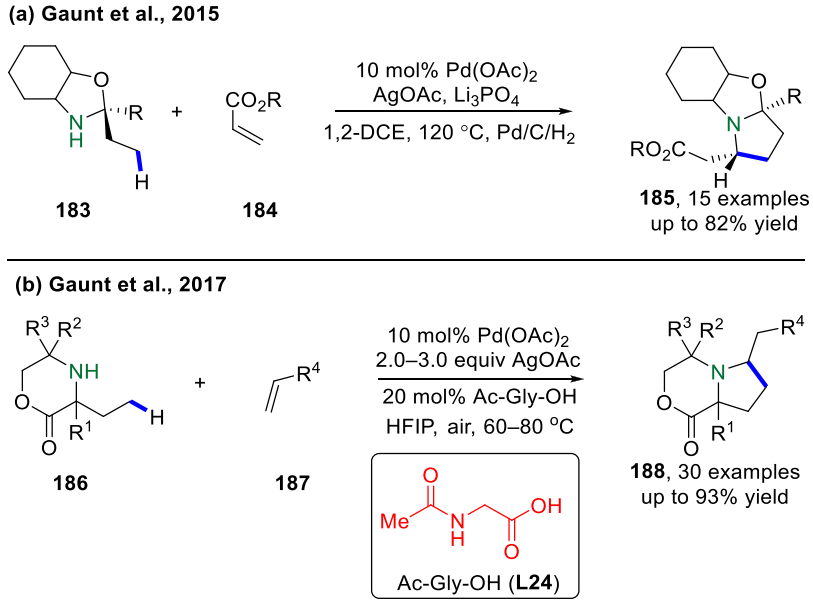
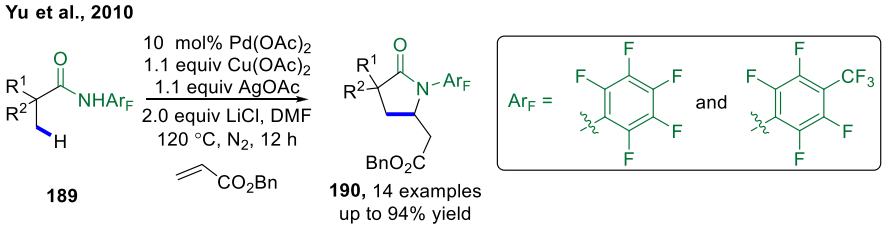
Scheme 36. (a) Palladium-Catalyzed C(sp^3)−H Alkenylation of Amino Alcohol Derivatives[80] and (b) Palladium-Catalyzed C(sp^3)−H Alkenylation of Morpholinone Derivatives[133]



Scheme 37. Palladium-Catalyzed, CONHAr$_F$-Directed Alkenylation of β-C(sp^3)−H Bonds[134]



previous work in ligand-accelerated catalysis, the Yu group has been re-investigating the palladium-catalyzed, carboxylic acid-directed C(sp^3)−H functionalization through the design of new ligands.

In 2017, the Yu group developed a novel protocol using innate carboxylic acids as the DGs, which was enabled by pyridine-type ligands (Scheme 24a).[111] The base, $Na_2HPO_4{\cdot}7H_2O$, was proposed to deprotonate the acid substrates to allow Pd coordination. Unnatural amino acid building blocks can be efficiently prepared using this method, but heteroaryl iodides are incompatible with the reaction conditions. Contemporaneously, Zhao and co-workers established a palladium-catalyzed β-C(sp^3)−H arylation of carboxylic acids and α-amino acids prompted by Ac-Gly-OH (**L24**) ligand (Scheme 24b). This reaction could be run at 10 g scale in good yield, demonstrating the practical utility of this reaction.[112]

In the subsequent year, the Yu group reported a new class of chiral ligands, mono-*N*-protected aminoethyl amines, that enable the enantioselective C−H activation of free carboxylic acids without the use of auxiliary DGs (Scheme 24c).[113] One challenge in developing this reaction is that stereoselectivity is much harder to control due to the highly flexible metal−carboxylate intermediate when compared with metal−amide DG complexes. After extensive screening, the *N*-acetyl-protected amino group (NHAc) was found to be crucial for achieving high enantioselectivity. A variety of chiral carboxylic acids were synthesized through enantioselective arylation of cyclopropanecarboxylic acid and *N*-phthaloyl-protected 2-aminoisobutyric acid using **L25** as chiral ligand. This methodology was applied to the late-stage C(sp^3)−H arylation of itanapraced, a promising drug candidate for neurological disorders. In 2019, Maiti and co-workers expanded the palladium(II)-catalyzed arylation of free aliphatic acids to bring about reaction at the distal γ-C(sp^3)−H bond using Ac-Gly-OH (**L24**) as ligand via a six-membered palladacycle intermediate (**118**, Scheme 24d).[114] Mechanistic studies indicated that C−H activation is irreversible and is the rate-determining step. The Shi group also reported the Pd(II)-catalyzed γ-C(sp^3)−H arylation of *tert*-leucine and peptide derivatives thereof with the assistance of free carboxylic acid by using Boc-Tle-OH (**L26**) as the ligand (Scheme 24e).[115] In this study, the weakly coordinating carboxylate DG outcompetes the strongly coordinating bidentate DG of the peptide backbone, providing the products of γ-C(sp^3)−H arylation of the Tle residue exclusively.

Other weakly coordinating monodentate DGs have also been reported. The enantioselective arylation of cyclopropyl methylamines via a Pd(II)/Pd(IV) catalytic cycle with an MPAA ligand (**L27**) was developed by Yu and co-workers in 2015 (Scheme 25).[116] The Pd(II)/Pd(0) catalytic cycle was ruled out because no desired product was detected without the addition of the silver salt. The Yu group succeeded in using aryl iodide compounds that contain electron-donating or electron-withdrawing substituents in the *para*, *meta*, and *ortho* positions as arylating reagents. The scalability of the reaction was also demonstrated in a 5 mmol scale reaction between cyclo-

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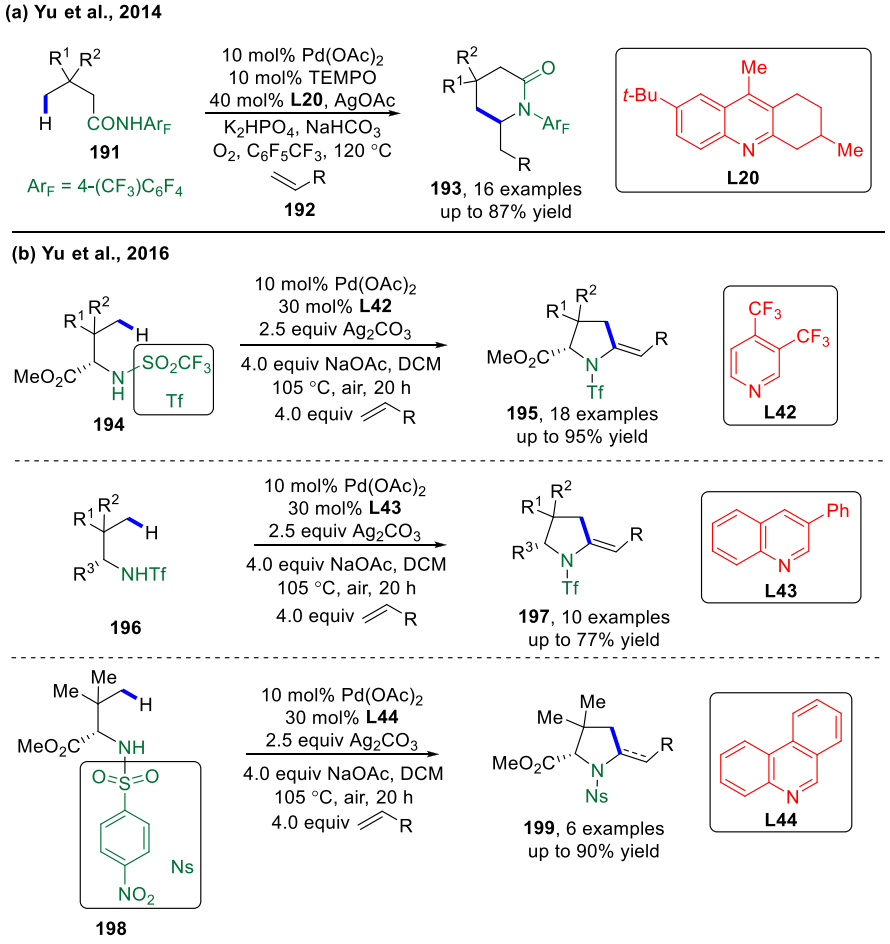
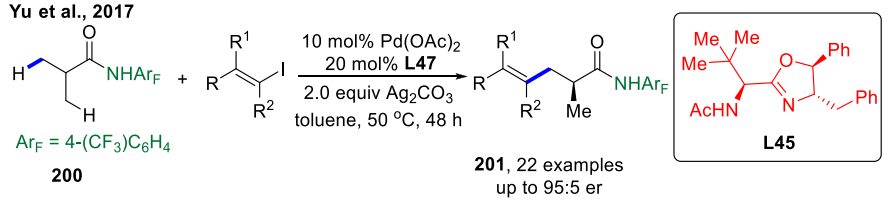
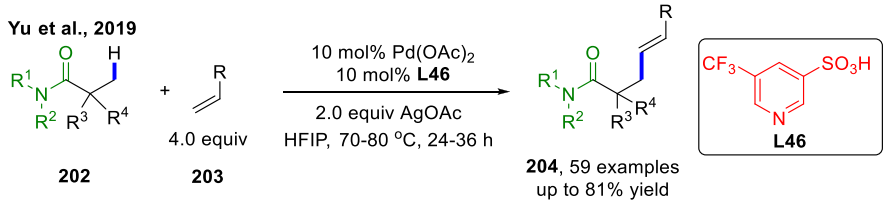
Scheme 38. (a) Palladium-Catalyzed γ-C(sp³)−H Alkenylation of Aliphatic Carboxamides[135] and (b) Palladium-Catalyzed γ-C(sp³)−H Alkenylation of Aliphatic Amines[136]



Scheme 39. Palladium-Catalyzed Enantioselective C(sp³)−H Alkenylation of Isobutyric Amides[101]



Scheme 40. Carbonyl-Directed β-C(sp³)−H Alkenylation of Native Amides (Yu et al., 2019).[137]



propylmethylamine and methyl-2-iodobenzoate, which produced the arylated product in 89% isolated yield and 98.6% ee. Notably, the MPAA ligand can override substrate-controlled diastereoselectivity in substrates that contain a chiral center.

In 2018, Young and co-workers presented the first example of CO_2-mediated, amine-directed C(sp³)−H arylation. CO_2 was added in the form of dry ice and reacted reversibly with the amine to form a carbamic acid moiety. Both primary and secondary aliphatic amines can be arylated selectively at the γ-C−H positions (Scheme 26).[117] Young and co-workers found that an α-tertiary center was not required for the primary amine substrates. A wide range of aryl iodides were tolerated and gave the desired products in good yields. The proposed role of CO_2 as a transient DG that reacts in situ to form the corresponding carbamic acid was supported by an experiment in which the amine·CO_2 adduct was prepared, subjected to the reaction

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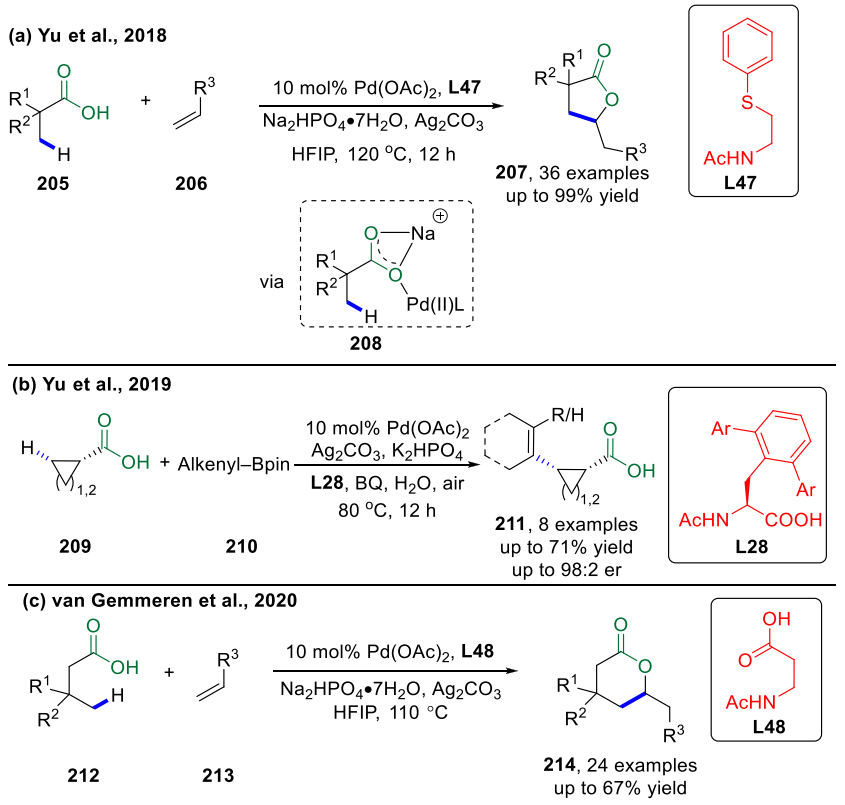
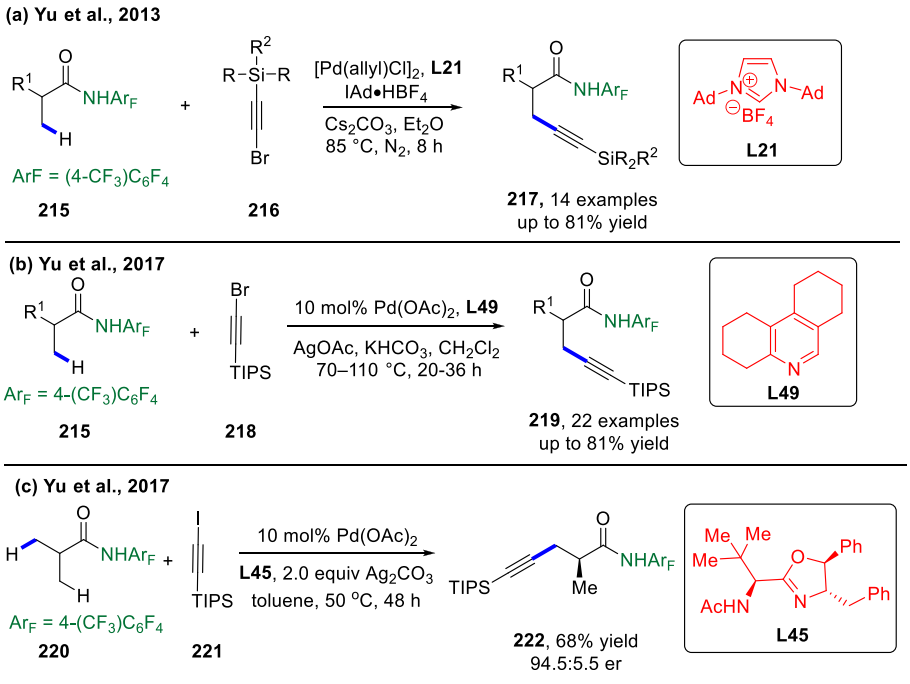
Scheme 41. (a) Ligand-Enabled β-C(sp^3)−H Olefination of Free Carboxylic Acids,[138] (b) Enantioselective C(sp^3)−H Olefination of Free Carboxylic Acids,[104] and (c) Ligand-Enabled γ-C(sp^3)−H Olefination of Free Carboxylic Acids[139]



Scheme 42. (a) CONHAr$_F$ (Ar$_F$ = p-CF$_3$C$_6$F$_4$)-Directed C(sp^3)−H Alkynylation with an N-Heterocyclic Carbene Ligand under Pd(0) Catalysis,[140] (b) CONHAr$_F$ (Ar$_F$ = p-CF$_3$C$_6$F$_4$)-Directed C(sp^3)−H Alkynylation under Pd(II) Catalysis Enabled by Pyridine-Based Ligands,[141] and (c) CONHAr$_F$ (Ar$_F$ = p-CF$_3$C$_6$F$_4$)-Directed Enantioselective C(sp^3)−H Alkynylation of Isobutyriamide with a Chiral MPAO Ligand[101]



conditions, and found to be catalytically competent. It was suggested that the concerted metalation/deprotonation step may be irreversible because no deuteration was observed when the reaction was performed in AcOD.

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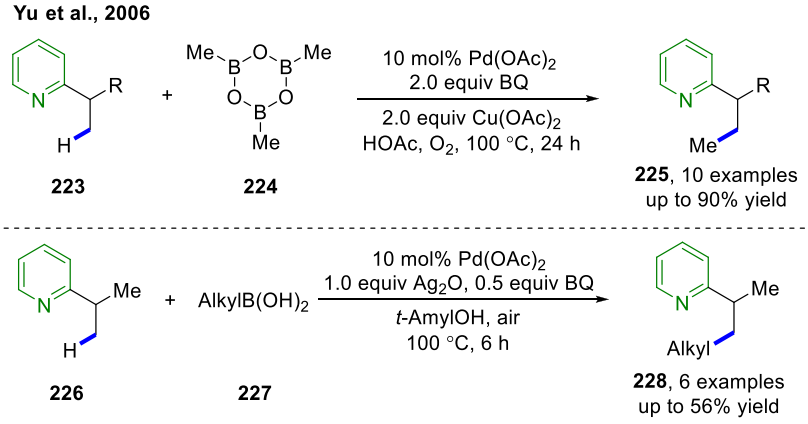
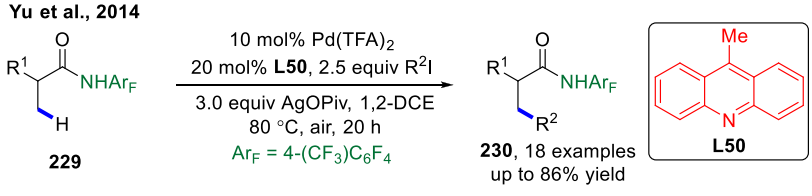
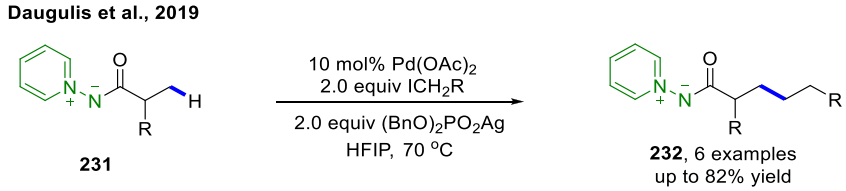
Scheme 43. Pyridine -Directed C(sp^3)−H Alkylation with Methylboroxine or Alkylboronic Acids[142]



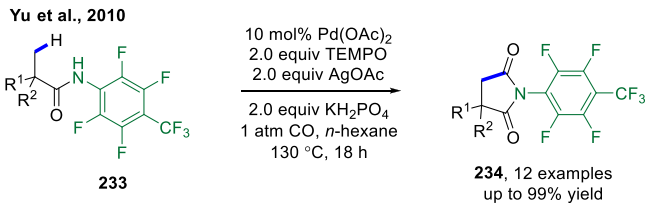
Scheme 44. CONHAr$_F$ (Ar$_F$ = *p*-CF$_3$C$_6$F$_4$)-Directed *β*-C(sp^3)−H Alkylation with Alkyl Iodides[143]



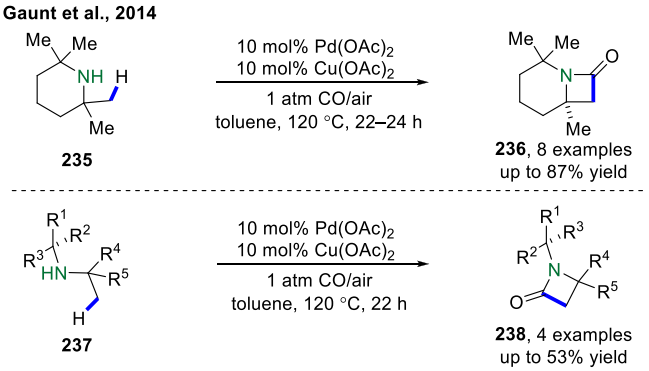
Scheme 45. 1-Aminopyridinium Ylide-Directed *β*-C(sp^3)−H Alkylation with Alkyl Iodides[79]



Scheme 46. CONH−*p*-CF$_3$C$_6$F$_4$-Directed Carbonylation of *β*-C(sp^3)−H Bonds[144]



Scheme 47. Palladium-Catalyzed C−H Carbonylation of Aliphatic Amines[145]



2.1.1.1.2. Monodentate-Directing-Group-Assisted C(sp^3)−H Arylation via Pd(II)/Pd(0) Catalysis. Organoboron reagents are widely used for traditional cross-coupling reactions. The integration of organoboron nucleophiles as coupling partners in C−H activation processes opens new possibilities in terms of the redox processes involved. In 2007, Yu and co-workers reported the first example of Pd(II)-catalyzed, carboxyl-directed arylation of *β*-C(sp^3)−H bonds in simple aliphatic acids (Scheme 27a).[86] In this work, arylboronic esters were employed as coupling partners. Recently, enantioselective C(sp^3)−H arylation of cyclopropanecarboxylic acids and cyclobutanecarboxylic acids under Pd(II)/Pd(0) catalysis was also documented by the Yu group (Scheme 27b).[118] Using either MPAA ligand (**L28**) or mono-*N*-protected aminoethyl amine (MPAAM) ligand (**L29**) was key to the success of this method. The enantioenriched arylated carboxylic acid products could be converted to cyclopropyl amines without loss of optical activity.

In 2008, Yu and co-workers developed a palladium-catalyzed arylation of C(sp^3)−H bonds with aryl boronic acids by using CONHOMe as the DG (Scheme 28).[119] Notably, CONHOMe groups can be transformed easily to esters, amides, or corresponding alkane fragments. Furthermore, the silver salt in this system can be replaced with air as a stoichiometric oxidant.

In 2011, the Yu group reported enantioselective C−H activation reactions of cyclopropanes using a novel MPAA (**L30**) as the ligand. In this reaction, an acidic CONHAr$_F$ (Ar$_F$ = *p*-CNC$_6$F$_4$) group was employed as a weakly coordinating DG (Scheme 29a).[120] The best ligand found for asymmetric

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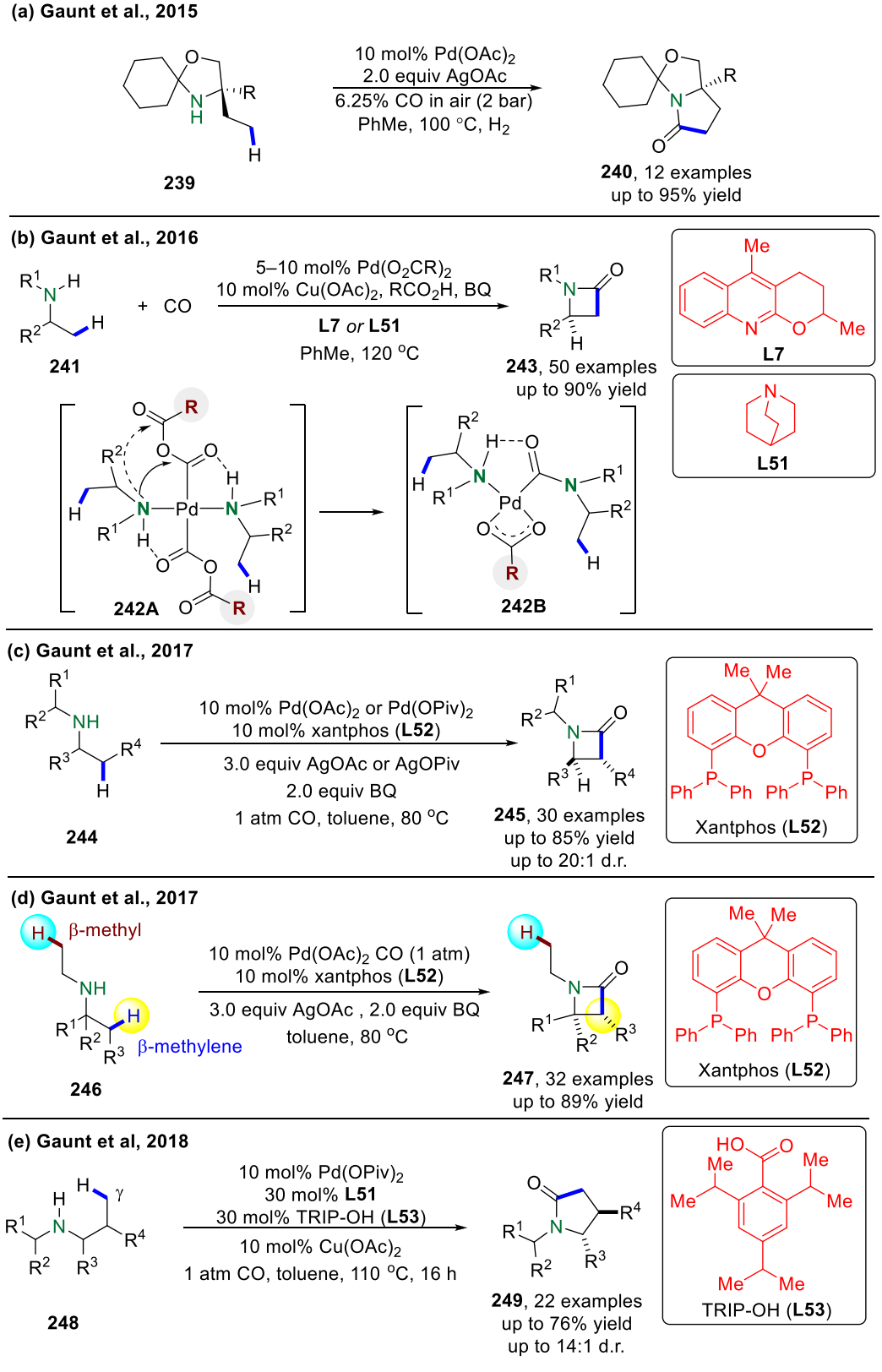
Scheme 48. (a) Palladium-Catalyzed γ-Methyl C(sp^3)−H Carbonylation of Amino Alcohol Derivatives,[80] (b) Palladium-Catalyzed β-Methyl C(sp^3)−H Carbonylation of Less Hindered Aliphatic Amines to β-Lactams,[146] (c) Palladium(II)-Catalyzed β-Methylene C(sp^3)−H Carbonylation of Free Secondary Aliphatic Amines to *trans*-Disubstituted β-Lactams,[147] (d) Palladium(II)-Catalyzed β-Methylene C(sp^3)−H Carbonylation of α-Tertiary Amines in the Presence of More Reactive β-Methyl C−H Bonds,[148] and (e) Palladium(II)-Catalyzed γ-C(sp^3)−H Carbonylation of Free(NH) Secondary Aliphatic Amines to *trans*-Disubstituted 2-Pyrrolidines[149]



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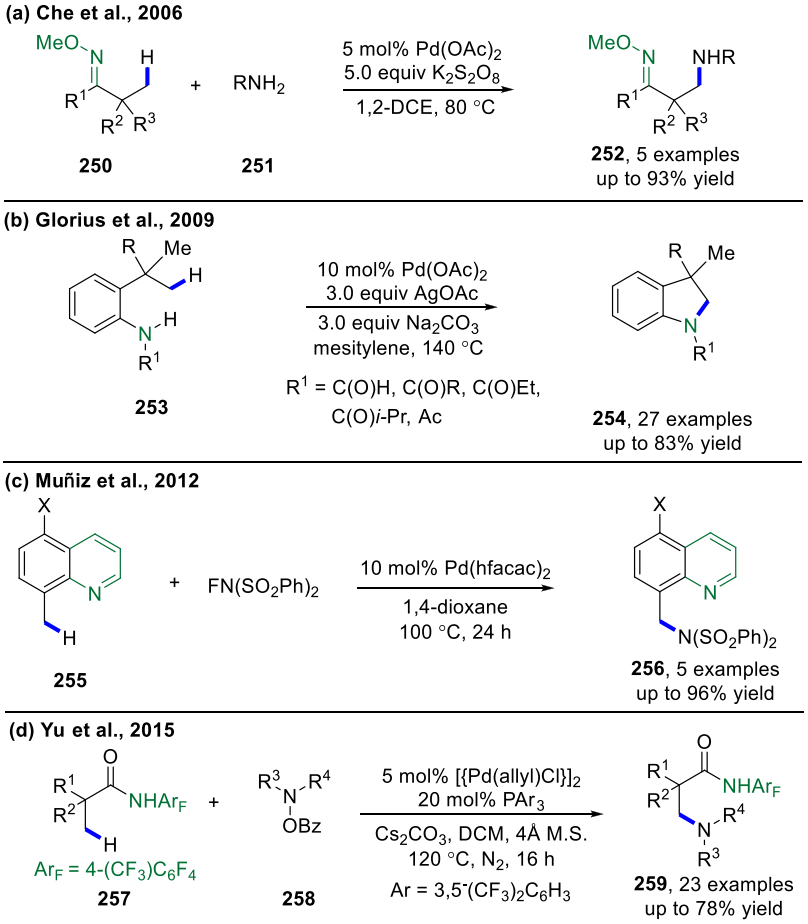
Scheme 49. (a) Oxime-Directed Intermolecular C(sp^3)−H Amidation via C(sp^3)−H Activation/Nitrene Insertion,[150] (b) Amide-Directed Intramolecular Amidation of Unactivated C(sp^3)−H Bonds,[151] (c) Intermolecular Amidation of Benzylic C(sp^3)−H Bonds,[152] and (d) CONH−*p*-(CF$_3$)C$_6$F$_4$-Directed Intermolecular *β*-C(sp^3)−H Amination[153]



induction in the C−H/R−BX$_n$ cross-coupling reactions was identified by extensive screening of chiral ligands with structurally diverse *N*-protecting groups and amino acid backbones. Various cyclopropanes substituted with alkyl and aryl groups at the *α*-position with respect to the amide DG can be tolerated, producing the desired products in up to 81% yield and 92% ee under mild conditions. However, this method is limited to the functionalization of relatively activated cyclopropyl C−H bonds.

In 2014, Yu and co-workers developed an enantioselective C−H arylation reaction of cyclobutanecarboxylic acid derivatives using arylboron reagents as arylating agents (Scheme 29b).[121] The key to the success of this method was the discovery of a new class of chiral ligands, mono-*N*-protected *α*-amino-*O*-methylhydroxamic acids (**L31**), which are derived from MPAAs. However, substrates that contain *α*-hydrogen atoms give poor yields and enantioselectivities.

In 2015, a quinoline-based ligand was designed to promote cross-coupling reactions of *β*-C(sp^3)−H bonds in carboxylic acid derivatives that bear a *p*-CF$_3$C$_6$F$_4$ amide auxiliary with arylsilanes (Scheme 30).[122] The optimized reaction conditions for the coupling of alanine-derived amide **141** with various organosilicon reagents were Pd(OAc)$_2$ (10 mol %), **L32** (20 mol %), ArSi(OEt)$_3$ (2.0 equiv), and AgF (3.0 equiv) as additive in 1,4-dioxane (1.0 mL) at 110 °C for 8 h, followed by the addition of a second batch of organosilicon (2.0 equiv) and AgF (3.0 equiv) with subsequent heating for an additional 10 h. A variety of electron-rich and electron-poor triethoxyarylsilanes were tolerated in the arylation reaction. However, only 45% yield of the arylated product could be obtained when an amide derived from 2-methylpentanoic acid was subjected to the standard conditions. After extensive screening of ligands and bases, a variety of amides derived from aliphatic acids could be arylated in good yields by the use of **L20** as ligand and KHCO$_3$ as base.

In 2014, monodentate triflimide-directed, palladium(II)-catalyzed coupling of *γ*-C(sp^3)−H bonds with arylboron reagents enabled by an MPAA ligand was discovered by Yu and co-workers.[123] Interestingly, the steric impact of the ligand on the reactivity of the catalytic system was observed when the D-enantiomer of *N*-acetyl-*tert*-leucine (D-Ac-Tle-OH,**L33**) was used. A broad range of arylboron reagents and a variety of alkyl amines were cross-coupled under the reaction conditions (Scheme 31a). Notably, arylboron reagents could be replaced with aryl iodide reagents as coupling partners, such that *γ*-C(sp^3)−H arylation alternatively took place via a Pd(II)/Pd(IV) catalytic cycle. To solve the problem that arose from removal of the triflyl DG within the substrates, Yu and co-workers developed a method that employs the readily removable nosyl protecting group for *γ*-C(sp^3)−H arylation of alkyl amines, as enabled by a *N*-acetyl-protected aminomethyl oxazoline (APAO) ligand (Scheme 31b, **L34**).[124]

In 2018, Yu and co-workers expanded the *γ*-C(sp^3)−H arylation of cyclopropyl methylamines to acyclic alkylamines by

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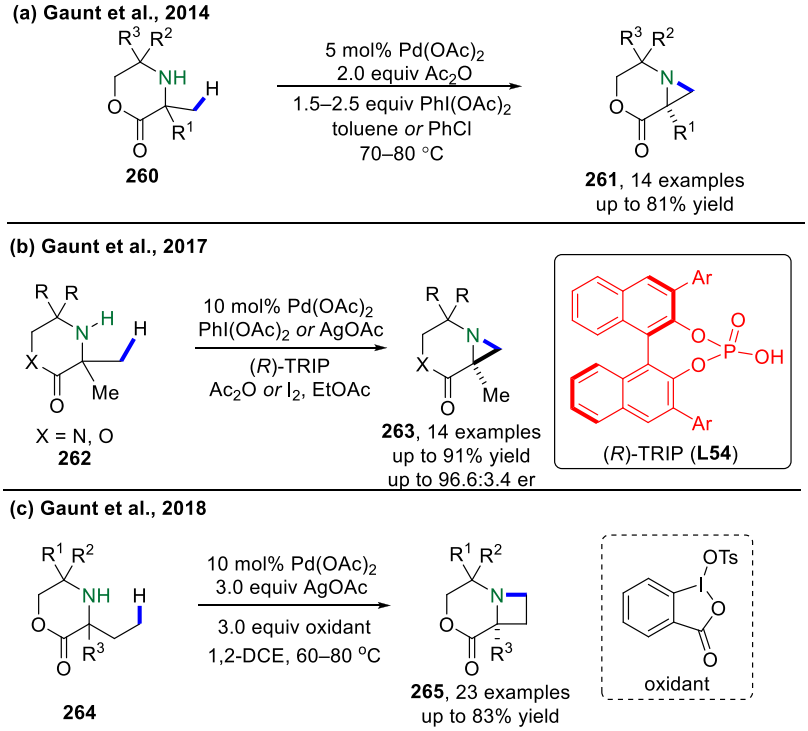
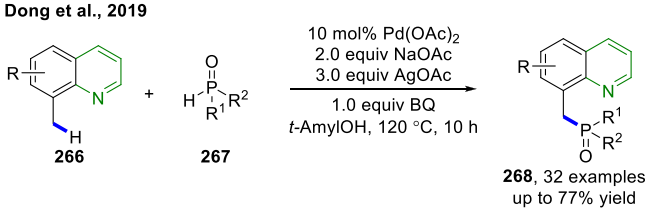
Scheme 50. (a) Palladium-Catalyzed Intramolecular β-C(sp^3)−H Amination of Aliphatic Amines to Prepare Aziridines,[145] (b) Palladium-Catalyzed Enantioselective C(sp^3)−H Amination of Aliphatic Amines,[155] and (c) Palladium-Catalyzed Intramolecular γ-C(sp^3)−H Amination to Azetidines[156]



Scheme 51. Palladium-Catalyzed Phosphonation of C(sp^3)−H Bonds[157]



using chiral APAO ligands via Pd(II)/Pd(0) catalysis (Scheme 31c).[125] They observed that APAQ and MPAA ligands did not improve the yield and enantioselectivity significantly. When *N*-acetyl- protected amino oxazoline (APAO) chiral ligands were used, the enantioselectivity improved to 98% ee. The stereocenters on both the side chain and the oxazoline moiety of the ligand play key roles in chiral induction. The reaction conditions were $Pd(OAc)_2$ (10 mol %), ligand (15 mol %), ArBpin (2.0 equiv), Ag_2CO_3 (2.0 equiv), and H_2O (5.5 equiv) as the additives and Na_2CO_3 (2.0 equiv) as the base in *t*-Amyl-OH at 80 °C for 12 h. Kinetic resolution of unsymmetrical amines via enantioselective γ-C(sp^3)−H coupling has also been investigated and realized (Scheme 31c).

In 2015, He and Gaunt developed a palladium-catalyzed C−H arylation of secondary aliphatic amines with arylboronic esters that is promoted by an MPAA ligand (Scheme 32a).[126] A range of alicyclic amine derivatives, such as piperidine derivatives and compounds with azepine or morpholine scaffolds, efficiently afforded the corresponding arylated products in good yields. The scope of arylboronic acid pinacol esters (ArBPin) was also investigated, and ArBPin compounds that have substituents at the *meta* and *para* positions of the aromatic ring afford the desired products in higher yields than ArBpin compounds that have substituents at the *ortho* position. They have also investigated the enantioselective C−H arylation of **155** with PhBPin by exploring a range of amino-acid ligands under similar reaction conditions. A 60% ee was obtained when MPAA **L37** was used as chiral ligand. Recently, Gaunt and co-workers developed a MPAA-promoted, palladium-catalyzed γ-C(sp^3)−H arylation of tertiary alkylamines.[127] Ac-Tle-OH (**L38**) lowered the energy of γ-C(sp^3)−H activation relative to β-hydride elimination, which made the arylation reaction proceed smoothly with (hetero)arylboronic acids.

$Pd(TFA)_2$-catalyzed, thioamide-directed C(sp^3)−H arylation of saturated azaheterocycles was developed by the Yu group in 2015.[128] 1,4-Benzoquinone (BQ) is essential for this transformation; its proposed role is in promoting reductive elimination. It was also observed that the terminal methyl groups of the thioamide are not functionalized and that $Pd(OAc)_2$ affords only a trace amount of product. Both arylboronic acid and heteroarylboronic acids are tolerated under standard conditions, providing the corresponding products **161** in good to excellent yields (Scheme 33).

In 2017, the Yu group demonstrated that chiral phosphoric acids are effective anionic ligands for enantioselective amine α-C(sp^3)−H arylation (Scheme 34a).[129] No desired arylation products were obtained when chiral MPAA ligands were employed. Chiral anionic phosphates were investigated due to the enhanced reactivity of $Pd(TFA)_2$ compared to $Pd(OAc)_2$, which indicates that the identity of the anionic ligand plays a significant role in this reaction. In the end, a bulky triisopropylbenzothioamide DG on the pyrrolidine and $Pd_2(dba)_3$ were observed to be the most suitable in terms of reactivity and enantiocontrol. Gong and co-workers also reported a thioamide-directed, palladium(II)-catalyzed enantioselective C(sp^3)−H arylation that involves a chiral anionic

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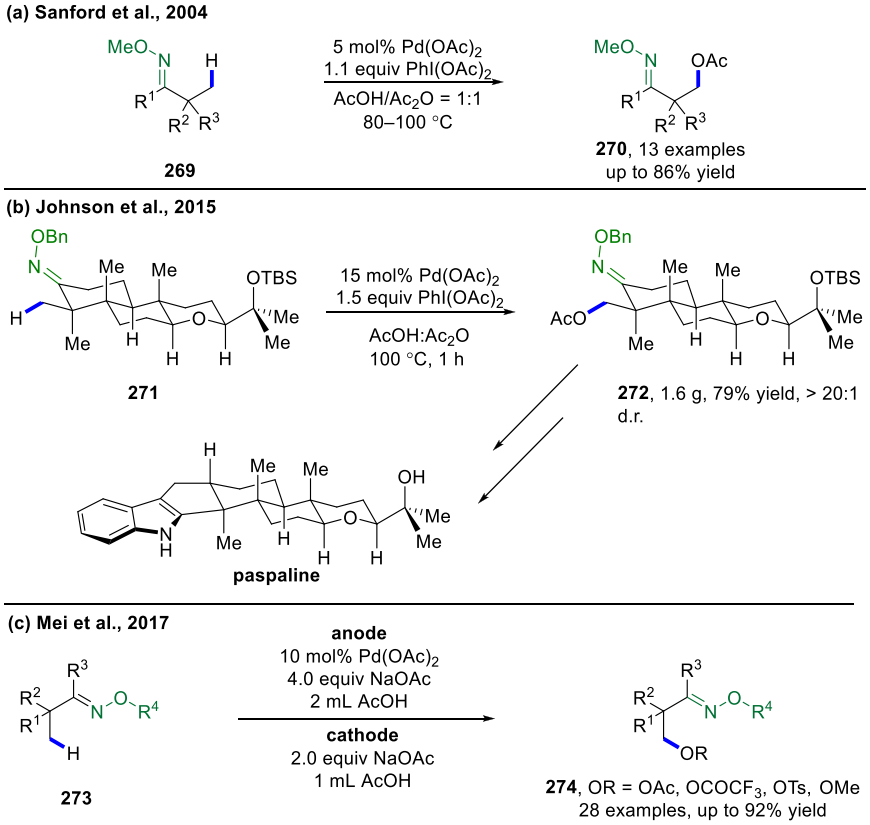
Scheme 52. (a) Palladium-Catalyzed, Oxime-Directed Intermolecular C(sp^3)−H Acetoxylation,[158] (b) Application of C(sp^3)−H Oxygenation in the Total Synthesis of Paspaline,[160] and (c) Palladium-Catalyzed C(sp^3)−H Oxygenation via Electrochemical Oxidation[161]



Co(III) complex (**164**) and a chiral phosphoramidite ligand (**L40**) (Scheme 34b).[130]

2.1.1.2. Alkenylation. While transition-metal-catalyzed olefination of C(sp^2)−H bonds has been widely investigated, olefination of unactivated C(sp^3)−H bonds remains rare. To enable olefination of unactivated C(sp^3)−H bonds, strongly coordinating nitrogen-based, monodentate DGs have been employed. For example, in 2011, Sanford and co-workers reported a palladium-catalyzed, pyridine-directed C(sp^3)−H alkenylation using air as the oxidant and AcOH as the solvent (Scheme 35a).[131] In 2016, Yu and co-workers developed a pyrazole-directed C(sp^3)−H olefination enabled by an MPAA ligand **L41** (Scheme 35b).[132]

In 2015, Gaunt and co-workers developed a palladium-catalyzed C(sp^3)−H alkenylation of amino alcohol derivatives.[80] The conditions they found were $Pd(OAc)_2$ (10 mol %) and acrylate (3 equiv) in the presence of AgOAc and Li_3PO_4 in 1,2-dichloroethane at 120 °C. A wide range of pyrrolidines that contain a variety of useful functional groups were synthesized (Scheme 36a). In 2017, He and Gaunt further developed a palladium-catalyzed C(sp^3)−H alkenylation of morpholinones to synthesize various pyrrolidine moieties in good yields and excellent regio- and diastereoselectivities (Scheme 36b).[133]

Directed C(sp^3)−H olefination with weakly coordinating DGs was pioneered by Yu and co-workers. In 2010, Yu and co-workers developed a Pd(II)-catalyzed, monodentate $CONHAr_F$ (Ar_F = C_6F_5 and *p*-$CF_3C_6F_4$)-directed C(sp^3)−H alkenylation/1,4-conjugate addition with benzyl acrylate, which affords the corresponding lactam products in good to excellent yields.[134] In accordance with their previous report, electron-withdrawing substituents (CF_3, F, and NO_2) on the *N*-aryl group improve the yield significantly. Cyclopropyl methylene C−H bonds and substrates that contain α-hydrogen atoms are also olefinated efficiently (Scheme 37).

In 2014, Yu and co-workers detailed a ligand-promoted, Pd(II)-catalyzed γ-C(sp^3)−H olefination/cyclization with $CONHAr_F$ (Ar_F = *p*-$CF_3C_6F_4$) as the DG (Scheme 38a).[135] After extensive screening, a quinoline-based ligand (**L20**) was found to be crucial for realizing this transformation. Notably, this ligand can also be used to facilitate sequential γ-carbonylation followed by γ-olefination of pivalamide to give highly functionalized all-carbon quaternary centers. In 2016, the Yu group developed a Pd(II)-catalyzed γ-C(sp^3)−H olefination of triflyl (Tf)- and 4-nitrobenzenesulfonyl (Ns)-protected amines in which the C(sp^3)−H olefinated products undergo an in situ, aza-Wacker oxidative cyclization or an intramolecular conjugate addition to afford a variety of C-2 alkylated pyrrolidines (Scheme 38b).[136] 3,4-Bis(trifluoromethyl)pyridine (**L42**) was identified to be the optimal ligand for Tf-protected α-amino esters, while 3-phenylquinoline (**L43**) was capable of promoting the γ-C(sp^3)−H olefination of a range of Tf-protected alkyl amines. Furthermore, Ns-Tle-OMe (**198**) was olefinated with acrylates and styrenes using phenanthridine (**L44**) as the ligand. Interestingly, saturated pyrrolidines were obtained when methyl vinyl ketone, 1-phenylprop-2-en-1-one, and acrylonitrile were used as coupling partners.

In 2017, Yu and co-workers showed that chiral MPAO ligand **L45** was able to promote Pd(II)-catalyzed, enantioselective β-alkenylation of isobutyric amides (Scheme 39).[101] The acidic $CONHAr_F$ (Ar_F = *p*-$CF_3C_6F_4$) was again used as an efficient DG

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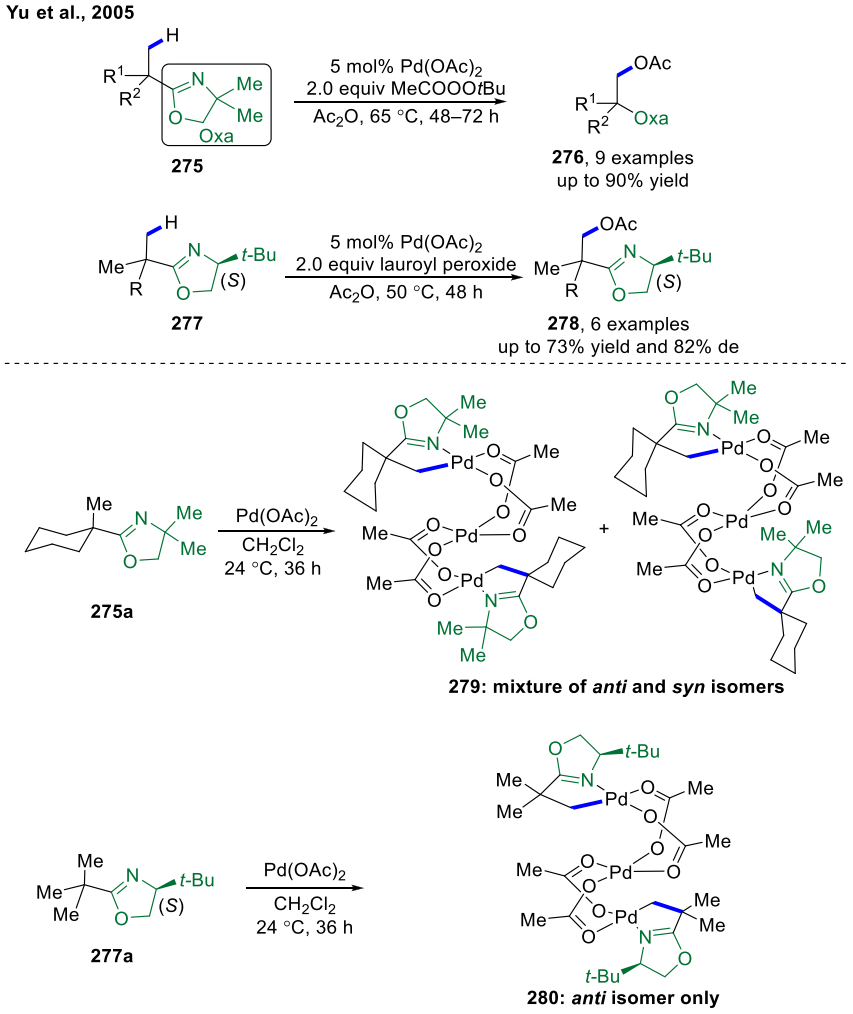
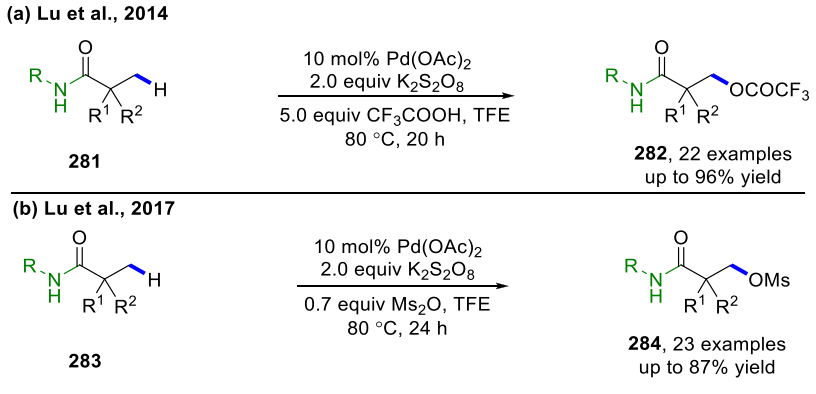
Scheme 53. Palladium-Catalyzed, Oxazoline-Directed C(sp^3)−H Acetoxylation[162]



Scheme 54. Palladium-Catalyzed β-C(sp^3)−H Acyloxylation and Mesyloxylation of Simple Amides[164,165]



to enable the synthesis of olefinated products in high enantioselectivities (up to 95:5 er).

All of the C(sp^3)−H olefination reactions described above require a specific directing auxiliary group, and the majority of examples yield cyclized products, which may or may not be desirable depending on the envisioned application. In 2019, Yu and co-workers developed a Pd(II)-catalyzed C(sp^3)−H olefination directed by the carbonyl group of native amides (Scheme 40).[137] The electron-deficient pyridine-3-sulfonic acid ligand (**L46**) was found to be crucial for the conversion of secondary and tertiary amides to the corresponding olefinated products without in situ cyclization.

In 2018, the Yu group detailed a β-C(sp^3)−H olefination of free carboxylic acids that is promoted by an *N*-acetyl-protected aminoethyl phenyl thioether ligand (**L47**).[138] A broad range of free carboxylic acids undergo olefination followed by in situ 1,4-addition, providing the corresponding γ-lactone products that can be readily opened to give either the β-olefinated or γ-hydroxylated aliphatic acids (Scheme 41a). Recently, palladium-(II)-catalyzed enantioselective C(sp^3)−H alkenylation of free

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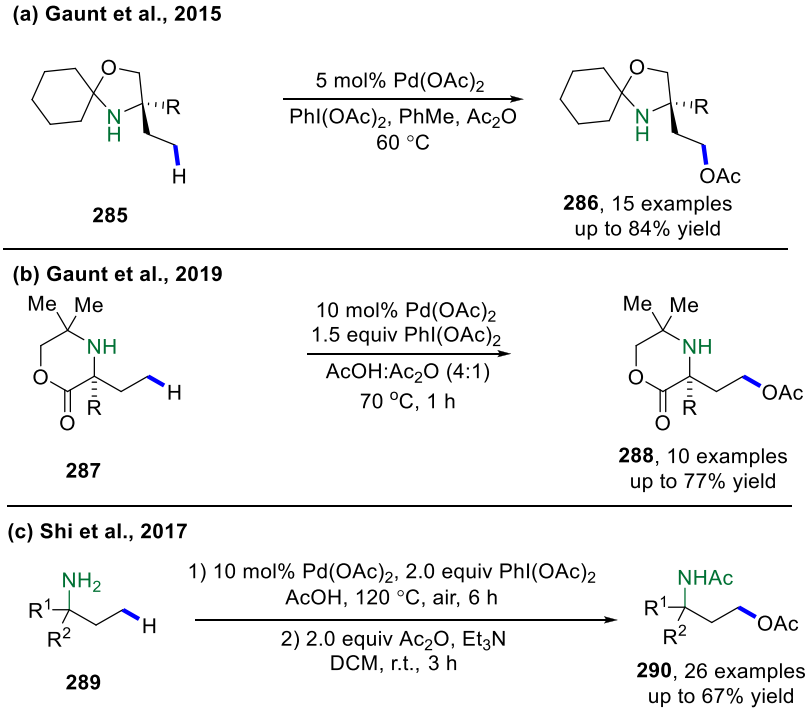
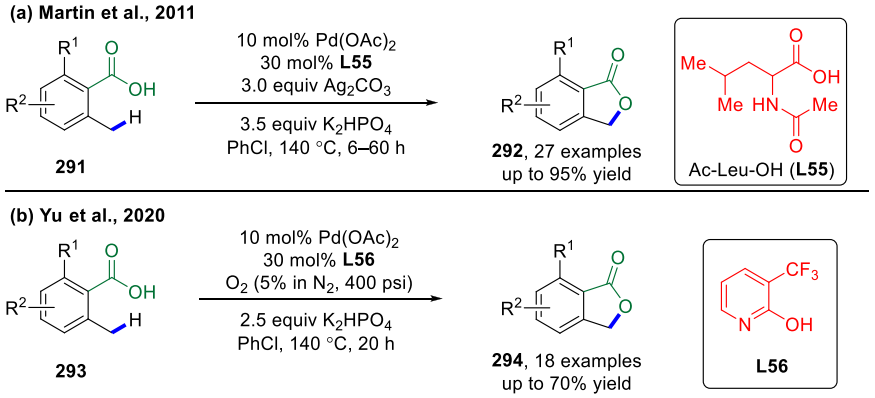
Scheme 55. (a) Pd-Catalyzed C(sp^3)−H Acetoxylation of Amino Alcohol Derivatives,[80] (b) Pd-Catalyzed C(sp^3)−H Acetoxylation of Morpholinone Derivatives,[166] and (c) Pd-Catalyzed C(sp^3)−H Acetoxylation of Primary Amines[167]



Scheme 56. (a) Palladium-Catalyzed, Carboxylate-Directed C(sp^3)−H Lactonization Using Silver Carbonate as Oxidant[168] and (b) Improved C(sp^3)−H Lactonization using Molecular Oxygen as Oxidant[169]



carboxylic acids with alkenyl-Bpin was also discovered by the Yu group.[118] A variety of olefin-containing chiral acids were produced in high enantioselectivities (up to 98:2 er) using MPAA (**L28**) as chiral ligand, providing a valuable scaffold for organic synthesis and medicinal chemistry (Scheme 41b). Carboxylate-directed, palladium(II)-catalyzed γ-C(sp^3)−H olefination of free carboxylic acids was also demonstrated by the van Gemmeren group in 2020.[139] *N*-Ac-β-alanine (**L48**) was identified to be an efficient ligand (Scheme 41c). It is worth noting that *N*-Ac anthranilic acid derived ligands could also significantly promote this reaction.

2.1.1.3. Alkynylation. Alkyne functional groups are useful intermediates in organic synthesis owing to their ability to participate in many different types of reactions, such as cycloaddition and metathesis. While cross-coupling reactions between alkynes and aryl (pseudo)halides have been well developed, the alkynylation of unactivated C(sp^3)−H bonds remained largely undeveloped until the past decade. In 2013, Yu and co-workers achieved the first C(sp^3)−H alkynylation reaction of simple amides **215** with alkynyl bromides **216** directed by their own developed monodentate CONHAr$_F$ (Ar$_F$ = *p*-$CF_3C_6F_4$) DG under Pd(0) catalysis (Scheme 42a).[140] Although this reaction proceeded through a Pd(0)/Pd(II) catalytic cycle, these findings inspired their further studies of developing C(sp^3)−H alkynylation using Pd(II) catalysis. In 2017, they successfully expanded this alkynylation protocol to a Pd(II)/Pd(IV) catalytic cycle by employing pyridine-based ligands. β-Alkynylation and γ-alkynylation of C(sp^3)−H bonds of aliphatic amides using the same monodentate DG under palladium(II) catalysis were achieved. Pyridine-based ligand **L49** was identified to be the optimal one and a variety of amides containing α-tertiary or α-quaternary carbon centers were competent under the optimized reaction conditions (Scheme 42b).[141] In the same year, they developed an asymmetric version by desymmetrization of the *gem*-dimethyl group. The Pd(II)-catalyzed enantioselective β-alkynylation of isobutyramide **220**

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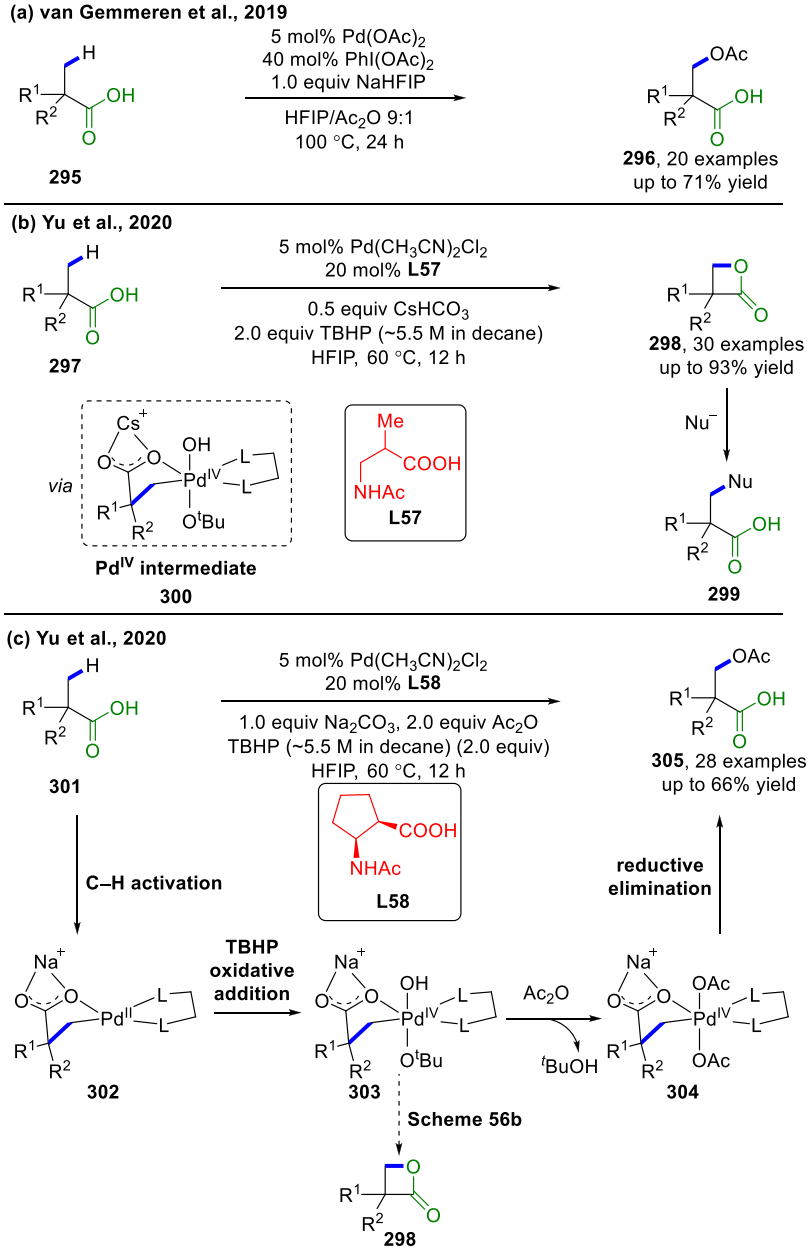
Scheme 57. (a) Palladium-Catalyzed β-C(sp^3)−H Acetoxylation of Aliphatic Carboxylic Acids,[170] (b) Palladium-Catalyzed β-C(sp^3)−H Lactonization,[171] and (c) Palladium-Catalyzed β-C(sp^3)−H Acetoxylation of Aliphatic Carboxylic Acids with Ac_2O[172]



bearing the same DG with alkynyl iodide **221** using MPAO **L45** as chiral ligand was achieved, giving the product **222** in 94.5:5.5 er and 68% yield (Scheme 41c).[101]

2.1.1.4. Alkylation. Employing *alkyl* coupling partners (i.e., C(sp^3) organometallics or alkyl halides) in C(sp^3)−H activation and in cross-coupling reactions generally is more challenging because the resulting alkyl−M intermediates are prone to undergo rapid β-hydride elimination. The first protocol for palladium(II)-catalyzed C(sp^3)−H alkylation with either methylboroxine or alkylboronic acids was developed by the Yu group in 2006 (Scheme 43).[142] For the examples that involve methylboroxine, the authors propose that the methylboroxine assists in the C−H activation step by first coordinating with the pyridyl group and then chelating to $Pd(OAc)_2$ to direct the C−H bond cleavage.

A ligand-promoted, palladium(II)-catalyzed C(sp^3)−H alkylation of monodentate CONH-(p-CF_3)C_6F_4 amides using alkyl iodides as the alkylating agents was reported by Yu and co-workers in 2014 (Scheme 44).[143] The reaction conditions for this system are $Pd(TFA)_2$ (10 mol %) as the precatalyst, 9-methylacridine **L50** (20 mol %) as ligand, and AgOPiv as the additive in 1,2-dichloroethane at 80 °C for 20 h. In this system, aliphatic amides that bear bulkier α-substituents give the alkylated products in higher yields. A 1-aminopyridinium ylide-directed, palladium(II)-catalyzed ligand-free C(sp^3)−H alkylation using dibenzyl phosphate silver salt as the additive was reported by Daugulis in 2019, providing an alternative way to accomplish C(sp^3)−H alkylation using palladium catalysis (Scheme 45).[79]

2.1.1.5. Carbonylation. In 2010, Yu and co-workers described a novel palladium(II)-catalyzed β-C(sp^3)−H carbonylation/cyclization reaction of *N*-arylamides under a CO (1 atm) atmosphere (Scheme 46).[144] The succinimide products could be hydrolyzed with TFA/AcOH under reflux to give 2,2-

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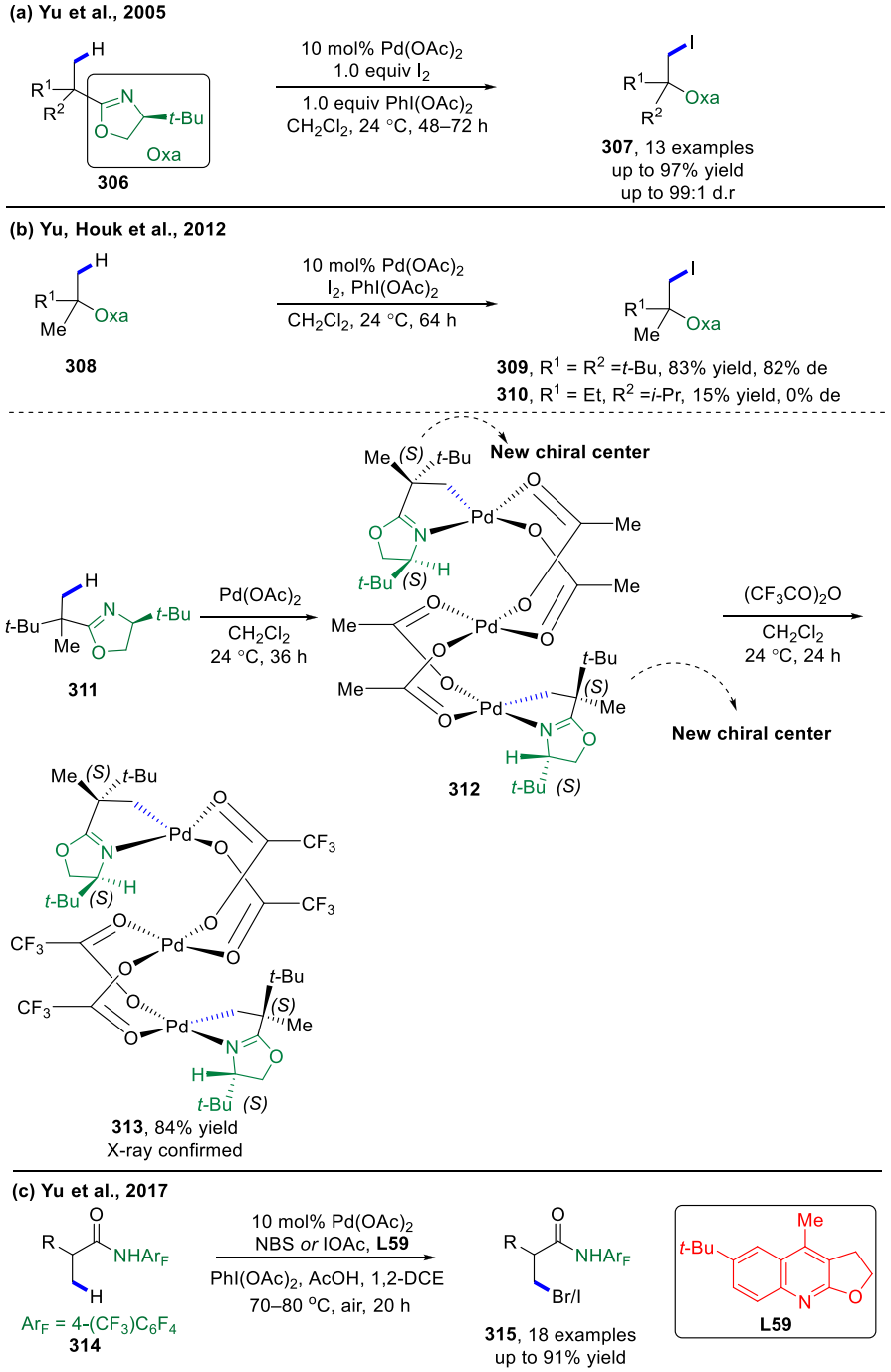
Scheme 58. (a) Palladium-Catalyzed, Oxazoline-Directed Monoiodination of Methyl C(sp^3)−H Bonds,[173] (b) Characterization of a Chiral Trinuclear C(sp^3)−Pd Complex and Computational Studies,[175] and (c) Ligand-Enabled Pd(II)-Catalyzed C(sp^3)−H Bromination and Iodination of Aliphatic Amides[176]



dimethylsuccinic acids or treated with NaOMe in methanol at room temperature to open the cyclic imide at the less hindered carbonyl, providing the corresponding methyl carboxy amide. Other DGs, such as carboxylic acids, hydroxamic acids, oxazolines, and pyridines were investigated under the same conditions, and no desired product was obtained in these cases.

Palladium-catalyzed direct C−H activation of free-NH aliphatic amines has been a long-standing challenge. Recently, the Gaunt group has made significant contributions to overcome these challenges. In 2014, Gaunt and co-workers reported a palladium-catalyzed C(sp^3)−H carbonylation of hindered aliphatic amines via an unusual four-membered palladacycle.[145] A broad range of β-lactams were produced via palladium-catalyzed activation of the β-methyl C(sp^3)−H bonds of secondary amine substrates (Scheme 47). The reaction conditions were found to be $Pd(OAc)_2$ (10 mol %) with $Cu(OAc)_2$ (10 mol %) as the oxidant in toluene at 120 °C under a CO/air mixture at atmospheric pressure for 22 h. A variety of secondary amines, including cyclic and acyclic amines are effective substrates, producing the resulting β-lactams in good yields.

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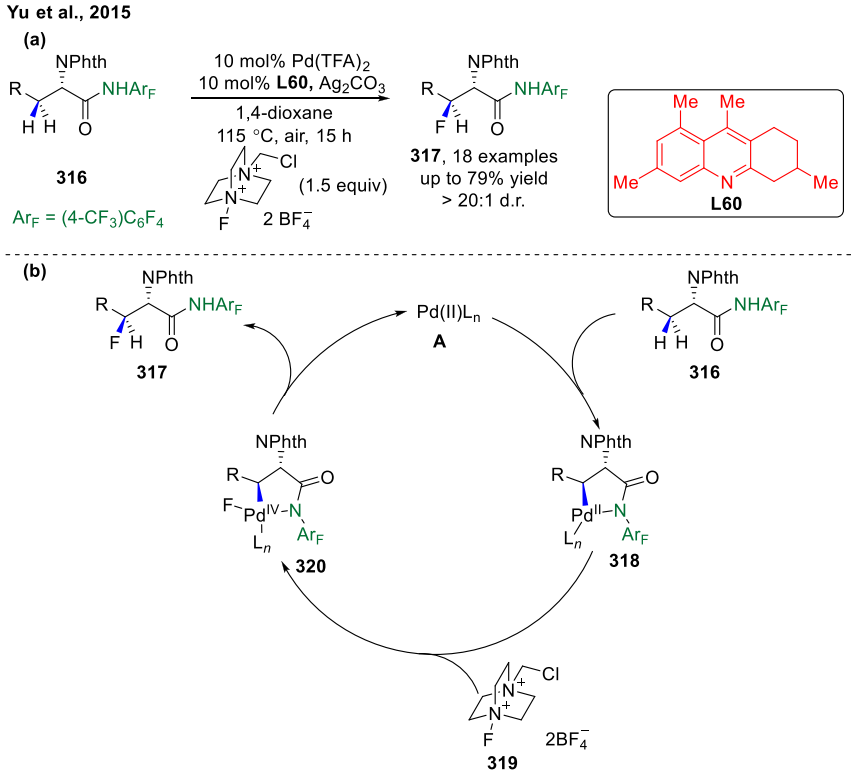
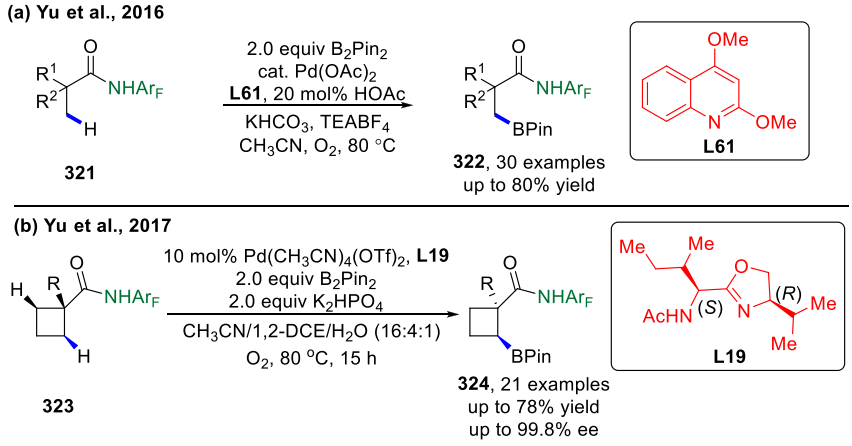
Scheme 59. Pd-Catalyzed, CONH−*p*-$CF_3C_6F_4$-Directed *β*-C(sp^3)−H Fluorination of Amino Acid Derivatives[177]



Scheme 60. (a) Pd(II)-Catalyzed, CONH−*p*-$CF_3C_6F_4$-Directed *β*-C(sp^3)−H Borylation of Aliphatic Carboxamides[178] **and (b) Pd(II)-Catalyzed Enantioselective C(sp^3)−H Borylation of Cyclobutane Carboxamides**[179]



Shortly after, Gaunt and co-workers successfully realized a palladium-catalyzed C(sp^3)−H carbonylation of amino alcohol derivatives.[80] The reaction conditions are $Pd(OAc)_2$ (10 mol %) and AgOAc (2 equiv) in toluene at 100 °C with stirring under 6.25% CO in air at a slightly positive pressure. A wide range of pyrrolidinone products with a variety of useful functional groups were synthesized under the reaction conditions (Scheme 48a). Gaunt and co-workers observed that a strongly electron-withdrawing group adjacent to the amine lowers the efficiency of the transformation. Notably, a small amount of the *α*,*β*-unsaturated pyrrolidinone byproduct was observed in all cases. To simplify isolation, upon completion of the carbonylation reaction, the reaction vessel was charged with hydrogen gas, which converted the mixture to solely the saturated pyrrolidinone.

Although Pd(II)-catalyzed *β*-C(sp^3)−H carbonylation of hindered amines have been achieved previously,[80] the direct application of this protocol to more commonly encountered, less sterically hindered amine counterparts failed to give the desired products. To fill this gap, Gaunt et al. elegantly developed a general protocol to enable the palladium(II)-catalyzed C(sp^3)−H carbonylation of unprotected, less hindered aliphatic amines in 2016 (Scheme 48b).[146] The use of a bulky carboxylic acid ligand (1-adamantane carboxylic acid or 2,4,6-trimethylbenzoic acid), is key to this carbonylation reaction. The sterically hindered carboxylate ligand was believed to be involved in ligand exchange on $Pd(OAc)_2$, which led to the formation of a sterically biased palladium anhydride intermediate (**242A**) and steered the amine attack at the internal carbonyl of the anhydride intermediate to generate carbamoyl-

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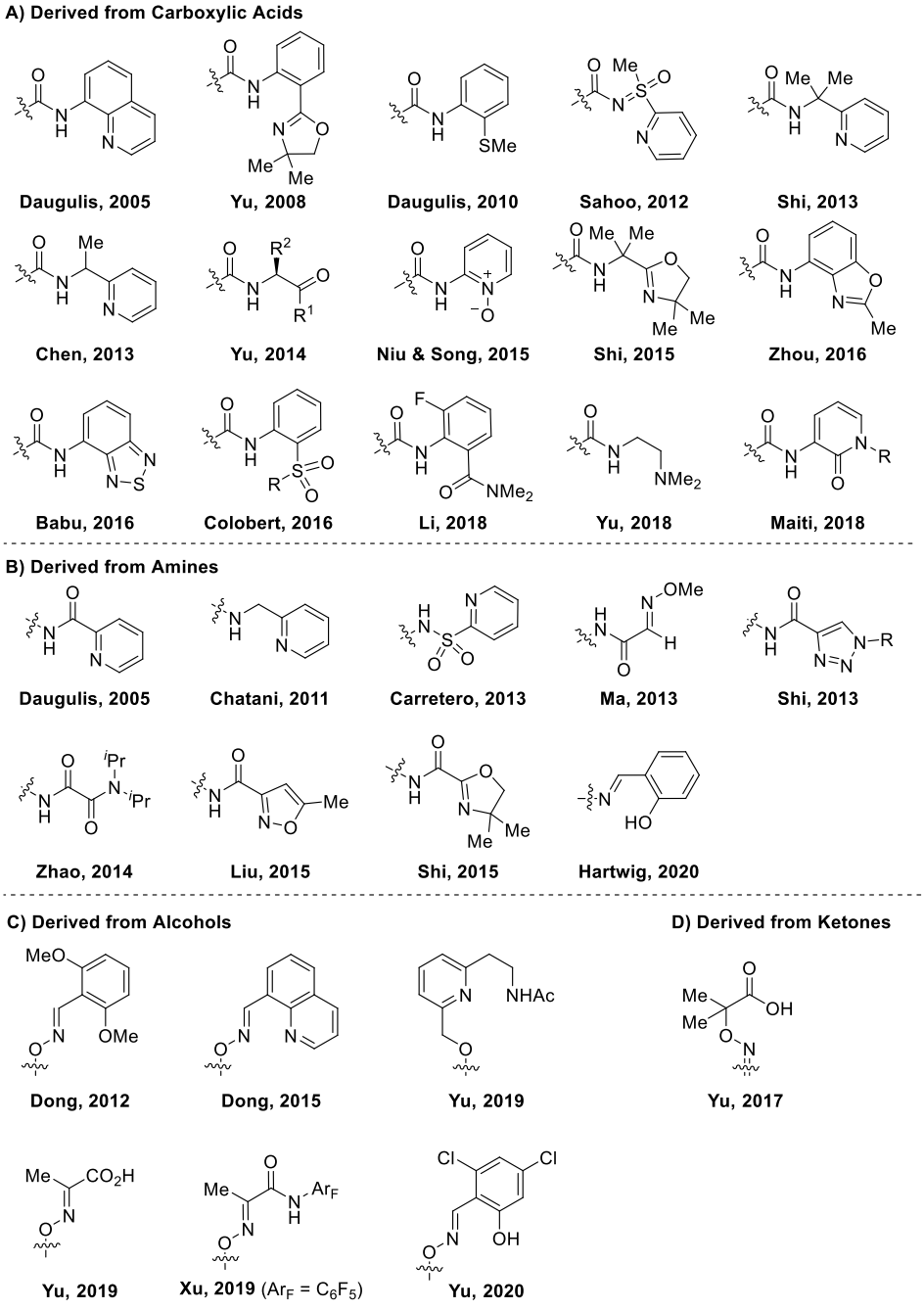

Figure 4. Representative bidentate DGs for C(sp^3)−H activation.

Pd species **242B**. Differing from the classical mechanism of C−H carbonylation, the insertion of CO to form the acylpalladium intermediate **242A** is proposed to occur prior to C−H bond cleavage in this process.

Due to the increased steric interactions, Pd-catalyzed methylene C(sp^3)−H carbonylation remains particularly challenging. In 2017, the unprecedent palladium(II)-catalyzed methylene C−H carbonylation of unprotected secondary aliphatic amines was successfully achieved by the Gaunt group, providing *trans*-disubstituted *β*-lactams **246** in excellent yields and selectivity (Scheme 48c).[147] Interestingly, the concentration of CO can control the pathway of the C−H carbonylation process. Only the *β*-lactam product is obtained when the reaction is set up under a pure CO atmosphere, whereas the *γ*-lactam product could be observed when a CO/air mixture was used.

In 2017, the Gaunt group achieved the selective carbonylation of *β*-methylene C−H bonds of *α*-tertiary amines in the presence of conventionally more reactive and less hindered *β*-methyl C−H bonds (Scheme 48d).[148] They hypothesized that the selectivity originated from the orientation of the activating C−H bond proximal to palladium to avoid the steric repulsion with a second ligated *α*-tertiary amine. From their continuous efforts toward the use of secondary aliphatic amines as valuable feedstocks in C−H activation strategy, they reported the highly diastereoselective synthesis of *trans*-4,5-disubstituted 2-pyrrolidines via a Pd(II)-catalyzed secondary aliphatic amine-directed *γ*-methyl C(sp^3)−H carbonylation in 2018 (Scheme 48e).[149]

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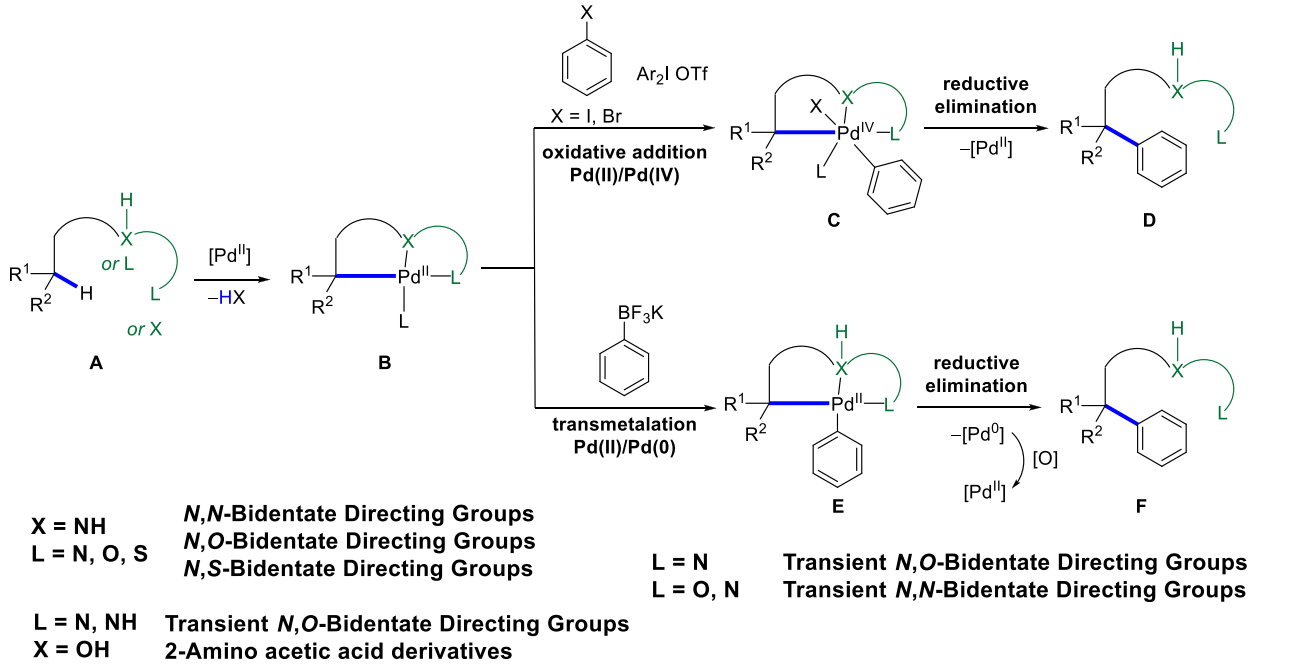
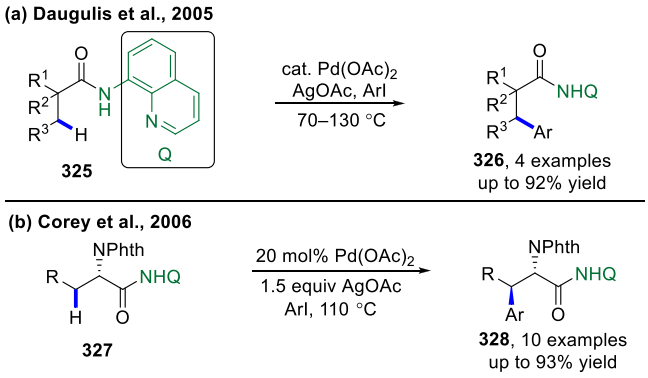
Scheme 61. Overview of Bidentate-DG-Assisted C−H Bond Arylation



Scheme 62. (a) Pd-Catalyzed, 8-Aminoquinoline-Directed C(sp^3)−H Arylation of Aliphatic Carboxamides[180] and (b) Pd-Catalyzed, 8-Aminoquinoline -Directed β-C(sp^3)−H Arylation of Amino Acids[188]



2.1.2. Carbon−Heteroatom Bond Formation.

2.1.2.1. Carbon−Nitrogen Bond Formation. Because amines are very common in pharmaceuticals and natural products, it is attractive to develop versatile methods to forge C−N bonds through C(sp^3)−H activation. In 2006, Che and co-workers reported a palladium-catalyzed, oxime-directed, cascade C-(sp^3)−H activation/nitrene insertion to afford amidated products in good yields with remarkable regio- and chemoselectivity (Scheme 49a).[150] Amidation at secondary C(sp^3)−H bonds was not observed. In 2009, palladium-catalyzed, amide-directed intramolecular amidation of unactivated C(sp^3)−H bonds was reported by Glorius and co-workers (Scheme 49b).[151] Surprisingly, functionalization of the C(sp^3)−H bond takes place over functionalization of the C(sp^2)−H bond. When the *N*-acetyl group is replaced by *N*-formyl, -propionyl, or -isobutyryl, the corresponding products are formed in reduced yields. When *N*-pivaloyl, -benzoyl, or -trifluoroacetyl groups are used as DGs, no cyclization products are obtained. The reaction tolerates various functional groups, such as ethers, sulfones, carboxylic esters, thioethers, acetals, silanes, and ketones. However, the yield of the reaction dramatically drops when 5- and 6-substituted substrates are employed. In 2012, the Muñiz group reported a palladium-catalyzed intermolecular benzylic C(sp^3)−H amidation with NFSI (Scheme 49c).[152]

In 2015, Yu and co-workers developed a CONH-(*p*-CF_3)C_6F_4-directed, Pd(0)/PAr_3-catalyzed intermolecular C-(sp^3)−H amination of simple aliphatic amides using an electron-deficient triarylphosphine ligand and *O*-benzoyl hydroxylmorpholine as the aminating reagent (Scheme 49d).[153] The amination reaction is sensitive to the substitution pattern of the substrates, limiting its use to aliphatic amides that bear a quaternary α-carbon that contains at least one β-methyl group. The following observations support the proposed Pd(0)/Pd(II) cycle: (1) $Pd(TFA)_2$ is not effective as a precatalyst for this transformation; however, excellent yields are obtained by using [{Pd-(allyl)Cl}$_2$] or [Pd(dba)$_2$]. (2) External oxidant is unnecessary when a Pd(0) catalyst is employed. (3) These reactions are inhibited by Ag(I) salts.

In 2014, the Gaunt group developed a palladium-catalyzed C(sp^3)−H amination of aliphatic amines to give strained nitrogen heterocycles through a four-membered cyclopalladation pathway.[145] A methyl group adjacent to unprotected secondary unactivated amines is selectively transformed into synthetically versatile aziridines (Scheme 50a). A range of nucleophiles can then open the aziridine to form highly substituted amine products in good yields. The same group evaluated the mechanism through reaction kinetics and theory, and acetic acid was found to promote the rate of the reaction by suppressing the generation of the off-cycle bis-amine−palladium complex.[154] In 2017, Gaunt and co-workers used chiral anionic BINOL-phosphoric acid ligands to realize an enantioselective version of the C(sp^3)−H amination (Scheme 50b).[155] By combining benziodoxole tosylate and AgOAc as oxidants, the Gaunt group extended the β-C−H amination to γ-C−H amination, which leads to the formation of azetidines (Scheme 50c).[156] Based on their experimental findings and calculations,

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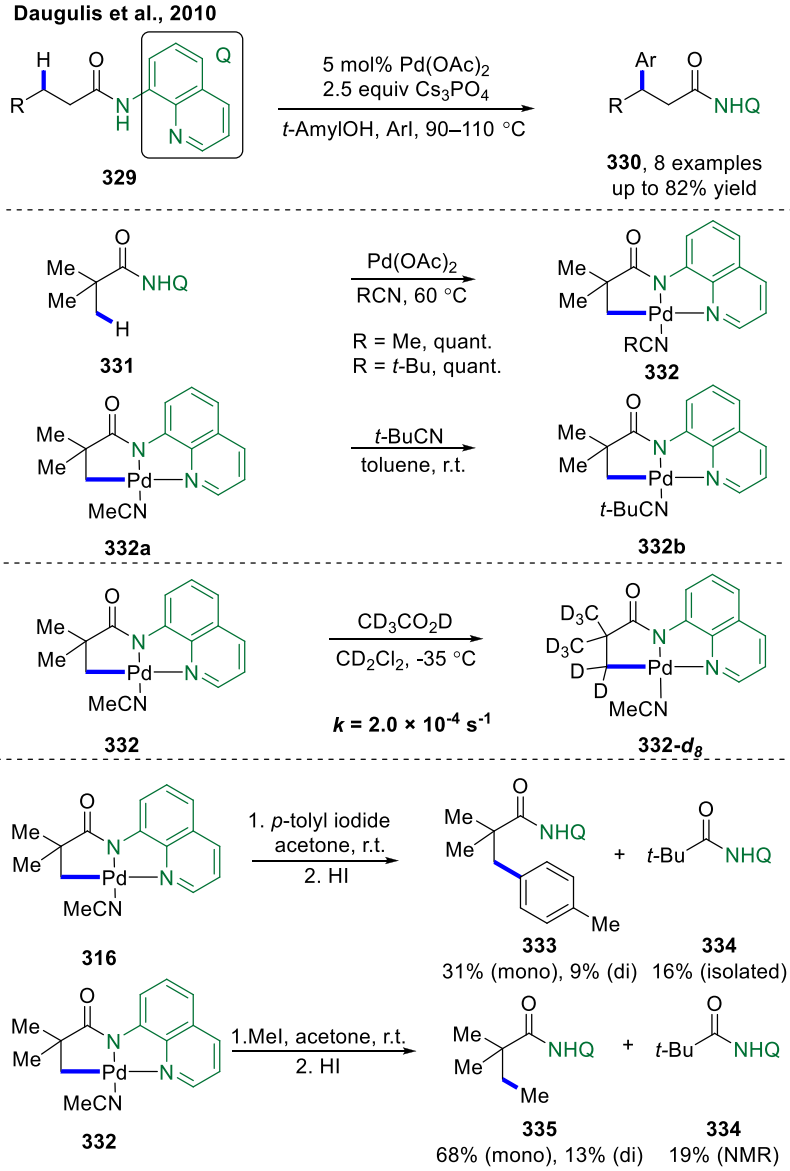
Scheme 63. Pd-Catalyzed β-Methylene C(sp^3)−H arylation of 8-Aminoquinoline Amides and Mechanistic Studies[181]



the γ-C−H amination was the net result of γ-C−OTs bond formation followed by the displacement by the amino group.

2.1.2.2. Carbon−Phosphorus Bond Formation. Phosphonation of benzylic C(sp^3)−H bonds was reported by the Dong group in 2019 (Scheme 51).[157] This is the only example of a palladium-catalyzed C(sp^3)−H bond phosphonation reaction, and it is directed by pyridine. Only 8-methylquinoline derivatives reacted smoothly under the optimized conditions.

2.1.2.3. Carbon−Oxygen Bond Formation. In 2004, an efficient method for the Pd-catalyzed, oxime-directed oxygenation of unactivated methyl C(sp^3)−H bonds using $PhI(OAc)_2$ as oxidant was discovered by Sanford and co-workers (Scheme 52a).[158] The reaction conditions are $Pd(OAc)_2$ (5 mol %) and $PhI(OAc)_2$ (1.1 equiv) in $AcOH/Ac_2O$ (1:1) at 80−100 °C for 1.5−3.5 h. The reaction is thought to proceed through directed C(sp^3)−H bond cleavage followed by oxidative addition of $PhI(OAc)_2$ to form a Pd(IV) intermediate and then reductive elimination to form the C(sp^3)−O bond and regenerate the Pd(II) catalyst. The regioselectivity of this transformation was examined by employing a series of aliphatic ketone *O*-methyl oximes. Notably, no β-hydride elimination was observed in any of these systems, which was attributed to the rigidity of the palladacycle intermediates. Under the reaction conditions, mono-oxygenation of primary β-C−H bonds occurs in preference to secondary β-C−H bonds or γ-C−H bonds. Interestingly, structurally rigid *trans*-decalone *O*-methyl oxime is oxygenated at an unactivated secondary C(sp^3)−H bond with high diastereoselectivity. Based on this result, C−H activation and subsequent C(sp^3)−O bond formation are postulated to proceed with high stereoselectivity. Pyridyl-directed oxygenation of unactivated C(sp^3)−H bonds was also reported by the Sanford group in the same year.[159] The oxime-directed oxygenation of C(sp^3)−H bonds was later used by the Johnson group for the total synthesis of paspaline (Scheme 52b).[160] In 2017, Mei and co-workers reported a palladium(II)-catalyzed C(sp^3)−H oxygenation via electrochemical oxidation, which provides an alternative to conventional stoichiometric oxidants (Scheme 52c).[161] Cyclic voltammogram (CV) of an oxazoline-containing, cyclometalated palladium(II) complex suggested

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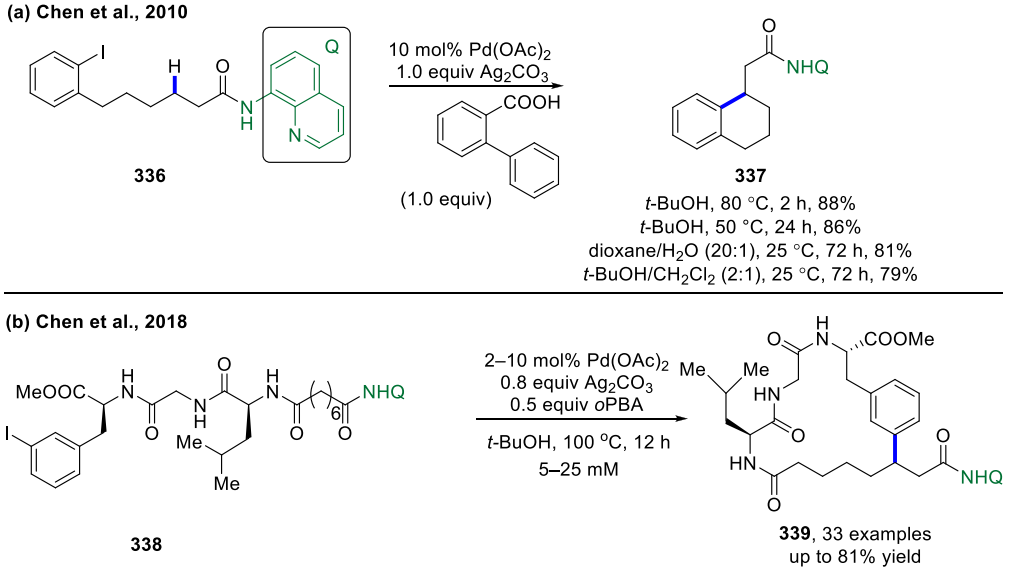
Scheme 64. (a) Pd-Catalyzed, 8-Aminoquinoline-Directed Intramolecular Methylene β-C(sp^3)−H Arylation[189] and (b) Synthesis of Peptide Macrocycles via Palladium-Catalyzed Intramolecular C(sp^3)−H Arylation[190]



that the anode could oxidize the alkyl palladium(II) intermediate to a high-valent Pd(III) or Pd(IV) species.

In 2005, Yu and co-workers reported the palladium-catalyzed, oxazoline-directed acetoxylation of unactivated methyl C(sp^3)−H bonds using MeCOOO*t*Bu as oxidant and Ac_2O as a promoter (Scheme 53).[162] The diastereoselective C(sp^3)−H acetoxylation was also achieved in moderate diastereoselectivity (up to 82% de) using a (*S*)-4-*tert*-butyloxazoline as DG. To avoid the oxidation of α-hydrogen atom to the nitrogen in the chiral oxazoline DG, lauroyl or benzoyl peroxide was used as the stoichiometric oxidant for the diastereoselective reaction. A 3:2 mixture of *anti* and *syn* trinuclear C(sp^3)−Pd complexes was isolated by stirring substrate **275a** with 1.5 equiv of $Pd(OAc)_2$ in CH_2Cl_2 at 24 °C for 36 h. Remarkably, only the *anti*-isomer was obtained from chiral substrate **277a**, which suggests that the stereocenter on the chiral oxazoline DG controls the geometry of the trinuclear complex. A palladium-catalyzed, Boc-directed acetoxylation of *N*-methylamines with IOAc as the oxidant has also been demonstrated by the Yu group.[163]

In 2014, Zhou and Lu reported a palladium-catalyzed acyloxylation of unactivated C(sp^3)−H bonds of simple amides with $CF_3CO_2H/K_2S_2O_8$. A variety of amides were successfully converted to the corresponding β-acyloxy amides in good yields (Scheme 54).[164] By use of methanesulfonic anhydride (Ms_2O), various β-mesyloxy amides could also be obtained. Furthermore, the β-mesyloxy amides could be easily transformed to β-fluoroamides and β-lactams.[165]

In 2015, Gaunt and co-workers reported a palladium-catalyzed C(sp^3)−H acetoxylation of amino alcohol derivatives (Scheme 55a).[80] The reaction conditions are $Pd(OAc)_2$ (5 mol %) and $PhI(OAc)_2$ in a mixed solvent system of toluene and Ac_2O at 60 °C. A broad range of substrates that contain alkyl chains with varying substitution patterns, protected hydroxyl groups, carbonyl moieties, and nitrogen-containing heterocycles were successfully acetoxylated under the standard conditions. In 2019, they reported the palladium-catalyzed C(sp^3)−H acetoxylation of morpholinone derivatives (Scheme 55b).[166] These two examples were limited to the acetoxylation of secondary amines, while a Pd-catalyzed γ-C(sp^3)−H acetoxylation of primary aliphatic amines was uncovered by Shi and co-workers in 2017 (Scheme 55c).[167] Protonation of the primary amine with AcOH was found to accelerate the reaction.

The formation of benzolactones via palladium-catalyzed, carboxylate-directed C(sp^3)−H lactonization was disclosed by the Martin group in 2011 (Scheme 56a).[168] This transformation is significantly promoted by a MPAA ligand, namely, Ac-Leu-OH (**L55**). Silver carbonate was used as the stoichiometric oxidant, and a silver benzoate salt was proposed as the reactive intermediate. Yu and co-workers further improved this process by the use of molecular oxygen as the sole oxidant in 2020 (Scheme 56b).[169] 3-Trifluoromethyl-2-pyridone (**L56**) was found to be a crucial ligand to promote the oxygenation reaction. Notably, this represents a rare example of C−H oxygenation via Pd(II)/Pd(0) catalysis.

Palladium-catalyzed β-C(sp^3)−H acetoxylation of free carboxylic acids was reported by the van Gemmeren group in 2019 (Scheme 57a).[170] The inorganic base plays a key role in this reaction, with NaHFIP offering the best yield. A breakthrough of Pd-catalyzed β-C(sp^3)−H lactonization of free alkyl aliphatic acids to synthesize the highly strained β-lactones was made by Zhuang and Yu in 2020 (Scheme 57b).[171] The reaction is catalyzed by $Pd(CH_3CN)_2Cl_2$ (10 mol %) with α-methyl-*N*-acetyl β-alanine **L57** (20 mol %) as the ligand, TBHP (in decane, 2.0 equiv) as the oxidant, and $CsHCO_3$(0.5 equiv) as the base in HFIP solvent. TBHP is proposed to promote the intramolecular C(sp^3)−O reductive elimination from the Pd(IV) center to produce the β-lactone product due to the steric hindrance of *t*-BuO^-. The highly strained β-lactones can be converted into a variety of functionalized alkyl aliphatic acids upon reaction with different nucleophiles. By switching the ligand from α-methyl-*N*-acetyl β-alanine **L57** to the cyclopentane-based *N*-acetyl β-amino acid **L58**, Yu and co-workers were able to develop the palladium(II)-catalyzed β-C(sp^3)−H acetoxylation of free carboxylic acids using Ac_2O (Scheme 57c).[172] When the reaction is performed without Ac_2O under otherwise standard conditions, γ-, δ-, and ε-lactone products are obtained for the first time. Substrates containing α-hydrogen were also converted to lactones under the standard conditions. The authors proposed a Pd(II)/Pd(IV) catalytic cycle involving the following sequence of events: Aliphatic acid **301** undergoes

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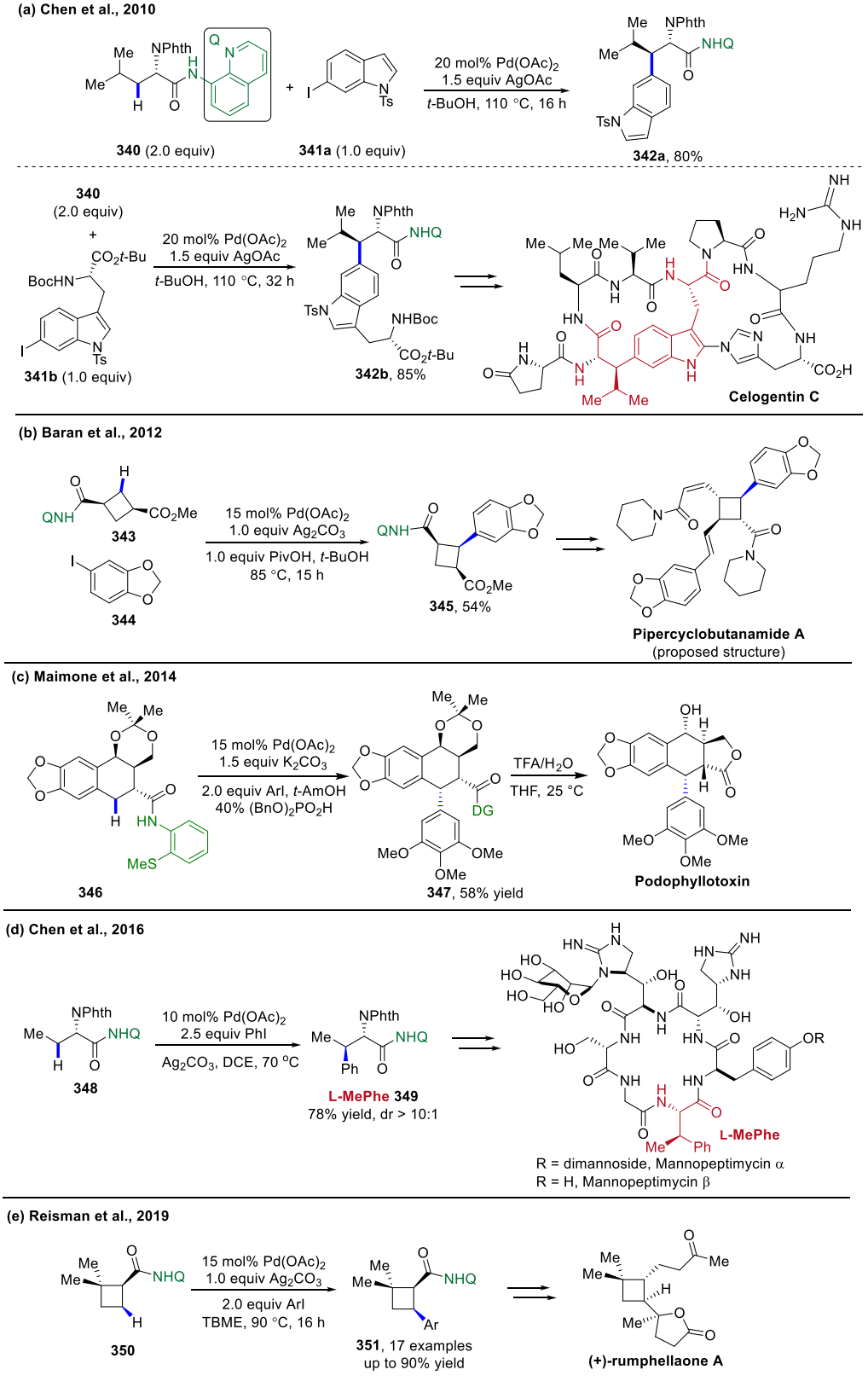
Scheme 65. (a) Synthesis of the Key Leu-Trp Intermediate of Celogentin C via 8-Aminoquinoline-Directed Methylene C(sp^3)−H Arylation,[191] (b) Total Synthesis of the Proposed Structure of Pipercyclobutanamide A via 8-Aminoquinoline-Directed Sequential C(sp^3)−H Arylation and Olefination,[192] (c) Total Synthesis of Podophyllotoxin via 8-Aminoquinoline-Directed C(sp^3)−H Arylation,[193] (d) Synthesis of the Key L-MePhe Building Block of Mannopeptimycins via 8-Aminoquinoline-Directed Methylene C(sp^3)−H Arylation,[194] and (e) 8-Aminoquinoline-Directed Cyclobutyl C(sp^3)−H Arylation as a Key Step in Total Synthesis of (+)-Rumphellaone A[195]



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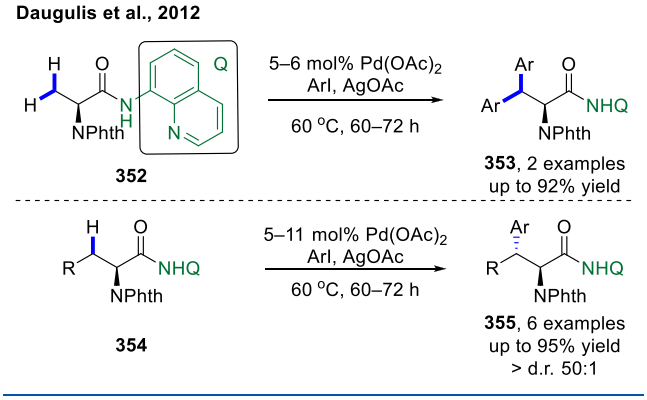
Scheme 66. Pd(II)-Catalyzed β-C(sp^3)−H Arylation of *N*-Phthaloyl-Protected α-Amino Acids[196]



palladium(II)-catalyzed β-C(sp^3)−H activation to give palladacycle intermediate **302**, which is oxidized by TBHP to form Pd(IV) intermediate **303**. In the presence of Ac_2O, intermediate **303** could undergo ligand exchange to generate intermediate **304**. Finally, β-acetoxylated product **305** is produced via reductive elimination. In the absence of Ac_2O, the lactone product **298** is formed instead, as demonstrated in Scheme 57b.[171]

2.1.2.4. Carbon−Halogen Bond Formation. In 2005, Yu and co-workers reported the first palladium-catalyzed, oxazoline-directed, diastereoselective iodination of unactivated C−H bonds under mild conditions (Scheme 58a).[173] The trinuclear palladium alkyl species **312** was obtained as a single isomer in 60% yield by stirring substrate **311** with $Pd(OAc)_2$ (1 equiv) in CH_2Cl_2 at 24 °C for 36 h (Scheme 58b). The formation of new chiral centers was confirmed by treating **312** with trifluoroacetic acid, which allowed the isolation and X-ray analysis of **313** as the major *syn*-(*S*,*S*) complex. Moreover, they isolated PdI_2 as a powder from the catalytic reaction mixture in quantitative yield. Based on these results, they rationalized that IOAc generated *in situ* from the reaction of AgOAc and I_2 converts PdI_2 into $Pd(OAc)_2$ to close the catalytic cycle.[174] They observed low reactivity and stereoselectivity when 4-isopropyl-oxazoline was used as the DG, and computational calculations support this finding by revealing that the catalyst resting state of 4-isopropyl-oxazoline is more stable than the catalyst resting state of 4-*tert*-butyl-oxazoline.[175] In 2017, the Yu group reported that quinoline-type ligands could enable C(sp^3)−H bromination and iodination of various aliphatic amides-directed by CONH−*p*-$CF_3C_6F_4$ (Scheme 58c).[176] Moreover, in this same paper they also showed one example of a free carboxylic acid-directed C(sp^3)−H bromination of pivalic acid.

In 2015, Yu and co-workers developed a ligand-enabled, Pd(II)-catalyzed C(sp^3)−H fluorination reaction of α-amino acids utilizing Selectfluor as the fluorination reagent and monodentate CONH−(*p*-CF_3)C_6F_4 as the directing group (Scheme 59).[177] After extensive screening, the reaction was found to be sensitive to the amount of Selectfluor, Ag_2CO_3, and 1,4-dioxane. Ultimately, a wide range of unnatural, enantiopure, *anti*-β-fluoro-α-amino acids could be synthesized. They proposed a reaction mechanism in which the quinolone ligand (**L60**) coordinates to $Pd(TFA)_2$ to form the Pd(II)·(**L60**)$_n$ intermediate **A**. Then, coordination of the substrate followed by C(sp^3)−H activation affords intermediate **318**. Next, the oxidative addition of Selectfluor to intermediate **318** delivers intermediate **320** with a fluorine ligand attached to the Pd(IV) center. Finally, C(sp^3)−F reductive elimination from intermediate **320** affords the corresponding fluorinated product and regenerates the active Pd(II) species.

2.1.2.5. Carbon−Boron Bond Formation. In 2016, a ligand-promoted, palladium(II)-catalyzed C(sp^3)−H borylation of carboxamides that bear the weakly coordinating, monodentate $NHAr_F$ (Ar_F = *p*-$CF_3C_6F_4$) DG with bis(pinacolato)diboron as the borylating reagent was reported by Yu and co-workers (Scheme 60a).[178] The reaction system is compatible with methyl C(sp^3)−H bonds in both α-tertiary and α-quaternary carboxamides, as well as with methylene C(sp^3)−H bonds in a variety of alicyclic carboxyamides. In order to demonstrate the practicality of this transformation, the borylated products were converted to various organic synthons through carbon−carbon and carbon−heteroatom bond formation. In the next year, Yu and co-workers successfully developed an enantioselective C(sp^3)−H borylation of cyclobutane carboxamides via a Pd(II)/Pd(0) catalytic cycle using APAO ligand **L19** as chiral ligand (Scheme 60b).[179] Substrates that contain α-tertiary and α-quaternary carbon centers are compatible with this reaction. The use of APAO ligands is key to the success of this asymmetric borylation reaction.

2.2. Palladium-Catalyzed C(sp^3)−H Functionalization Using Bidentate Directing Groups

Arguably, bidentate directing auxiliaries are the most widely used strategy for realizing transition-metal-catalyzed non-activated C(sp^3)−H bond functionalization reactions. After the pioneering work of Daugulis and co-workers,[180,181] various types of DGs, including *N*,*N*-, *N*,*S*- and *N*,*O*-bidentate types,[21,33,182,183] have been developed as shown in Figure 4. Due to the fact that bidentate, DG-coordinated, cyclopalladated intermediates are often thermodynamically stable, various electrophilic coupling partners can be employed to oxidize these intermediates to produce Pd(IV) species that can then undergo reductive elimination to form carbon−carbon and carbon−heteroatom bonds. The widespread use of bidentate DGs, especially 8-aminoquinoline and related DGs, in C(sp^3)−H bond functionalization has motivated the development of a number of robust methods for cleaving or transforming these DGs for various synthetic applications. These methods have been thoroughly reviewed and thus will not be discussed here.[184−187]

2.2.1. Carbon−Carbon Bond Formation.

2.2.1.1. Arylation. Two pathways for bidentate-DG-assisted, nonactivated C(sp^3)−H bond arylation are outlined in Scheme 61. Generally, cyclopalladated intermediate **B** is generated after C(sp^3)−H activation, which is then followed by two distinct catalytic cycles involving either a Pd(II)/Pd(IV) or a Pd(II)/Pd(0) redox couple. Reaction of the palladacycle **B** with electrophilic coupling partners leads to Pd(IV) intermediate **C**, which then undergoes reductive elimination to release arylated product **D** and Pd(II). The alternate pathway proceeds through transmetalation with a nucleophilic coupling partner to afford the Pd(II) intermediate **E**, and reductive elimination furnishes arylated product **F** and Pd(0), which needs to be reoxidized to close the catalytic cycle. Thus far, only one example of bidentate-DG-assisted nonactivated C(sp^3)−H bond arylation that is believed to proceed via a Pd(II)/Pd(0) pathway has been reported.

2.2.1.1.1. C(sp^3)−H Arylation via Pd(II)/Pd(IV) Catalysis. While early work established that pyridine and various other related *N*-heterocycles were effective DGs in enabling C(sp^3)−

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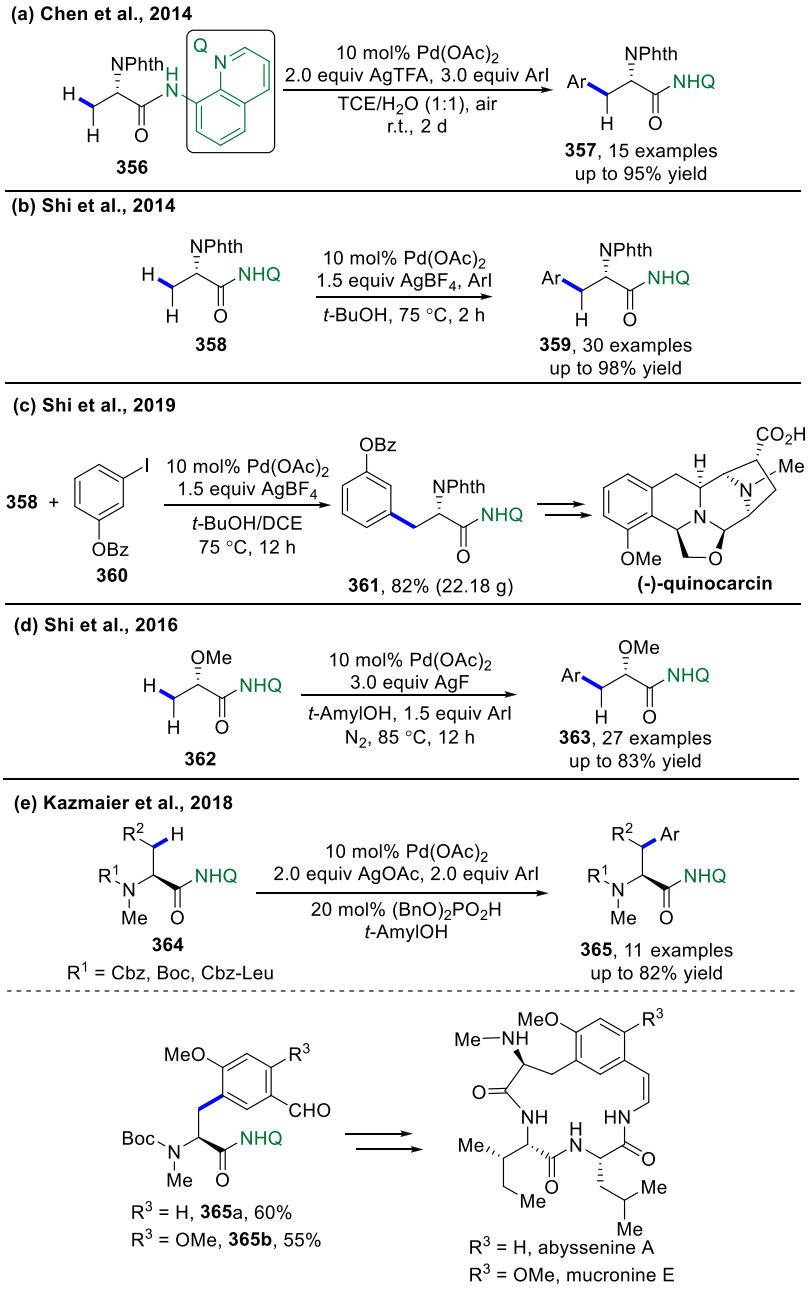
Scheme 67. (a) Pd-Catalyzed Monoarylation of Alanine β-Methyl C(sp^3)−H Bonds,[197] (b) Pd-Catalyzed β-Methyl C(sp^3)−H Monoarylation of Alanine,[198] (c) Scalable Formal Synthesis of (−)-Quinocarcin via β-Methyl C(sp^3)−H Monoarylation of Alanine,[199] (d) Pd-Catalyzed Monoarylation of Lactic Acid Directed by 8-Aminoquinoline,[200] and (e) Pd-Catalyzed C(sp^3)−H Arylation of *N*-Methyl Amino Acids and Peptides and the Application in Total Synthesis of Abyssenine A and Mucronine E[201]



H bond functionalization,[76] the products of such transformations have limited utility given that these heterocycles cannot be readily converted into other functional groups. Thus, the Daugulis group sought to develop a bidentate directing group that could enable these same transformations and be easily installed and removed. In 2005, they pioneeringly developed removable amide auxiliaries derived from 8-aminoquinoline (AQ) and picolinic acid (PA).[180] It was proposed that the bidentate coordination of these auxiliaries to the metal center facilitates both the C−H activation and the oxidative addition steps by stabilizing the Pd(IV) intermediate species, which were suspected to be involved in the mechanism The 8-aminoquinoline group laid the foundation for the rapid development of a myriad of *N,N*-bidentate auxiliaries to facilitate diverse catalytic C−H activation methods.

The palladium(II)-catalyzed arylation of primary C(sp^3)−H bonds and even more challenging secondary β-C(sp^3)−H bonds of carboxamide substrates was demonstrated by employing the 8-aminoquinoline auxiliary to provide a route for accessing β-functionalized carboxylic acids upon cleavage of the 8-aminoquinoline group (Scheme 62a).[180] The optimal conditions found were $Pd(OAc)_2$ (0.1−5 mol %) with AgOAc and an excess of an aryl iodide at 70−130 °C. The Corey group used the 8-aminoquinoline DG to functionalize C(sp^3)−H bonds in natural amino acid derivatives in 2006 (Scheme 62b).[188] An unexpected arylation of the γ-C−H bond via a six-membered

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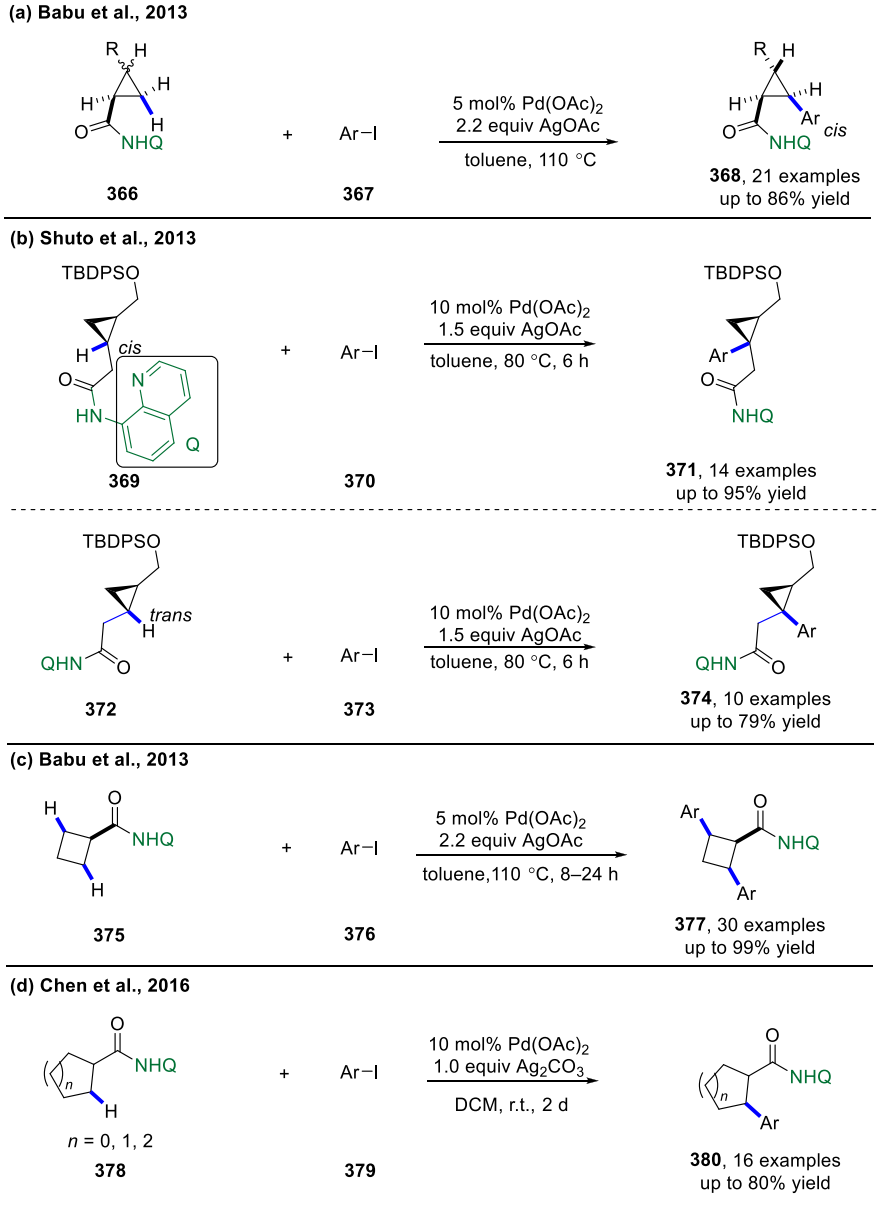
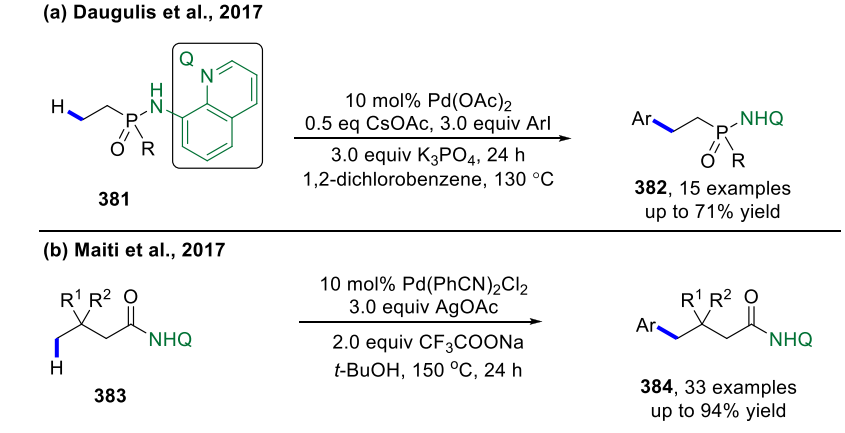
Scheme 68. (a) 8-Aminoquinoline-Directed Methylene C(sp^3)−H Arylation of Cyclopropanes,[202] (b) 8-Aminoquinoline-Directed Tertiary C(sp^3)−H Arylation of Cyclopropanes,[203] (c) 8-Aminoquinoline-Directed Methylene C(sp^3)−H Arylation of Cyclobutanes,[204] and (d) 8-Aminoquinoline-Directed C(sp^3)−H Arylation of Cyclopentanes and Cyclohexanes[205]



Scheme 69. (a) Pd-Catalyzed, 8-Aminoquinoline-Directed C(sp^3)−H Arylation of Phosphonamidates and Phosphinic Amides[206] and (b) Pd-Catalyzed, 8-Aminoquinoline-Directed γ-C(sp^3)−H Arylation[207]



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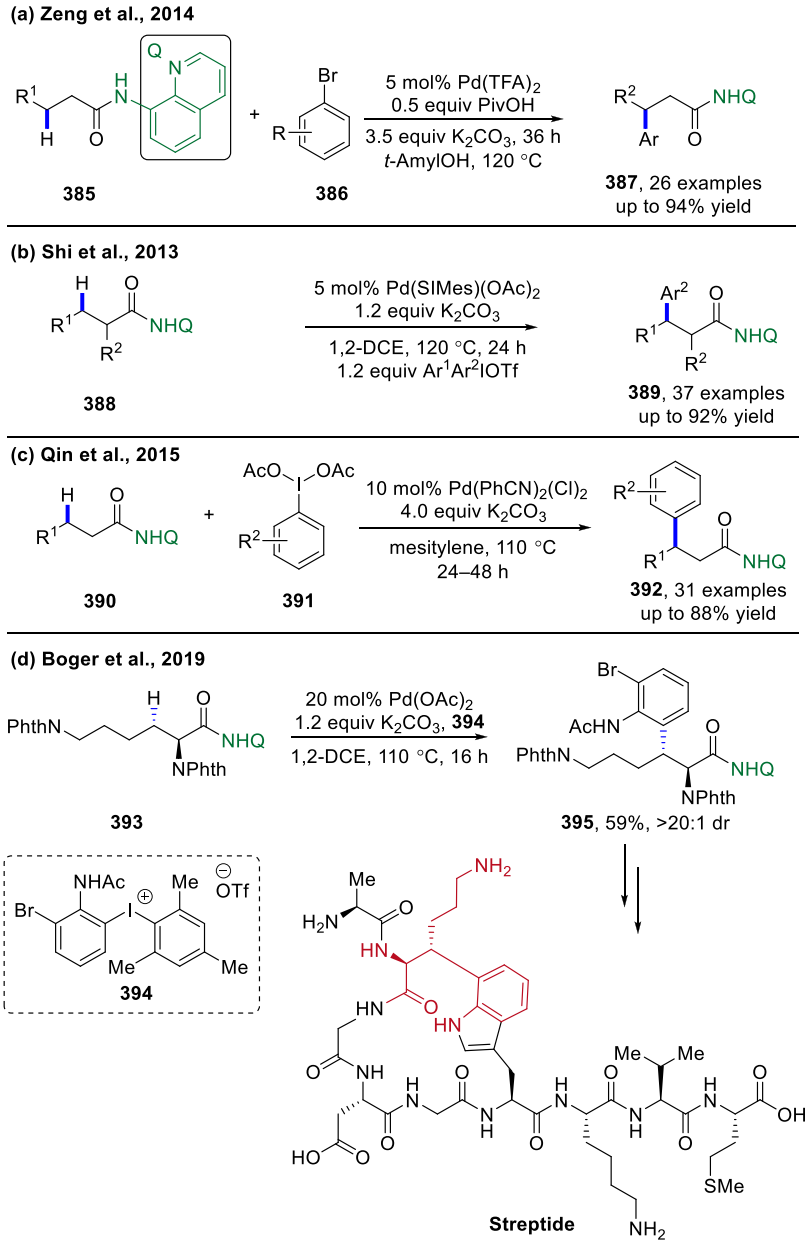
Scheme 70. (a) 8-Aminoquinoline-Directed C(sp^3)−H Arylation with Aryl Bromides,[208] (b) 8-Aminoquinoline-Directed C(sp^3)−H Arylation with Diarylhyperiodonium Triflates,[209] (c) 8-Aminoquinoline-Directed C(sp^3)−H Arylation with (Diacetoxyiodo)arenes,[210] and (d) 8-Aminoquinoline-Directed C(sp^3)−H Arylation of a Lysine Derivative Using a Hypervalent Iodonium Reagent for the Total Synthesis of Streptide[211]



palladacycle was observed when isoleucine was used as the substrate, indicating that γ-C−H bond activation can occur when the β-C−H bond is hindered.

In 2010, Shabashov and Daugulis expanded upon their preliminary study of 8-aminoquinoline-directed C(sp^3)−H arylation in 2005 and developed a robust method for secondary C(sp^3)−H arylation and alkylation directed by 8-aminoquinoline auxiliary (Scheme 63).[181] In comparison to their previous study, in this work, they carried out a systematic investigation of the activities of different bidentate directing groups. They also developed a procedure that replaces the expensive silver salts with cesium salts. To obtain further insights into the coordination mode of the substrate with Pd(II), Daugulis and co-workers characterized the C−H cleavage intermediate **332**. Palladacycle **332** was isolated in quantitative yield by combining the 8-aminoquinoline-derived pivalamide with palladium acetate in nitrile solvents at 60 °C for 3−4 h (Scheme 63). Acetonitrile is labile and easily replaced by *tert*-butyl isonitrile to afford complex **332b** in quantitative yield. Interestingly, complete H/D exchange of the aliphatic hydrogens was observed within minutes at room temperature when complex **332** was dissolved in CD_3CO_2D. At −35 °C, the first-order rate constant was measured to be $k = 2.0 \times 10^{-4}$ s^{-1}. Reactions between complex **332** and either *p*-tolyl iodide or iodomethane were conducted. Both mono- and disubstituted products were afforded in addition to the recovered amide starting material. Through these mechanistic studies, Daugulis and co-workers proposed a Pd(II)/Pd(IV) pathway that proceeds first through C−H activation and then through oxidative addition. Daugulis and co-workers were careful to note that they were unable to rule

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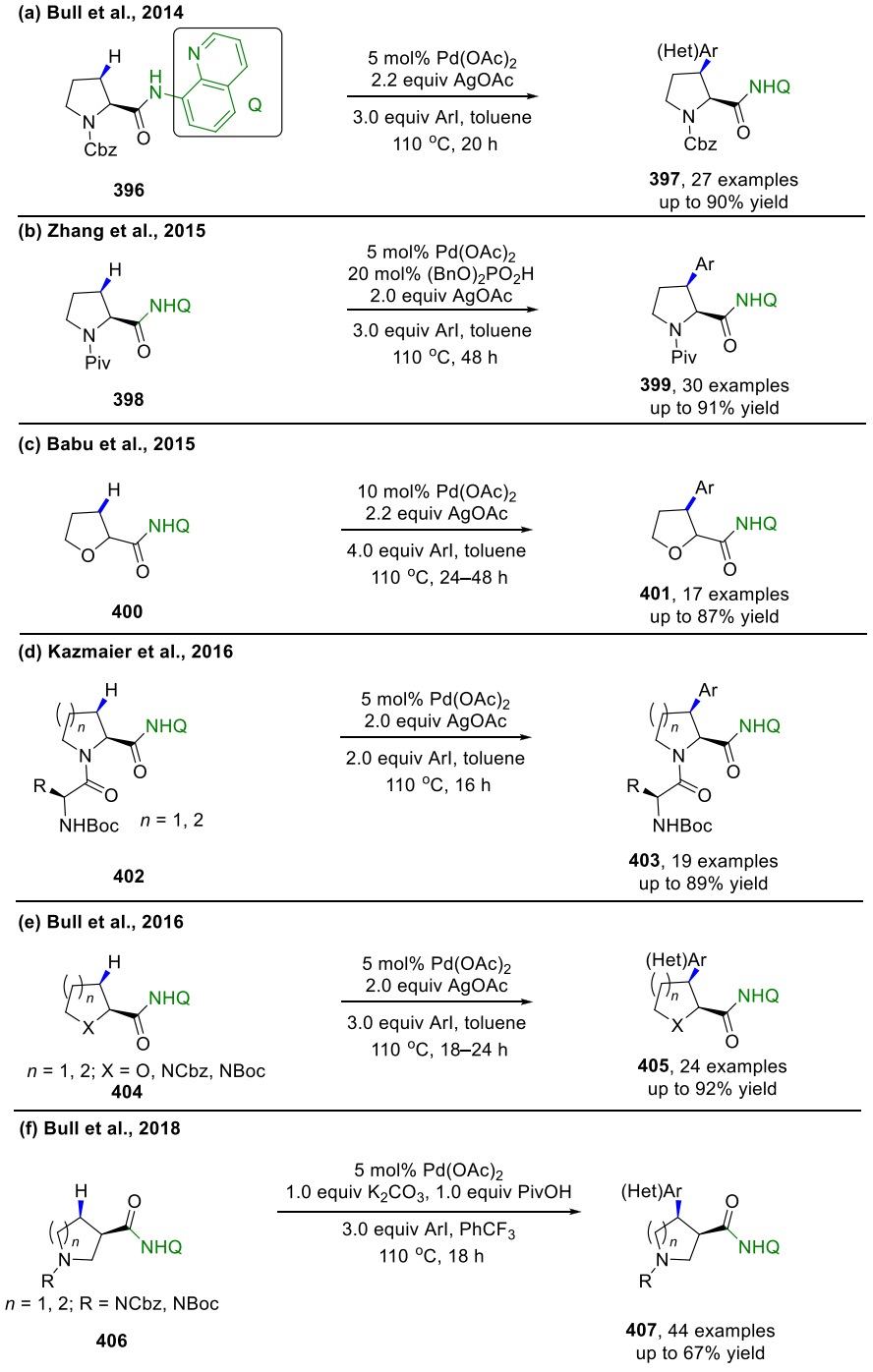
Scheme 71. 8-Aminoquinoline-Directed C(sp^3)−H Arylation of Aliphatic Heterocycles[212−217]



out the presence of an active Pd(III) dimeric species. However, in the strongly coordinating acetonitrile solvent, a dimeric Pd(III) species seems unlikely.

Inspired by the ability of the 8-aminoquinoline DG to enable C−H functionalization at the *β*-methylene position, Chen and co-workers reported a benzo-ring construction under mild reaction conditions via Pd(II)-catalyzed intramolecular C-(sp^3)−H arylation of a tethered aryl iodide (Scheme 64a).[189] After extensive screening of both aliphatic acids and benzoic acids, the addition of *ortho*-phenylbenzoic acid (*o*-PBA) was found to play a key role in the efficiency of the reaction and allows the transformation to proceed at room temperature. Also using *o*-PBA as the additive, Chen and co-workers reported a protocol for making peptide macrocycles via palladium-catalyzed, intramolecular C(sp^3)−H arylation (Scheme 64b).[190] The buttress from the cyclophane moiety makes the resulting peptide macrocycles more rigid and stable in their three-dimensional structure than flexible amides, esters, or disulfide linkers. Nonaromatic amino acids could also be cyclized through attachment of a prosthetic iodoaryl substituent. Even relatively small peptide macrocycles could be prepared using this transformation, despite the resulting ring strain.

The 8-aminoquinoline-directed, *β*-methylene C−H arylation was applied by the Chen group as a key C−C bond-forming step in the stereoselective synthesis of the bicyclic peptide celogentin C (Scheme 65a).[191] The 8-aminoquinoline auxiliary could be

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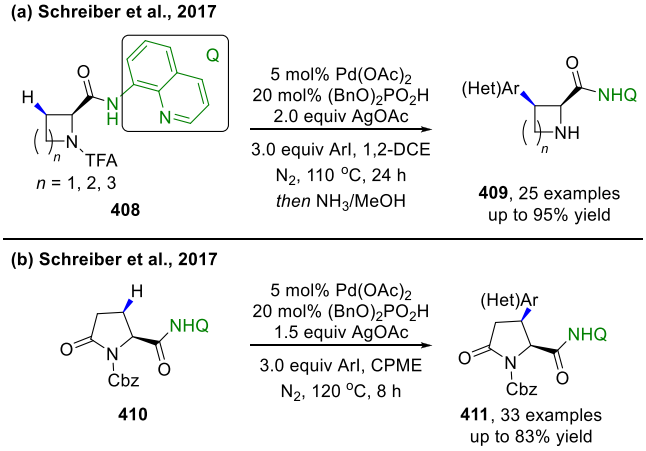
Scheme 72. 8-Aminoquinoline-Directed C(sp^3)−H Arylation of Pyroglutamic Acid Derivatives and Azetidines[218,219]



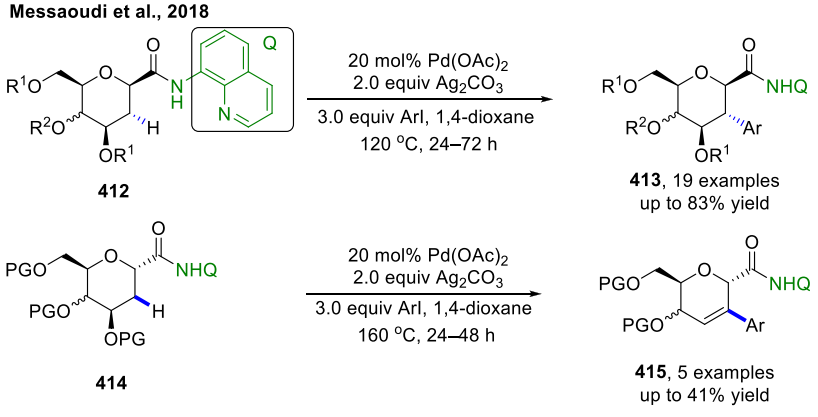
effectively detached under mild conditions. In 2012, Baran and co-workers also achieved the concise total synthesis of the originally proposed structure of pipercyclobutanamide A by 8-aminoquinoline-directed, palladium-catalyzed sequential intermolecular C(sp^3)−H arylation/alkenylation of the cyclobutanamide (Scheme 65b).[192] In 2014, the Maimone group reported a total synthesis of podophyllotoxin through palladium-catalyzed C(sp^3)−H arylation (Scheme 65c).[193] The arylation product was observed by tuning the conformation of the substrate. The Chen group also achieved the total synthesis of mannopeptimycins using 8-aminoquinoline-directed β-methylene C−H arylation of Phth-Abu-AQ **348** to build the key L-MePhe **349** in 2016 (Scheme 65d).[194] The 8-aminoquinoline-directed cyclobutyl C(sp^3)−H arylation strategy has also been used by Reisman and co-workers in the total synthesis of (+)-rumphellaone A (Scheme 64d).[195] Collectively, these examples demonstrate the enabling nature of directed C(sp^3)−H activation in complex molecule synthesis.

In 2012, the diarylation of methyl groups and the diastereoselective monoarylation of methylene groups of amino acids was achieved by Tran and Daugulis with the assistance of the 8-aminoquinoline DG (Scheme 66).[196] Notably, the 8-aminoquinoline DG can be removed with $BF_3 \cdot Et_2O$ in MeOH at 100 °C to afford the corresponding methyl ester.

In 2014, the Chen group described the Pd(II)-catalyzed monoselective β-methyl C(sp^3)−H arylation of an alanine derivative without erosion of the α-stereocenter by employing the 8-aminoquinoline DG (Scheme 67a).[197] By extending the reaction time to 2 days and reducing the reaction temperature to room temperature, Chen and co-workers were able to prevent a second arylation of the β-methyl group (Scheme 67a) that was observed by Daugulis and co-workers.[178] Shortly after, the Shi group independently reported an 8-aminoquinoline-directed β-methyl C(sp^3)−H monoarylation of an alanine derivative that required a reaction length of only 2 h (Scheme 67b).[198] A wide range of aryl iodides that bear synthetically useful functional groups can be used in this protocol, providing general and practical synthetic access to a variety of β-aryl-amino acids. They successfully applied this protocol in the scalable formal synthesis of (−)-quinocarcin in 2019. The key building block, β-aryl-α-amino acid **359**, was prepared in 82% yield on a 22.18 g scale with the retention of chirality (Scheme 67c).[199] In 2016, an efficient synthesis of chiral β-aryl-α-hydroxy acids via palladium-catalyzed C(sp^3)−H arylation of lactic acid through the assistance of the 8-aminoquinoline DG with the retention of chirality was reported by the Shi group (Scheme 67d).[200] After extensive screening, the best reaction conditions were $Pd(OAc)_2$ (10 mol %) as catalyst and AgF (1.5 equiv) as the additive at 75 °C for 2 h. A range of aryl and heteroaryl iodides bearing various functional groups underwent the arylation successfully. The synthetic importance of these protocols was demonstrated by the synthesis of LY519818 and tesaglitazar, two potential agonists against peroxisome proliferator-activated receptors. In the above examples involving amino acids, the amine is protected by the phthalimido (Phth) group. In 2018, Kinsinger and Kazmaier reported the β-C(sp^3)−H arylation of *N*-methylated amino acids and peptides using 8-aminoquinoline as DG (Scheme 67e).[201] This method has been used to synthesize the key building blocks **365a** and **365b**, which were successfully applied in the total synthesis of abyssenine A and mucronine E.

In 2013, palladium-catalyzed arylation of methylene C(sp^3)−H bonds of cyclopropanes with the assistance of the 8-aminoquinoline DG was reported by the Babu group (Scheme 68a)[202] and the Shuto group (Scheme 68b).[203] Notably, the Shuto group also demonstrated several examples of arylation of tertiary cyclopropyl C(sp^3)−H bonds.[203] In the same year, the diarylation of cyclobutane was also developed by the Babu group (Scheme 68c).[204] In 2016, the Chen group described a palladium-catalyzed direct arylation of methylene C(sp^3)−H

Scheme 73. Pd(II)-Catalyzed Diastereoselective C(sp^3)−H Arylation of Glycosides[220]



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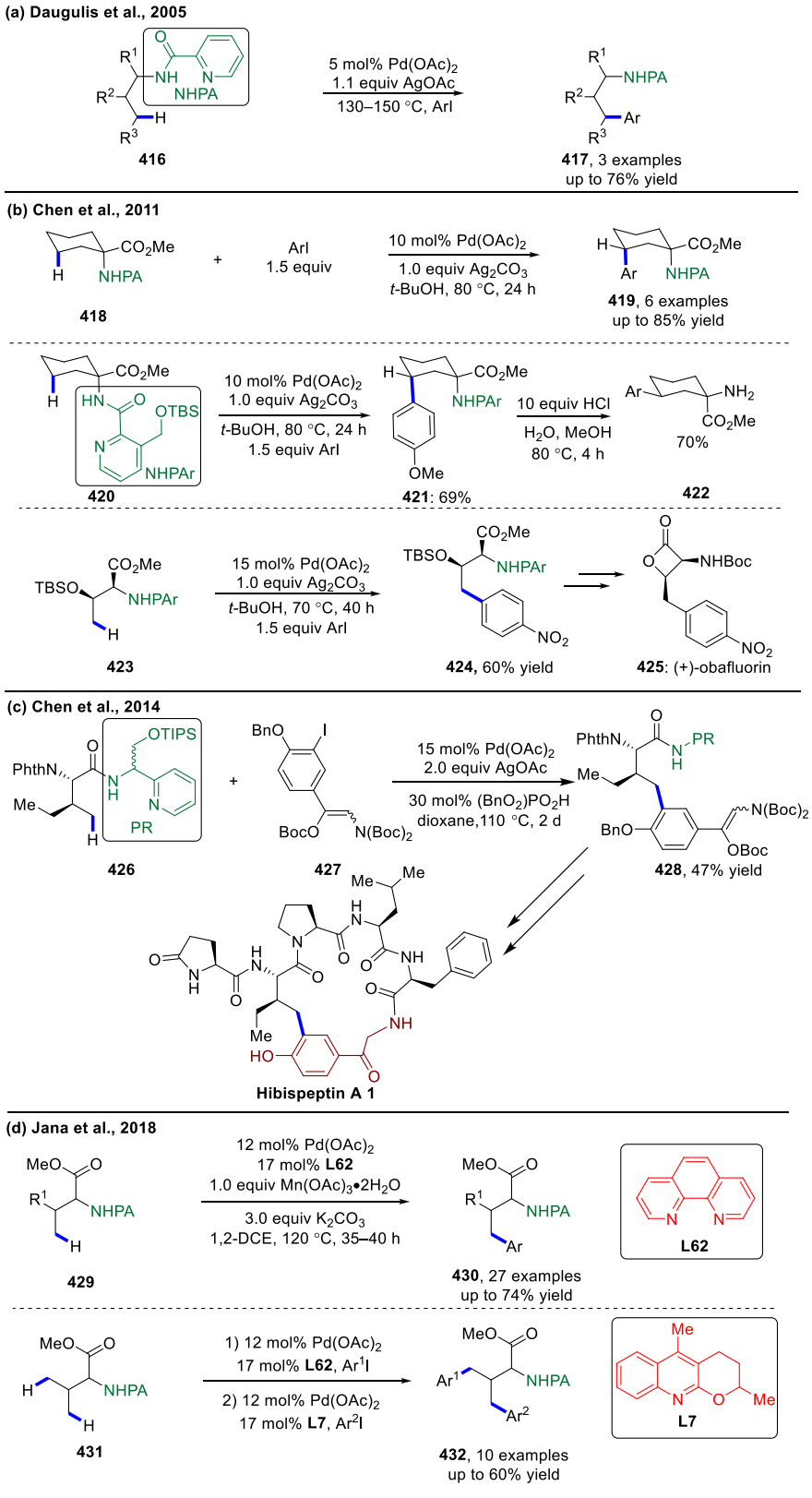
Scheme 74. (a) Pd-Catalyzed, Picolinamide-Directed γ-C(sp³)−H Arylation,[180] (b) Picolinamide-Directed C(sp³)−H Arylation and Formal Synthesis of (+)-Obafluorin,[221] (c) Total Synthesis of Hibispeptin A via Pd-Catalyzed C(sp³)−H Arylation Directed by Pyridylmethylamine-Based Auxiliary,[222] and (d) Picolinamide-Directed-C(sp³)−H Arylation for the Formation of Unnatural Amino Acid Derivatives[223]



bonds of cyclopentane and cyclohexane carboxamides at room temperature (Scheme 68d).[205]

In 2017, the Daugulis group reported a palladium-catalyzed, 8-aminoquinoline-directed β-C(sp³)−H arylation of phospho-

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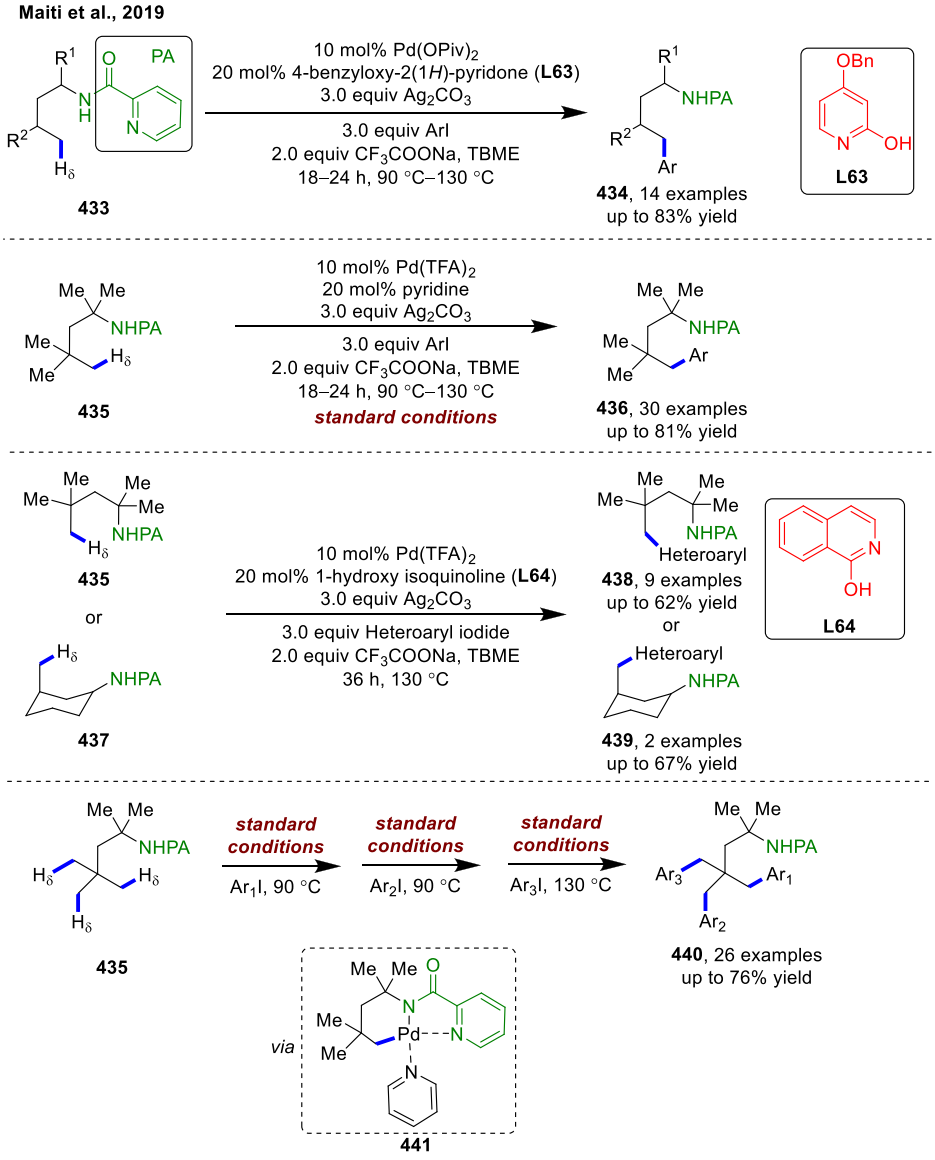
Scheme 75. Palladium-Catalyzed, Picolinamide-Directed δ-C(sp^3)−H Arylation[224]



namidates and phosphinic amides (Scheme 69a).[206] Unlike the arylation of aliphatic carboxamides, only primary C(sp^3)−H bonds could be functionalized in this protocol. Palladium-catalyzed, 8-aminoquinoline-directed arylation of γ-C(sp^3)−H bonds via a six-membered cyclopalladation pathway was developed by the Maiti group in 2017 (Scheme 69b).[207] In this case, the presence of substituents at the β-position is necessary to enable the activation of the typically less favored distal position.

While numerous reports have examined the use of aryl iodides as coupling partners in catalytic C(sp^3)−H arylation, other aryl electrophiles have been less extensively studied. In 2014, the Zeng group reported an intermolecular arylation of unactivated C(sp^3)−H bonds with aryl bromides with the assistance of the 8-aminoquinoline DG (Scheme 70a).[208] The reaction conditions are $Pd(TFA)_2$ (5 mol %), K_2CO_3 (3.5 equiv) as the base, and PivOH (50 mol %) as the additive in *t*-Amyl-OH at 120 °C for 36 h. In this system, various functional groups are well tolerated.

In 2013, the palladium-catalyzed direct arylation of primary and secondary C(sp^3)−H bonds with diarylhyperiodonium electrophiles with the assistance of the 8-aminoquinoline DG was reported by the Shi group (Scheme 70b).[209] Control experiments revealed that the reactivity of diarylhyperiodonium triflates is much higher than that of the corresponding aryl iodide under the same conditions. Moreover, the solubility of the counteranion of the diarylhyperiodonium salt was found to play a key role in the efficiency of this reaction. In 2015, the Qin group disclosed an unusual palladium-catalyzed direct arylation of secondary C(sp^3)−H bonds with (diacetoxyiodo)arene reagents, which are usually used as oxygen electrophiles in C−H acetoxylation (Scheme 70c).[210] In 2019, Boger and co-workers reported the secondary C(sp^3)−H arylation of a lysine derivative using diarylhyperiodonium electrophiles with the assistance of 8-aminoquinoline DG to provide a key intermediate (**377**) in the total synthesis of streptide (Scheme 70d).[211]

Saturated heterocycles are key building blocks in the synthesis of various bioactive compounds, including pharmaceuticals. The late-stage functionalization of these heterocycles could expand the structural diversity of screening libraries used in drug discovery. Palladium-catalyzed, directed C(sp^3)−H arylation of proline with the assistance of the 8-aminoquinoline DG was

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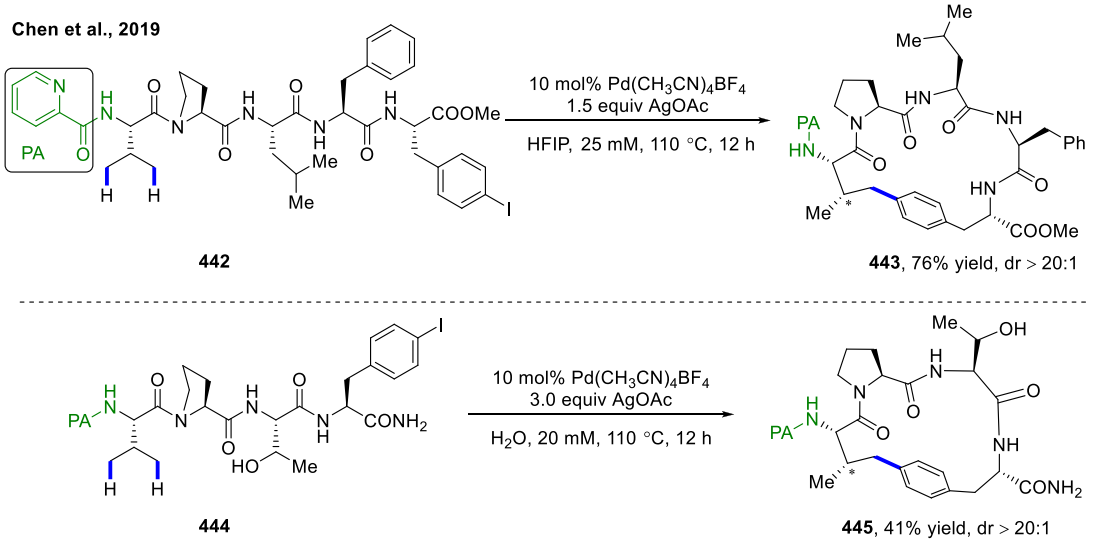
Scheme 76. Synthesis of Peptide Macrocycles via Palladium-Catalyzed, Picolinamide-Directed Intramolecular γ-C(sp^3)−H Arylation[225]



independently reported by the Bull and Zhang groups.[212−214] Stereospecific 8-aminoquinoline carboxamide-directed, palladium-catalyzed C(sp^3)−H arylation has been developed for a variety of backbones, such as pyrrolidines and piperidines by the Bull and Kazmaier groups,[215,216] tetrahydrofurans by the Babu group (Scheme 71),[217] and pyroglutamic acid derivatives[218] and azetidines[219] by the Schreiber group (Scheme 72). In 2018, Messaoudi and co-workers reported a palladium(II)-catalyzed, diastereoselective C(sp^3)−H activation of glycosyl carboxamides (Scheme 73).[220] They observed high yields of the C(sp^3)−H arylated products with β-glycosides. However, the α-glycosides under the same reaction conditions afforded arylated glucals that presumably arise from an AcOH elimination after the C(sp^3)−H arylation.

The first example of γ-C(sp^3)−H arylation of aliphatic amines using a strongly coordinating, pyridine-based *N,N*-bidentate DG was reported by Daugulis in 2005 (Scheme 74a).[180] Arylation of both primary and secondary γ-C(sp^3)−H bonds of aliphatic amine derivatives was achieved by employing a picolinamide (PA) auxiliary as the DG. Inspired by this study, a PA-directed, palladium-catalyzed γ-C(sp^3)−H arylation of aliphatic amines that could be run at substantially lower temperatures was reported by the Chen group in 2011 (Scheme 74b).[221] One of the main improvements is the use of equivalent aryl iodides instead of the use as solvent. In this system, the conformation of the C−H bond relative to the DG was observed to influence the regio- and stereoselectivity of this reaction. One disadvantage of these procedures is that the amide group of the PA auxiliary is difficult to cleave. In order to solve this problem, a modified picolinic acid was prepared based on the hypothesis that a silyl-protected hydroxymethyl group at the *ortho* position of the PA group would allow the auxiliary to retain its directing ability but would also facilitate amide cleavage through intramolecular acyl transfer upon treatment with acid. The application of this protocol was demonstrated in the synthesis of (+)-obafluorin from a readily accessible threonine derivative. In 2014, the Chen group also reported a new pyridylmethylamine-based auxiliary group for the total synthesis of hibispeptin A via Pd-catalyzed C(sp^3)−H arylation using a sterically hindered aryl iodide (Scheme 74c).[222] In 2018, the Jana group demonstrated that the picolinamide DG could also enable the efficient unsymmetrical γ-C(sp^3)−H diarylation of amino acids (Scheme 74d).[223] Ligands played a crucial role in promoting the reaction and tuning the mono- and unsymmetrical diarylations. They observed that bidentate 1,10-phenanthroline (**L62**) significantly improved the yield. Unsymmetrical diarylation was achieved by subjecting the monoarylated products to the second arylation conditions using quinoline-based ligand (**L7**).

In 2019, the Maiti and Paton groups reported a picolinamide-directed, palladium-catalyzed δ-C(sp^3)−H arylation of aliphatic amines via a six-membered palladacycle intermediate (Scheme 75).[224] Appropriately tuned ancillary ligands play a key role in this transformation. 4-Benzyloxy-2(1*H*)-pyridone (**L63**) was the best ligand for leucine, homoleucine, and analogous amine-derived substrates. Pyridine was identified as an efficient ligand to prevent the formation of diarylation byproducts when 2,4,4-trimethylpentan-2-amine (**435**) was employed as a substrate. Use of 1-hydroxy isoquinoline (**L64**) as ligand enabled more challenging heteroaryl iodides to serve as electrophilic coupling partners. Moreover, iterative arylation of 2,4,4-trimethylpentan-2-amine was also demonstrated (**435**). Interestingly, a pyridine coordinated [5,6]-fused cyclopalladated intermediate (**441**) was isolated and characterized. A set of control experiments revealed that intermediate **441** was a viable precatalyst for this transformation. DFT investigations indicated that the overall energy barrier was decreased significantly by employing the ligands due to their ability to break up the carboxylate-bridged trinuclear species that are otherwise stable in solution.

Although Chen and co-workers have developed an 8-aminoquinoline-directed, β-C(sp^3)−H arylation to generate peptide macrocycles,[190] the stereoselectivity of this protocol is limited. A subsequent report by the Chen group disclosed a PA-directed, γ-C(sp^3)−H arylation strategy to prepare peptide macrocycles with higher yield and stereoselectivity. Peptide **444**, which contains unprotected polar side chains, can also cyclize well in aqueous solution to give the corresponding cyclic peptide **445** (Scheme 76).[225]

Palladium-catalyzed, picolinamide-directed γ-C(sp^3)−H arylation of a variety of cycloalkyl amine derivatives, such as cyclopropyl methylamines,[226] 3-pinanamine,[227] cycloalkyl-amines,[228] rimantadine,[229] and saturated bicyclic amines,[230]

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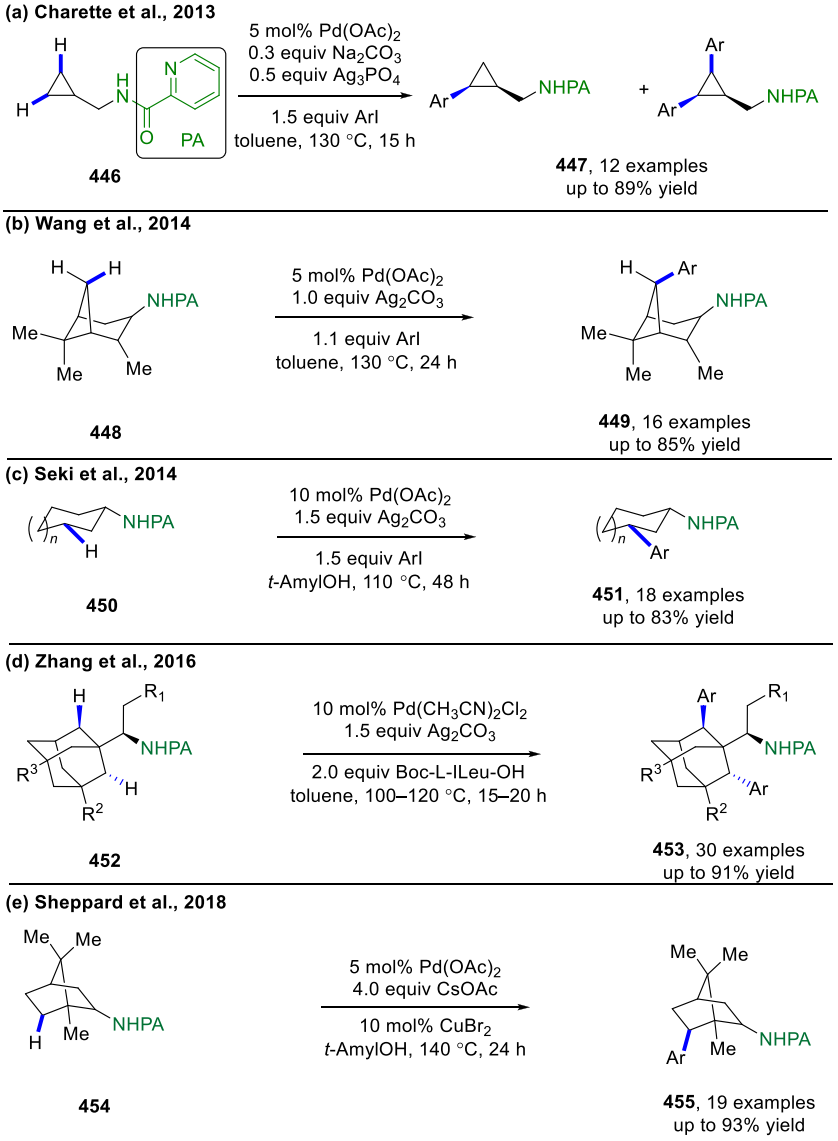
Scheme 77. Palladium Catalyzed, Picolinamide-Directed C(sp^3)−H Arylation of Aliphatic Carbocycles: (a) Cyclopropyl Methylamines;[226] (b) 3-Pinanamine;[227] (c) Cycloalkylamines;[228] (d) Rimantadine;[229] (e) Saturated Bicyclic Amines[230]



have been developed, further demonstrating the robustness of the picolinamide DG (Scheme 77).

In 2016, the Maes group reported picolinamide-directed, palladium-catalyzed C5-arylation of 3-aminopiperidine (Scheme 78a).[231] Upon use of catalytic 2,6-dimethylbenzoic acid as additive and a high reaction concentration, the yield of the products was improved significantly. In 2018, the Maulide group described the total synthesis of natural (−)-quinine and unnatural (+)-quinine using C(sp^3)−H arylation as a key step. Remarkably, unnatural (+)-quinine was synthesized for the first time, and its biological activity was studied (Scheme 78b).[232]

In 2013, the Shi group achieved the β-monoarylation of alanine using the newly developed 2-(pyridine-2-yl)isopropyl (PIP) DG.[233] After extensive screening, the conditions were found to be $Pd(OAc)_2$ (10 mol %), CuF_2 (1.5 equiv), and DMPU (5.0 equiv) in acetone (0.1 M) at 100 °C for 24 h. A range of aryl iodides that contain different functional groups were found to be compatible with this protocol, and the desired products were furnished in good yields with complete stereoselectivity under the reaction conditions (Scheme 79a). It is noteworthy that the PIP DG can also be removed in high yield without loss of enantiopurity of the arylated products through a mild *N*-nitrosylation/hydrolysis sequence.

The palladium-catalyzed direct arylation of unactivated methylene C(sp^3)−H bonds with aryl bromide reagents with the assistance of a PIP DG was reported by the Shi group in 2014 (Scheme 79b).[234] In this system, the reported reaction conditions are $Pd(OAc)_2$ (10 mol %), K_2CO_3 (2.5 equiv) as the base, and PivOH (20 mol %) as the additive in *t*-BuOH at 120 °C for 24 h. Both aryl iodide and bromide electrophiles are competent in this reaction as arylation reagents.

PIP-auxiliary-directed, palladium-catalyzed arylation of the C(sp^3)−H bonds was used as a key step in the syntheses of aeruginosin 98B and aeruginosin 298A by the Baudoin group in 2015 (Scheme 79c).[235] With PIP-amide as the DG in the presence of $Pd(OAc)_2$ as the catalyst and K_2CO_3 as the base, **467** underwent C(sp^3)−H arylation with *O*-benzyl-protected iodoarene **468** in CH_3CN to provide **469a** in 78% yield with complete regio- and stereoselectivity, even on gram scale. Cleavage of the PIP auxiliary under mild conditions with $NOBF_4$

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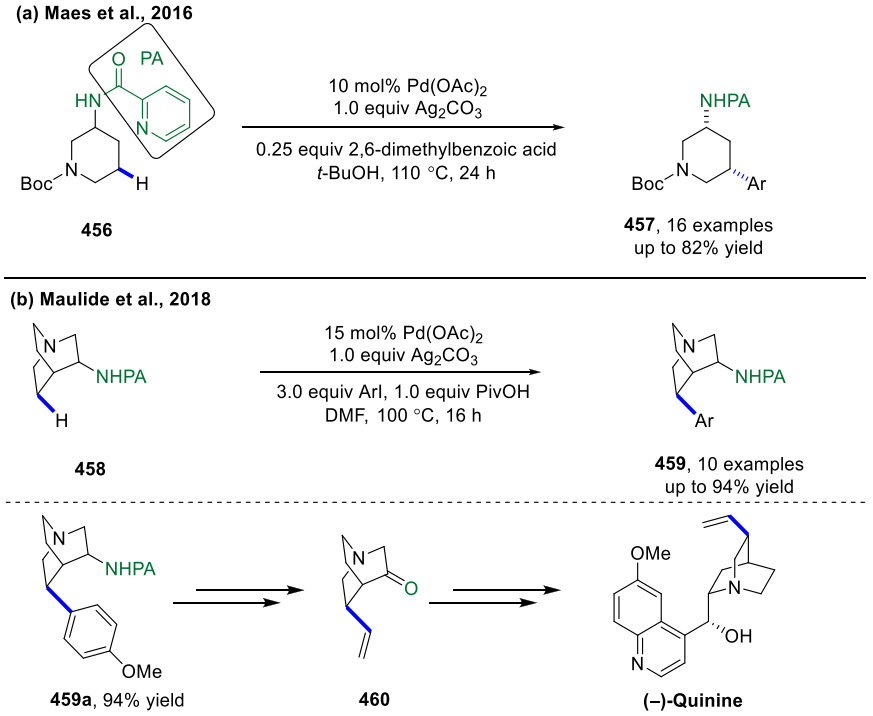
Scheme 78. (a) Palladium-Catalyzed, Picolinamide-Directed C(sp^3)−H Arylation of 3-Aminopiperidine[231] and (b) Total Synthesis of Quinine and Analogues Using Pd-Catalyzed C(sp^3)−H Arylation as a Key Step[232]



in pyridine at low temperature afforded the enantiopure carboxylic acid **470** in excellent yield. After several more steps, the aeruginosin family natural product syntheses were complete, with the aeruginosin 298A being made on an unprecedentedly large scale (700 mg).

Due to the difficulty in removal of the amide-derived DGs in complexed molecules, Baran and co-workers embarked on recognizing a more readily removable DG that can be removed under mild conditions. As demonstrated above, picolinamide has been recognized as a powerful DG in C(sp^3)−H functionalization. They rationalized that a picolinimide-based DG could meet this requirement, since imides are generally more labile to hydrolysis than amides. Based on this rationalization and after condition optimization, they successfully achieved the picolinimide-directed C(sp^3)−H diarylation of cyclobutane, and the picolinimide DG was easily removed with ammonia and catalytic scandium(III) trifluoromethanesulfonate (Scheme 80a).[236] Shortly after, 2-picolinimide was used by the Shi group as an efficient DG to assist the palladium-catalyzed C(sp^3)−H arylation of various simple aliphatic carboxylic acids (Scheme 80b).[237] The reaction was highly site-selective, favoring β-methyl C−H bonds for arylation over β-methylene, γ-methyl, benzene C−H, and β-benzylic C−H bonds. Therefore, a sequential methyl and methylene C(sp^3)−H arylation with different aryl iodides was achieved. Finally, the picolinimide can be easily cleaved by hydrolysis with $LiOH/H_2O_2$ at room temperature in a short time to give the corresponding free carboxylic acids or amides in high yields.

Due to the importance of the bidentate DG strategy in transition-metal-catalyzed C(sp^3)−H bond activation reactions, a variety of other *N*,*N*-bidentate, monoanionic DGs have also been developed. These *N*,*N*-bidentate, monoanionic DGs are similar to PA or AQ in that they connect through a native nitrogen or carboxylic acid, but they are easier to remove. In 2013, the palladium-catalyzed monoarylation of primary γ-C(sp^3)−H bonds of amino acid methyl esters that contain the easily detachable *N*-(2-pyridyl)sulfonyl DG was reported by Carretero and co-workers (Scheme 81a).[238] An unprecedented C(sp^3)−H arylation of dipeptides was also demonstrated with this method. Notably, the *N*-(2-pyridyl)sulfonyl auxiliary can be removed in one step when treated with Zn powder at 60 °C in a THF/NH_4Cl (aq) mixture for 16 h, giving the free primary amine in good yield. In 2013, a 2-methoxyiminoacetyl (MIA)-directed, palladium-catalyzed γ-arylation of substituted 2-aminobutanates was reported by Fan and Ma (Scheme 81b).[239] The MIA auxiliary could be removed easily by hydrolysis with 1 N KOH in 1,4-dioxane at room temperature. It could also be readily transformed into a glycine moiety, which could be used in peptide synthesis. A removable oxazoline-carboxylate auxiliary was developed by the Shi group for the direct arylation of γ-methylene C(sp^3)−H bonds of amine derivatives (Scheme 81c).[240] A wide range of aryl iodide reagents with different substituents were compatible under the reaction conditions. However, low diastereoselectivity was observed in the arylation of aliphatic γ-C(sp^3)−H bonds with substrates that bear chiral oxazoline-carboxylate auxiliaries.

Easily accessible, modular 1,2,3-triazole-type bidentate DGs, which are readily available through Cu(I)-catalyzed 1,3-dipolar cycloadditions, were first introduced by the Ackermann group for iron-catalyzed C−H arylation in 2014.[241] The modular properties enabled the diverse synthesis of various *N*-substituted 1,2,3-triazole DGs. In 2015, Ding and co-workers developed a palladium-catalyzed methyl C(sp^3)−H arylation of alanine with the assistance of *N*-hexyl 1,2,3-triazole amide bidentate DG (Scheme 82a).[242] In 2018, the Ackermann group reported the palladium-catalyzed methylene C(sp^3)−H arylation of phenylalanine derivative (**484**) with *N*-benzyl 1,2,3-triazole amide bidentate DG (Scheme 82b).[243] An unprecedented methyl C(sp^3)−H arylation of the internal triazole peptides was also achieved using 1,2,3-triazole amide as both bidentate DG and

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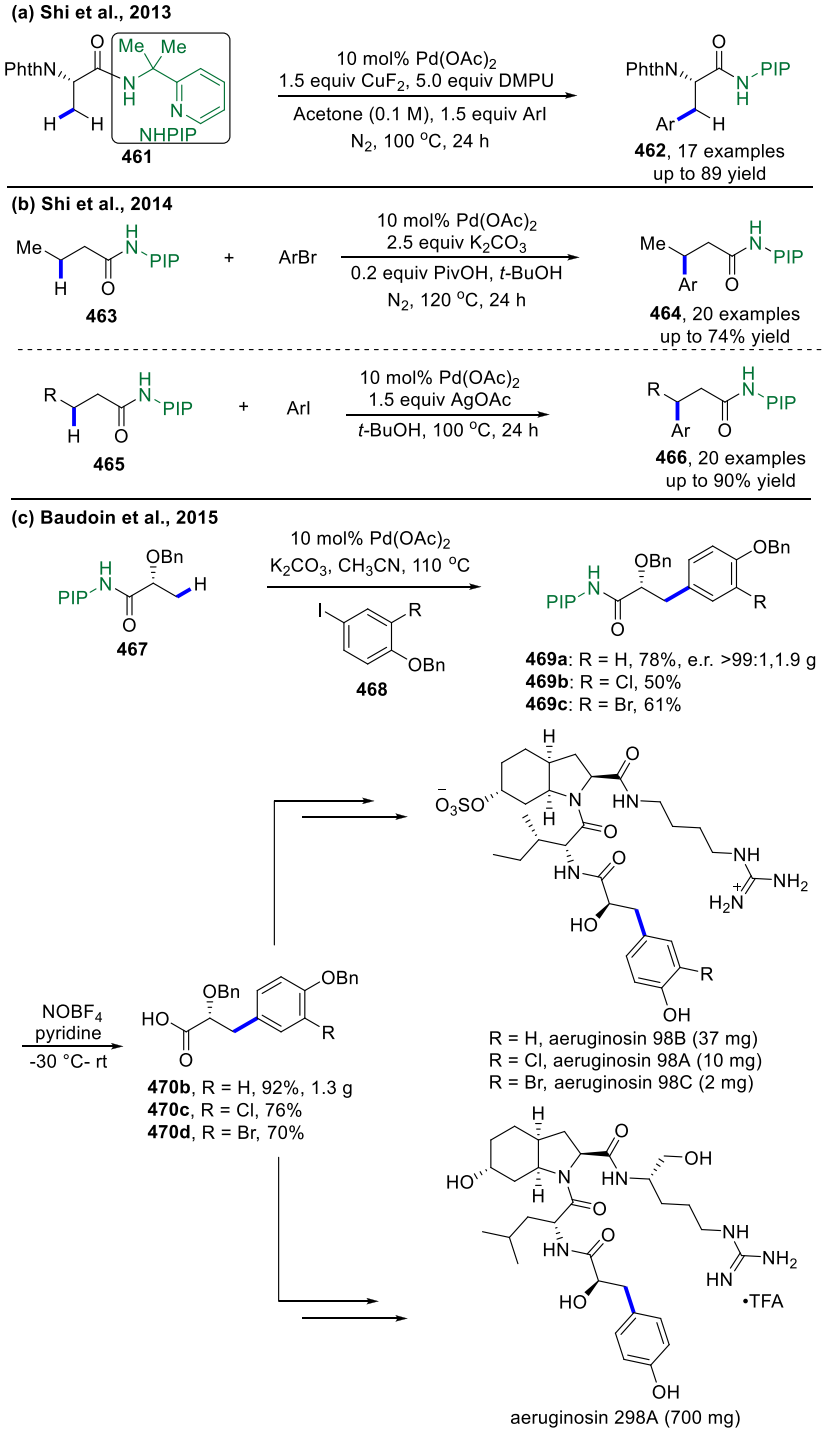
Scheme 79. (a) Pd-Catalyzed, PIP-Directed β-C(sp^3)−H Monoarylation of Bonds of Alanine,[233] (b) Pd-Catalyzed, PIP-Directed Methylene C(sp^3)−H Arylation with Aryl Bromides,[234] (c) PIP-Directed C(sp^3)−H Arylation as a Key Step in the Total Synthesis of Aeruginosins 98B and 298A[235]



peptide bond isostere. The Ackermann group also used a triazole-assisted C(sp^3)−H arylation strategy to introduce BODIPY fluorescent dyes into peptides (Scheme 82c)[244] and cyclobutanes (Scheme 82d).[245]

A type of easily available bidentate amino oxazoline DG was developed by the Shi group in 2015. Pd-catalyzed secondary C(sp^3)−H arylation of aliphatic carboxamides directed by this modifiable amino oxazoline DG was investigated. When a phenylalaninol-derived chiral amino oxazoline DG was used, diastereoselective benzylic C(sp^3)−H arylation proceed in moderate yields with good diastereoselectivity (Scheme 83a).[246] In 2015, a diastereoselective, β-methylene C(sp^3)−H bond arylation of cyclopropanes using an isoleucine-derived bidentate DG was developed by the Hong group (Scheme 83b).[247] They concluded that the diastereoselectivity was determined under Curtin−Hammett control in the oxidative addition step because C−H activation at either diastereotopic hydrogen is relatively facile.

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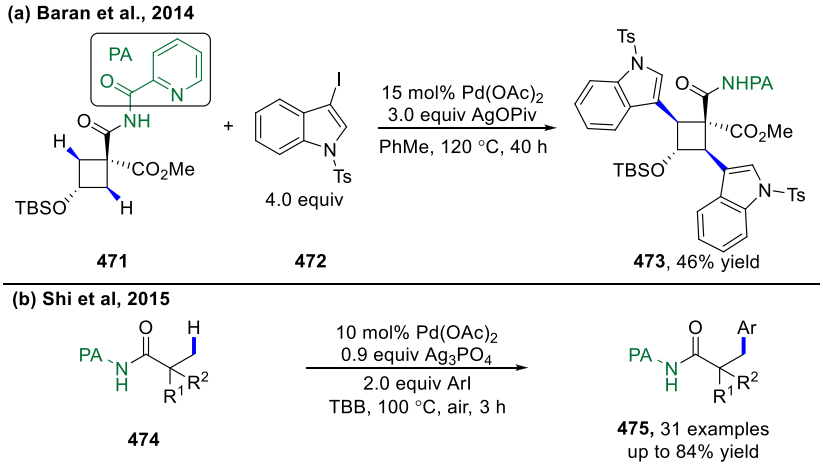
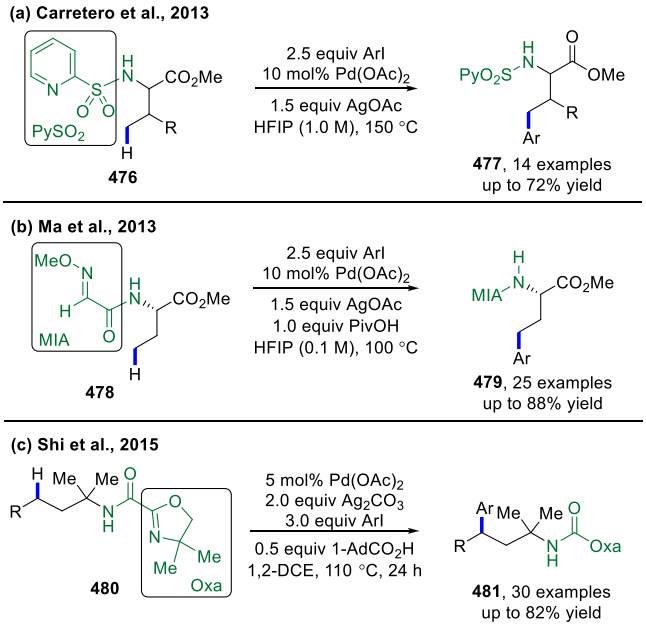
Scheme 80. (a) Picolinamide-Directed C(sp^3)−H Arylation of Cyclobutane Reported by the Baran Group[236] and (b) Picolinamide-Directed C(sp^3)−H Arylation Reported by the Shi Group[237]



Scheme 81. (a) *N*-(2-Pyridyl)sulfonyl Amide-Directed γ-C(sp^3)−H Arylation of Amino Acid Derivatives,[238] (b) MIA-Directed Palladium-Catalyzed γ-C(sp^3)−H Arylation of Substituted 2-Aminobutanates,[239] and (c) Palladium-Catalyzed, Amino Oxazoline Carboxylate-Directed γ-Methylene C(sp^3)−H Arylation[240]



Other *N*,*N*-bidentate auxiliaries for C(sp^3)−H arylation of aliphatic carboxylic acids, such as 5-methylisoxazole-3-carboxamide (Scheme 84a, MICA),[248] 4-amino-2,1,3-benzothiadiazole (Scheme 84b),[249] 2-methyl-7-aminobenzoxazole (Scheme 84c),[250] and 2-dimethylaminoethylamine (Scheme 84d),[251] have also been reported.

Generally, methods for the C−H functionalization of saturated azaheterocycles are dominated by functionalization of the highly activated C−H bonds α to nitrogen or the C−H bonds on exocyclic alkyl groups. In 2016, Sanford and co-workers developed a palladium-catalyzed transannular C−H arylation of a variety of alicyclic amines at sites remote from nitrogen (Scheme 85a).[252] An amide derived from *p*-$CF_3C_6F_4NH_2$ was found to be the most effective bidentate DG for activation of transannular secondary C(sp^3)−H bonds over C−H functionalization at the β-methyl sites. The conditions are as follows: $Pd(OAc)_2$ (5 mol %) with CsOPiv (3.0 equiv) in *t*-Amyl-OH at 130 °C for 18 h. The scope of the reaction is broad, tolerating a myriad of functional groups on the aryl iodide coupling partner, such as bromides, unprotected hydroxyl groups, and aldehydes. However, under standard conditions, only 12% yield of the corresponding C−H arylated product **512** was obtained with piperidine substrate **511**. The yield was improved to 44% by increasing the temperature and removing the solvent. Aminal formation is observed in the reaction for both the starting material and the product due to proximal C−H amination, which allowed them to isolate 55% of the desired product upon workup with $NaBH_4$. This method affords a variety of arylated alicyclic amines that would be challenging to prepare by traditional synthetic routes. Computational evidence suggests that excess ArI (30 equiv) is required to make the oxidative addition step favorable by thermodynamically overcoming the high energy requirements to form the C−H activation intermediate.[253]

In 2018, the Sanford group was able to lower the reaction temperature and reduce the equivalents of aryl iodides by employing pyridine-carboxylate (**L65**) and quinoline-carboxylate (**L66**) ligands that slow the decomposition of the catalyst (Scheme 85b).[254]

As a complement to the extensively studied *N*,*N*-bidentate DGs, *N*,*O*-bidentate DGs have also been explored as they likely facilitate the oxidation of Pd(II) to Pd(IV) because of increased electron density at the Pd(II) center. In 2015, Song, Niu, and co-workers disclosed a palladium-catalyzed β-methyl C(sp^3)−H arylation directed by a 2-aminopyridine-1-oxide moiety that proceeds without using silver salt additives as is required in comparable *N*,*N*-bidentate-directed reactions (Scheme 86a).[255] At nearly the same time, the Lu group reported a palladium-catalyzed, pyridine-*N*-oxide-directed β-methylene C(sp^3)−H arylation (Scheme 86b).[256] In this case, the addition of AgOAc significantly promoted this transformation and enabled the arylation of more challenging methylene C(sp^3)−H bonds.

The Zhao group developed an oxalyl amide as an *N*,*O*-bidentate DG for γ-C(sp^3)−H arylation of both aliphatic amines (Scheme 87a)[257] and amino acids derived from the amine units (Scheme 87b).[258] A wide array of functional groups are tolerated under the reaction conditions. Although a range of bidentate DGs have been developed for the effective C(sp^3)−H activation

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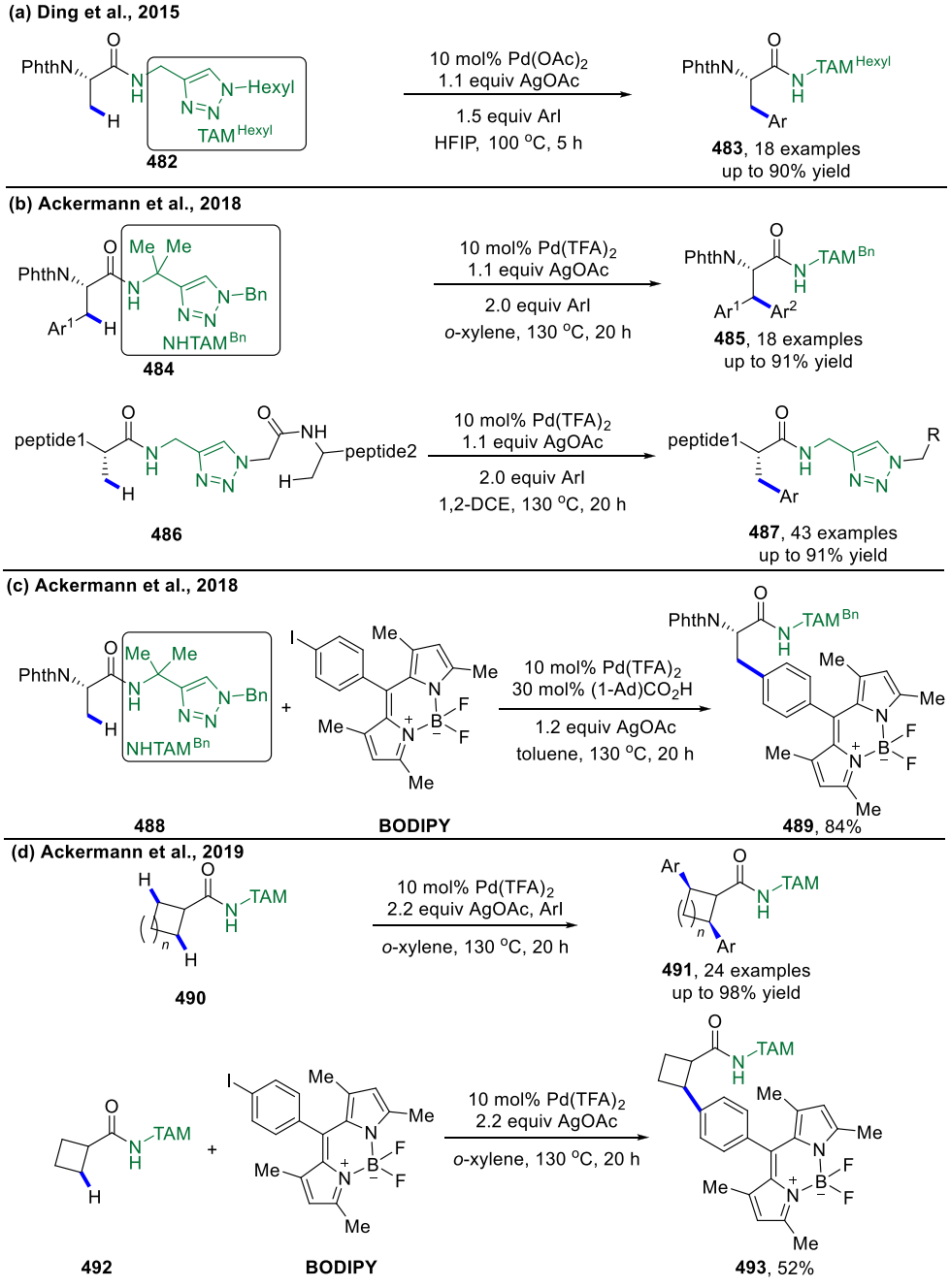
Scheme 82. (a) Pd-Catalyzed, Triazole-Directed Methyl C(sp^3)−H Arylation of Alanine C(sp^3)−H,[242] (b) Triazole-Directed Primary and Secondary C(sp^3)−H Arylation of Phenylalanine and Internal Isosteric Triazole Peptides,[243] (c) C(sp^3)−H Arylation for BODIPY Labeling of Peptides,[244] and (d) Methylene C(sp^3)−H Arylation for BODIPY Labeling of Cyclobutanes[245]



of carboxylic acids, the established reactions generally proceeded from the formation of five- or six-membered palladacycles and few examples occurred via seven-membered palladacycles. In 2016, Zhao and co-workers developed a new *N,O*-bidentate DG, glycine dimethylamide, which was efficient for *β*-C(sp^3)−H arylation of aliphatic carboxylic acids with *ortho*-substituted aryl iodides, a type of very challenging coupling partner for C−H arylation. Notably, the glycine dimethylamide bidentate DG could promote a subsequent intramolecular C(sp^2)−H amination to prepare 2-quinolinones through seven-membered palladation (Scheme 87c).[259] In 2018, Maiti and co-workers used 3-amino-1-methyl-1*H*-pyridin-2-one as an *N,O*-bidentate DG for both *β*- and *γ*-C(sp^3)−H arylation of carboxylic acid derivatives (Scheme 87d).[260] This protocol is efficient for direct arylation of both *β*-methylene and *γ*-methyl C(sp^3)−H bonds.

Inspired by the discovery that mono-*N*-protected amino acid ligands promote Pd(II)-catalyzed C(sp^3)−H activation through initial *N,O*-bidentate coordination, Yu and co-workers reasoned that native amino acids embedded in a peptide backbone could also bind to Pd(II) and facilitate activation of C(sp^3)−H bonds in the adjacent amino acid unit. As envisaged, arylation of C(sp^3)−H bonds at the N-terminus of various peptides could indeed be accomplished through native directivity without the need to install an external auxiliary (Scheme 88a).[261] Moreover, tri- and tetrapeptides could also be arylated with a wide range of

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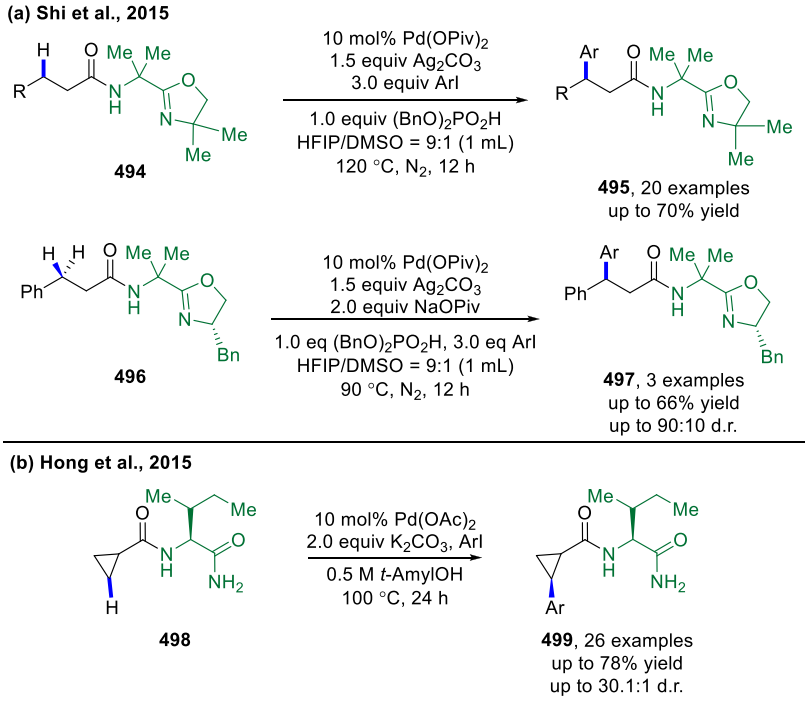
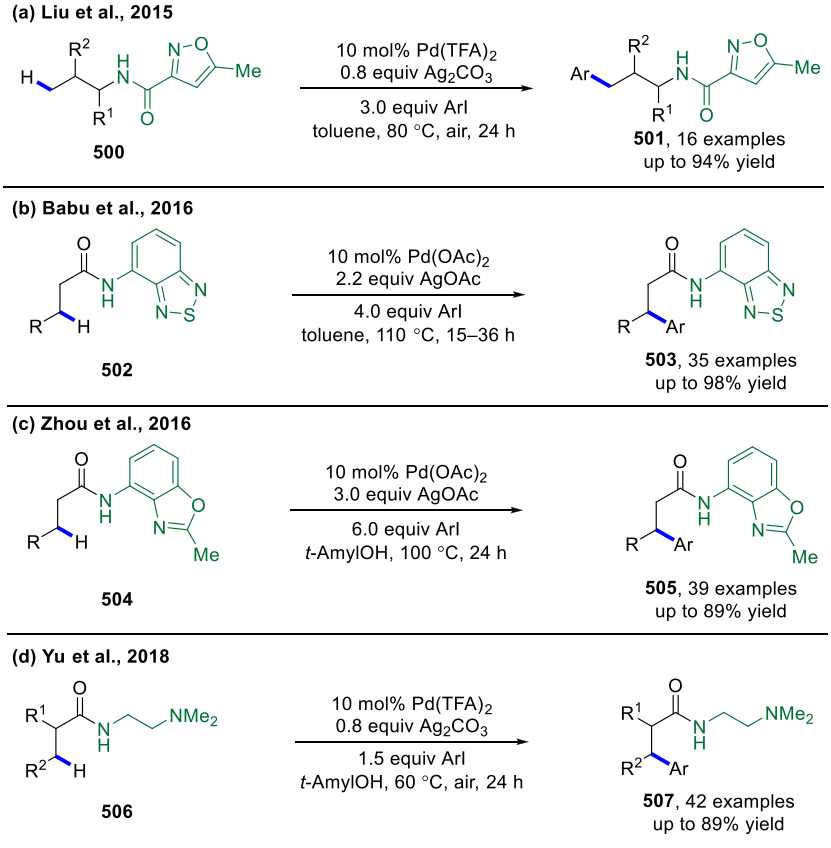
Scheme 83. (a) Amino Oxazoline-Directed γ-Methylene C(sp^3)−H Arylation[246] and (b) Isoleucine-NH$_2$-Directed C(sp^3)−H Arylation Reported by the Hong Group[247]



Scheme 84. (a) Isoxazole Carboxamide-Directed γ-C(sp^3)−H Bond Activation of α-Aminobutanoic Acid Derivatives,[248] (b) 4-Amino-2,1,3-benzothiadiazole-Directed β-C−H Arylation/Oxygenation of Carboxamides,[249] (c) 2-Methyl-7-aminobenzoxazole-Directed β-C(sp^3)−H Arylation,[250] (d) Aliphatic Diamine-Directed β-C(sp^3)−H Arylation[251]



aryl iodides to afford peptides with modified phenylalanine residues, which demonstrates the applicability of the Pd-catalyzed, directed C(sp^3)−H activation strategy in peptide synthesis and late-stage modifications.

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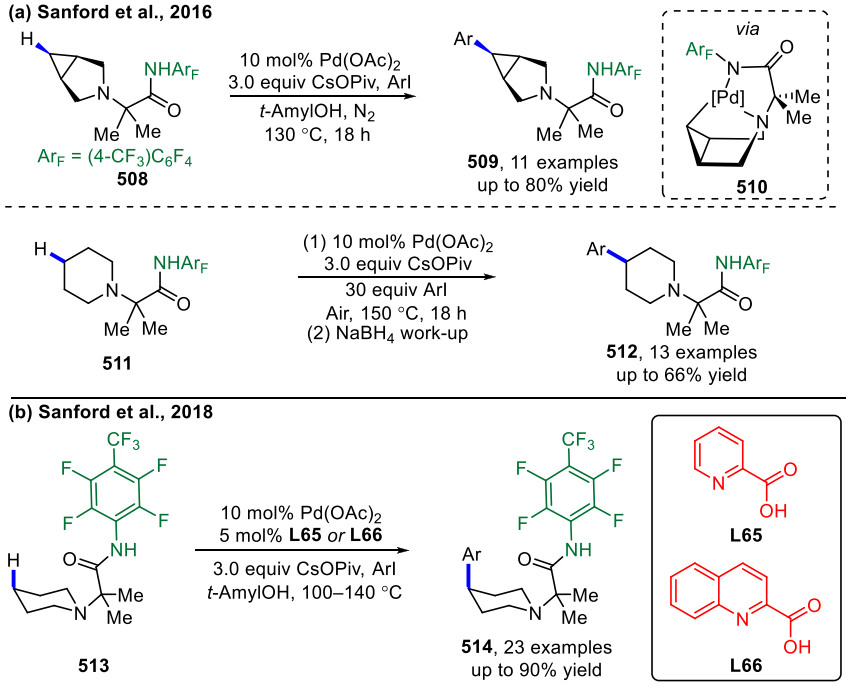
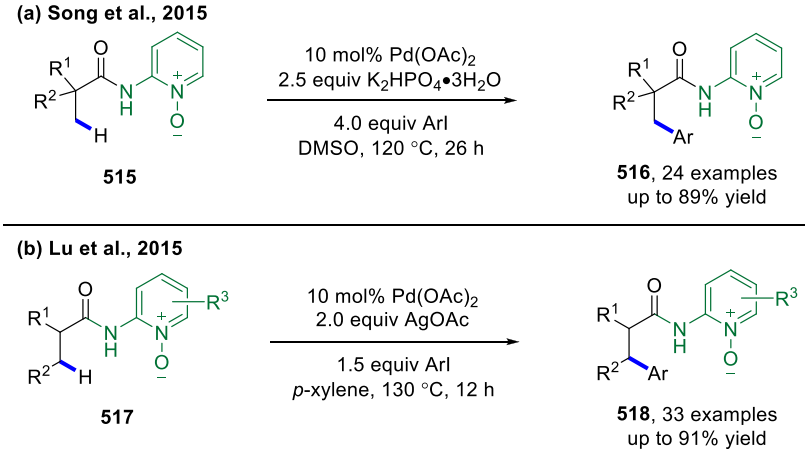
Scheme 85. (a) CONHAr$_F$ (Ar$_F$ = *p*-CF$_3$C$_6$F$_4$)-Directed Transannular C(sp^3)−H Arylation[252] and (b) CONHAr$_F$ (Ar$_F$ = *p*-CF$_3$C$_6$F$_4$)-Directed Transannular C(sp^3)−H Arylation of Azabicycloalkanes Enabled by Monodentate Nitrogen Ligand[254]



Scheme 86. Palladium-Catalyzed, 2-Aminopyridine-1-oxide-Directed C−H Arylation: (a) Methyl C(sp^3)−H Arylation;[255] (b) Methylene C(sp^3)−H Arylation[256]



The initial investigation of the reaction conditions with *N*-phthaloyl protected dipeptide as a substrate revealed that with use of hexafluoroisopropyl alcohol (HFIP) as solvent, full conversion of the substrate was observed. Further screening indicated that with removal of KF, higher selectivity for monoarylation of the dipeptide at the expense of yield was achieved. A wide range of aryl iodides that possess electron-donating or -withdrawing groups at the *ortho*, *meta*, or *para* position are competent coupling partners, and the desired products were isolated in good yields.

Various amino acids both at the C-terminus and N-terminus have also been surveyed. When a tripeptide was subjected to the optimized conditions, the presence of a carboxylic acid at the C-terminus inhibited the arylation and provided only 20% of the desired product. To remedy this problem, the benzyl or methyl ester starting material was used, and the yield increased greatly. Remarkably, selective arylation of tetrapeptides at the N-terminus has also been realized through minor modification of the reaction conditions. Based on the above results, the Yu group explored the functionalization of *O*-protected *α*-hydroxy aliphatic acid derivatives by utilizing an amino acid DG (Scheme 88b).[262] A wide range of *β*-aryl-*α*-hydroxy acids were obtained in moderate to good yields without unwanted epimerization of the stereocenters.

In 2017, the Albericio[263] and Wang[264] groups independently described the synthesis of macrocyclic peptides by means of amino acid backbone-directed, intramolecular *β*-C(sp^3)−H arylation (Scheme 89). A variety of cyclic peptides were prepared using this C(sp^3)−H arylation protocol in moderate to good yields, demonstrating the power of C−H activation strategy.

In 2017, Yu and co-workers discovered that 2,2-dimethyl aminooxyacetic acid is a competent bidentate auxiliary for *β*-C(sp^3)−H arylation of ketones via Pd(OAc)$_2$ catalysis (Scheme

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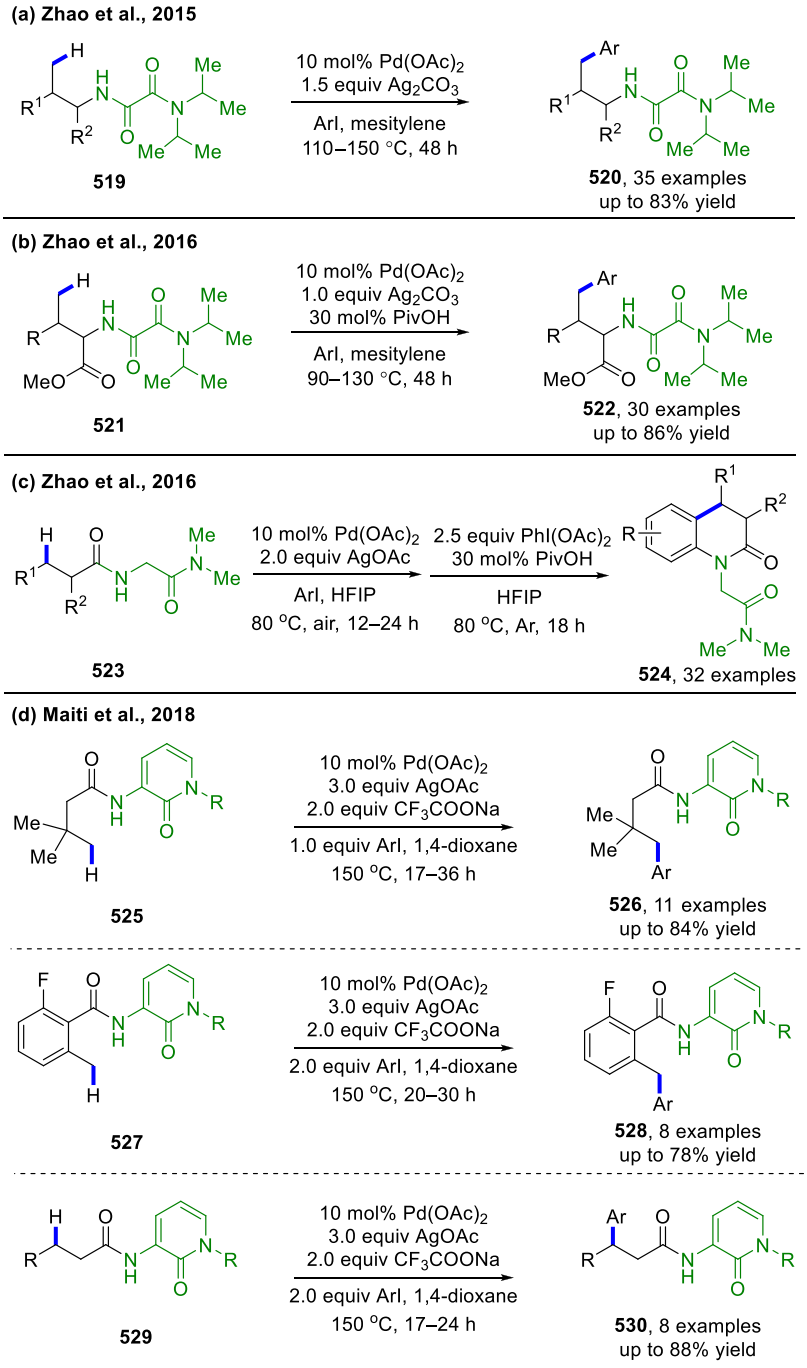
Scheme 87. Palladium-Catalyzed C(sp^3)−H Arylation Directed by *N,O*-Bidentate DGs: (a) Oxalyl Amide-Directed γ-C(sp^3)−H Arylation of Amines;[257] (b) Oxalyl Amide-Directed γ-C(sp^3)−H Arylation of Amino Acids[258] (c) Glycine Dimethylamide-Directed β-C(sp^3)−H Arylation of Aliphatic Carboxylic Acids;[259] (d) 3-Amino-1-methyl-1*H*-pyridin-2-one-Directed C(sp^3)−H Arylation of Carboxylic Acids[260]



90a). This directing auxiliary addresses many of the limitations in catalytic β-C(sp^3)−H arylation of ketones and derivatives thereof, such as limited ability to funtionalize methylene C(sp^3)−H bonds and narrow functional group tolerance.[265] During the DG optimization process, the Yu group found that the presence of *gem*-dimethyl substitution at the 2-position of the aminooxyacetic acid drastically increases the yield from 10% to 80%, which is attributed to the Thorpe−Ingold effect.[233] The utility of this transformation was demonstrated by direct C(sp^3)−H (hetero)arylation of santonin. Extension of this protocol to remote γ-C(sp^3)−H functionalization of ketones, however, was unsuccessful. Based on the proposed transition state, Yu and colleagues reasoned that an X-type ligand that displaces the acetate could accelerate the C−H activation step of γ-C(sp^3)−H functionalization. After extensive screening of 2-pyridone ligands, 2-pyridone (**L67**) bearing a nitro group at the 5-position was found to improve the yield to 70% in conjunction with the 2,2-dimethyl aminooxyacetic acid bidentate auxiliary (Scheme 90b).[266] Yu and co-workers also developed a pyruvic acid-derived DG for activation of γ-C(sp^3)−H bonds in preference to the β-C(sp^3)−H bonds of aliphatic alcohol-derived substrates (Scheme 90c).[267] The design principle for

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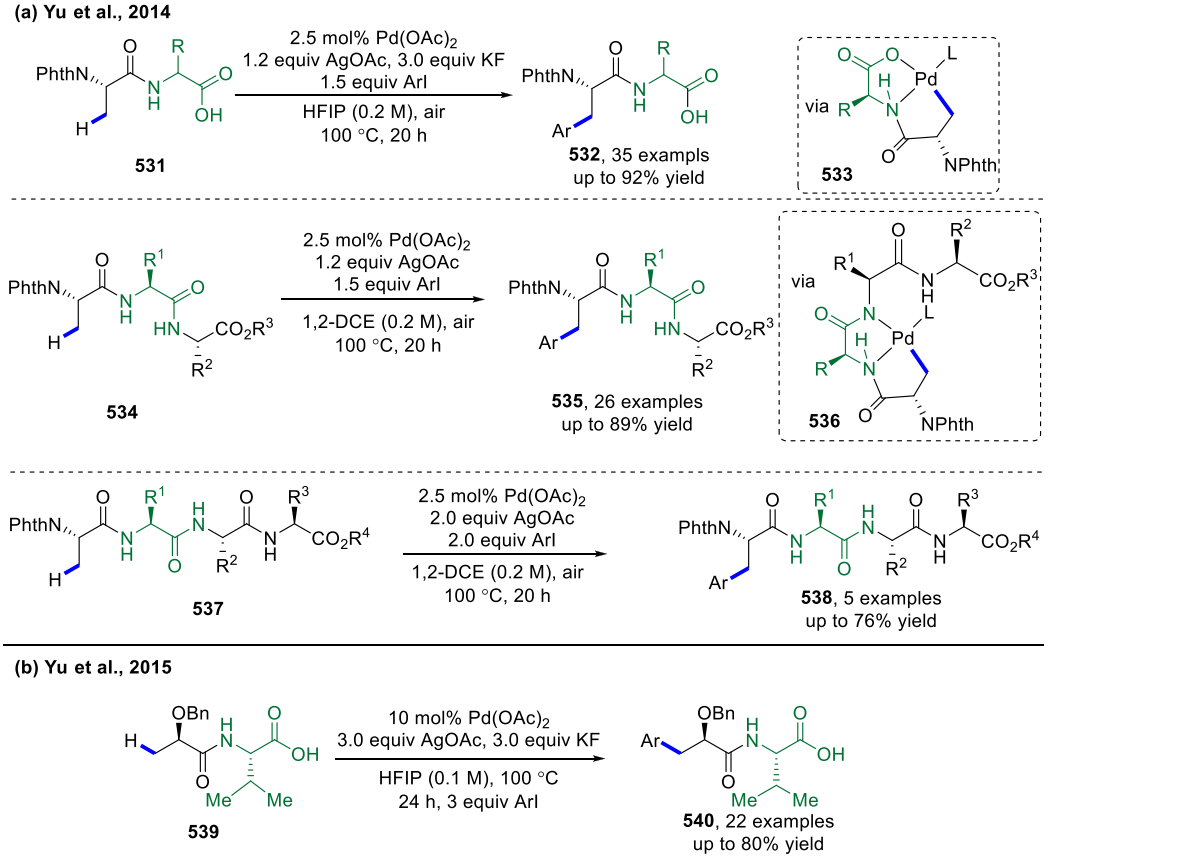
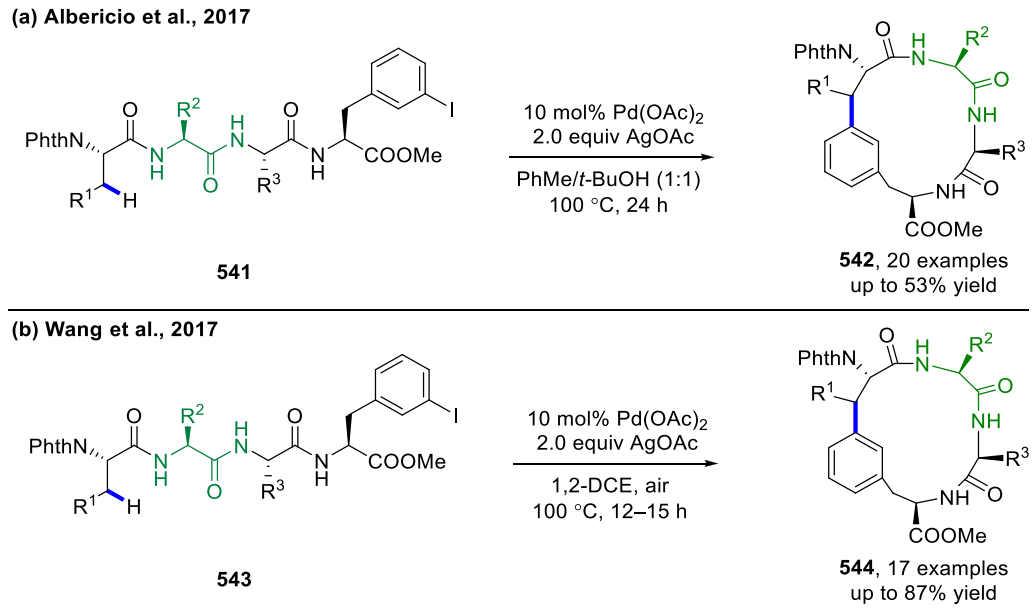
Scheme 88. (a) Amino Acid Backbone-Directed C(sp^3)−H Arylation[261] and (b) Amino Acid-Directed C(sp^3)−H Arylation of α-Hydroxy Acid Derivatives[262]



Scheme 89. Amino Acid-Directed C(sp^3)−H Arylation for Preparing Macrocyclic Peptides by (a) Albericio et al.[263] and (b) Wang et al.[264]



this DG was to destabilize the [5,5]-fused ring system compared to the alternative [5,6]-fused ring system by introducing a C−C double bond into the bicyclic structure, which increases ring strain in the former, thereby favoring six-membered cyclopalladation. Electron-deficient 2-pyridone ligands are required for this transformation as they stabilize the palladium catalyst and lower the transition-state energy for the C−H activation step. With the newly designed DG and optimized ligand (**L68**), arylation of both primary and secondary γ-C(sp^3)−H bonds could be achieved on acyclic and cyclic alcohols even in the presence of β-C(sp^3)−H bonds. A subsequent computational study reported by Dang and co-workers proposes an "outer-

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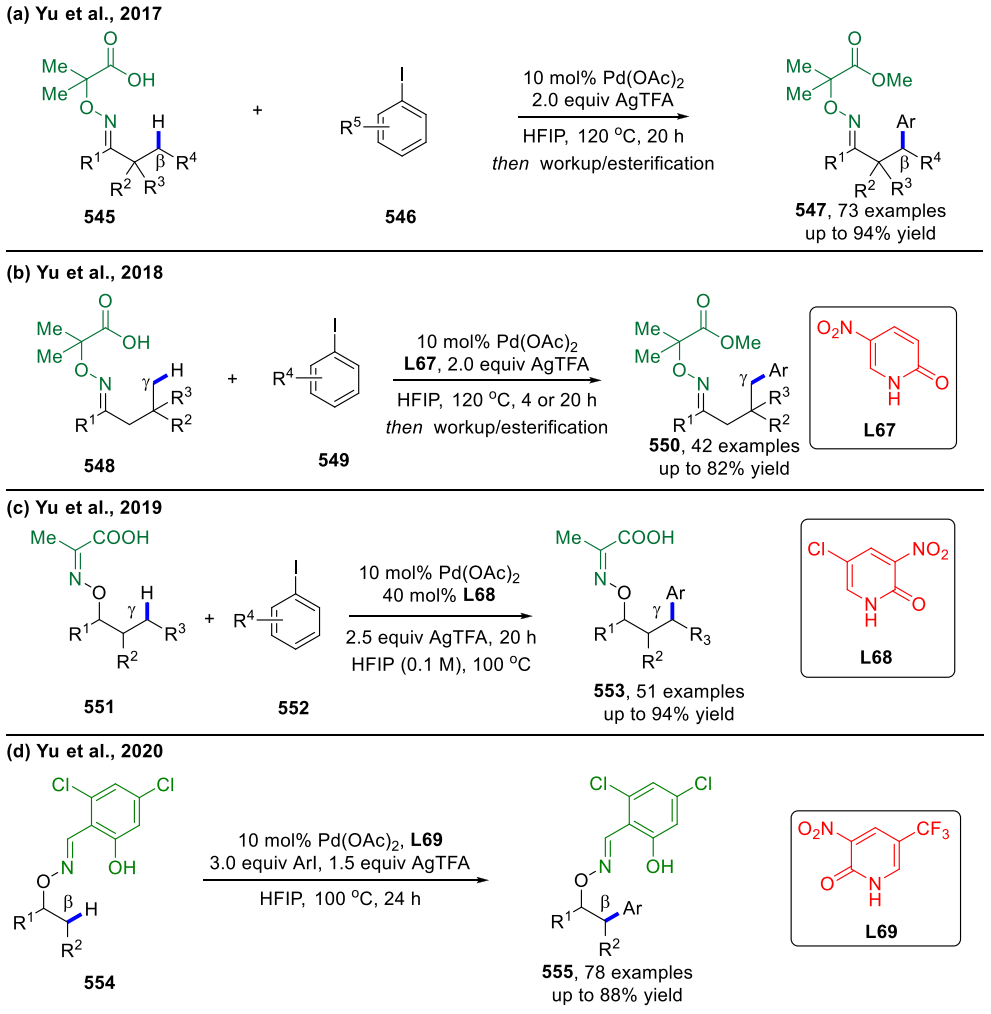
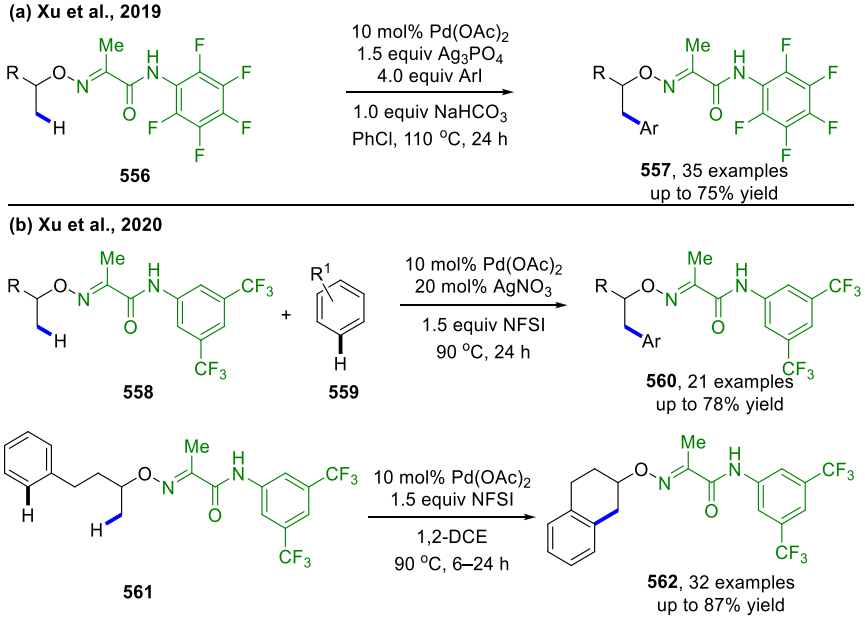
Scheme 90. (a) Palladium-Catalyzed β-C(sp^3)−H Arylation of Ketones Directed by 2,2-Dimethyl Aminooxyacetic Acid,[265] (b) Ligand-Enabled γ-C(sp^3)−H Arylation of Ketones Directed by 2,2-Dimethyl Aminooxyacetic Acid,[266] (c) Ligand-Enabled γ-C(sp^3)−H Arylation of Aliphatic Alcohols Directed by Pyruvic Acid Derived DG,[267] and (d) Ligand-Enabled β-C(sp^3)−H Arylation of Aliphatic Alcohols Directed by Dichloro-Substituted Salicylic Aldehyde Derived DG[269]



Scheme 91. Palladium-Catalyzed β-C(sp^3)−H Arylation of Alcohols[270,271]



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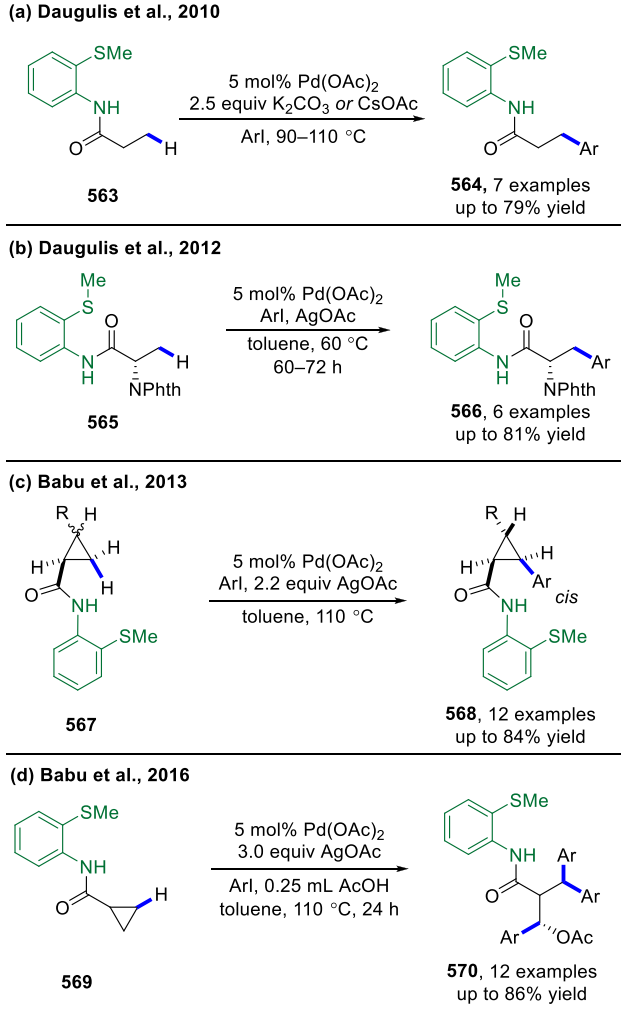
Scheme 92. (a) Pd-Catalyzed β-Methyl C(sp^3)−H Monoarylation of 2-Methylthioanilide Amides,[181] (b) β-Methyl C(sp^3)−H Monoarylation of *N*-Phthaloylalanine Derivatives,[196] (c) 2-Thiomethylamide-Directed β-C(sp^3)−H Arylation of Cyclopropanes,[202] and (d) 2-Thiomethylamide-Directed β-C(sp^3)−H Arylation/Ring Opening of Cyclopropanes[272]



sphere" mechanism that favors six-membered cyclopalladation, which contrasts with the often considered "inner-sphere" process that proceeds through a five-membered cyclopalladium intermediate.[268] By changing the [5,6]-fused palladacycle to the [6,5]-fused palladacycle using dichloro-substituted salicylic aldehydes as the DG, arylation of secondary β-C(sp^3)−H bonds of aliphatic alcohols was realized by Yu and co-workers in 2020 (Scheme 90d).[269] 2-Pyridone ligands remain the best choice for this transformation, and an electron-deficient pyridine (**L69**) was found to be optimal.

N-Pentafluorophenyl-pyruvamide-directed, palladium(II)-catalyzed primary β-C(sp^3)−H arylation of aliphatic alcohols was reported by the Xu group in 2019 (Scheme 91a).[270] Later, *N*-(3,5-ditrifluoromethylphenyl) pyruvamide was developed for both intra- and intermolecular cross-dehydrogenative-coupling (CDC) reactions between primary β-C(sp^3)−H bonds of aliphatic alcohols and C(sp^2)−H bonds of arenes (Scheme 92b).[271]

N,*S*-Bidentate DGs were pioneered by the Daugulis group in 2010 when they observed that selective monoarylation of primary C(sp^3)−H bonds in aliphatic acid substrates can be realized by using a 2-thiomethylthioaniline auxiliary, which provided improved selectivity in this reaction compared to 8-aminoquinoline (Scheme 92a).[181] By employing the same DG, Tran and Daugulis in 2012 demonstrated the monoarylation of the primary β-C(sp^3)−H bond of *N*-phthaloylalanine derivatives under relatively mild conditions (Scheme 92b).[196] Notably, the DG can be removed under Lewis acidic conditions with $BF_3{\cdot}Et_2O$ in MeOH at 100 °C to afford the corresponding methyl ester. The Babu group reported a palladium-catalyzed, 2-thiomethylaniline-directed β-C(sp^3)−H arylation of cyclopropane (Scheme 92c),[202] which was followed by ring opening of cyclopropane when acetic acid was used as the cosolvent (Scheme 92d).[272]

Gutekunst and Baran reported concise total syntheses of piperarborenine B and piperarborenine D using *N*,*S*-bidentate auxiliary-directed, palladium-catalyzed C(sp^3)−H arylation of cyclobutane as the key strategy (Scheme 93).[273] By use of 2-thiomethylaniline as the DG, it was found that **571** could be converted into desired product **573** in gram scale using $Pd(OAc)_2$ as the catalyst with the aid of PivOH and Ag_2CO_3 in HFIP at 90 °C for 36 h. Then, different pathways were utilized to access each of the desired natural products from intermediate **573**. In the first reaction pathway, after epimerization of the ester moiety, a second C(sp^3)−H arylation of **574** with 4-iodo-1,2-dimethoxybenzene (**575**) was performed under similar conditions to afford arylated product **550** in 81% yield with complete stereoselectivity. In the second reaction pathway, after epimerization of the amide moiety, the second C(sp^3)−H arylation of **578** with **575** was carried out under similar conditions to give arylated product **579** in 46% yield also with complete stereoselectivity. Both the DG and the ester moiety were hydrolyzed, and condensation with dihydropyridone then completed the synthesis of piperarborenine D (**577**) and piperarborenine B (**580**). Based on the same strategy, the Baran group also achieved the synthesis and structural revision of several piperarborenine family natural products via C−H activation logic using 2-thiomethylaniline as the DG.[236]

The oxidized form of 2-(methylthio)aniline, 2-methylsulfinyl aniline (MSOA), can be employed as an auxiliary for β-methyl and methylene C(sp^3)−H bond arylation with aryl iodides. In 2016, the Colobert group designed a chiral *N*,*S*-bidentate auxiliary for the palladium-catalyzed, diastereoselective C(sp^3)−H arylation of cyclopropanes (Scheme 94a).[274] Surprisingly, by treatment of starting material **581** with $Pd(OAc)_2$ in acetonitrile with pyridine (2.2 equiv), an unprecedented, pyridine-stabilized, C(sp^3)−H activated palladacycle intermediate **582** was obtained in a 60:40 dr with the sterically less demanding complex being slightly more prevalent. They hypothesized that this may explain the overall diastereoselectivity that improves when the bulkier sulfinyl auxiliary with the *t*-Bu group is used. In 2017, Colobert and co-workers used the same strategy to achieve the diastereoselective arylation of methylene C(sp^3)−H bonds of linear aliphatic carboxamides with up to 9:1 diastereoselectivity (Scheme 94b).[275] In the same year, MSOA was used as a DG for β-C(sp^3)−H arylation of linear aliphatic amides with sterically hindered aryl iodides by He, Chen, et al. (Scheme 94c).[276]

Palladium-catalyzed enantioselective C(sp^3)−H functionalization using strongly coordinating bidentate DGs remained largely undeveloped until the mid-2010s, largely because the racemic background reactions could easily occur in the absence of chiral ligands and because of the lack of available coordination

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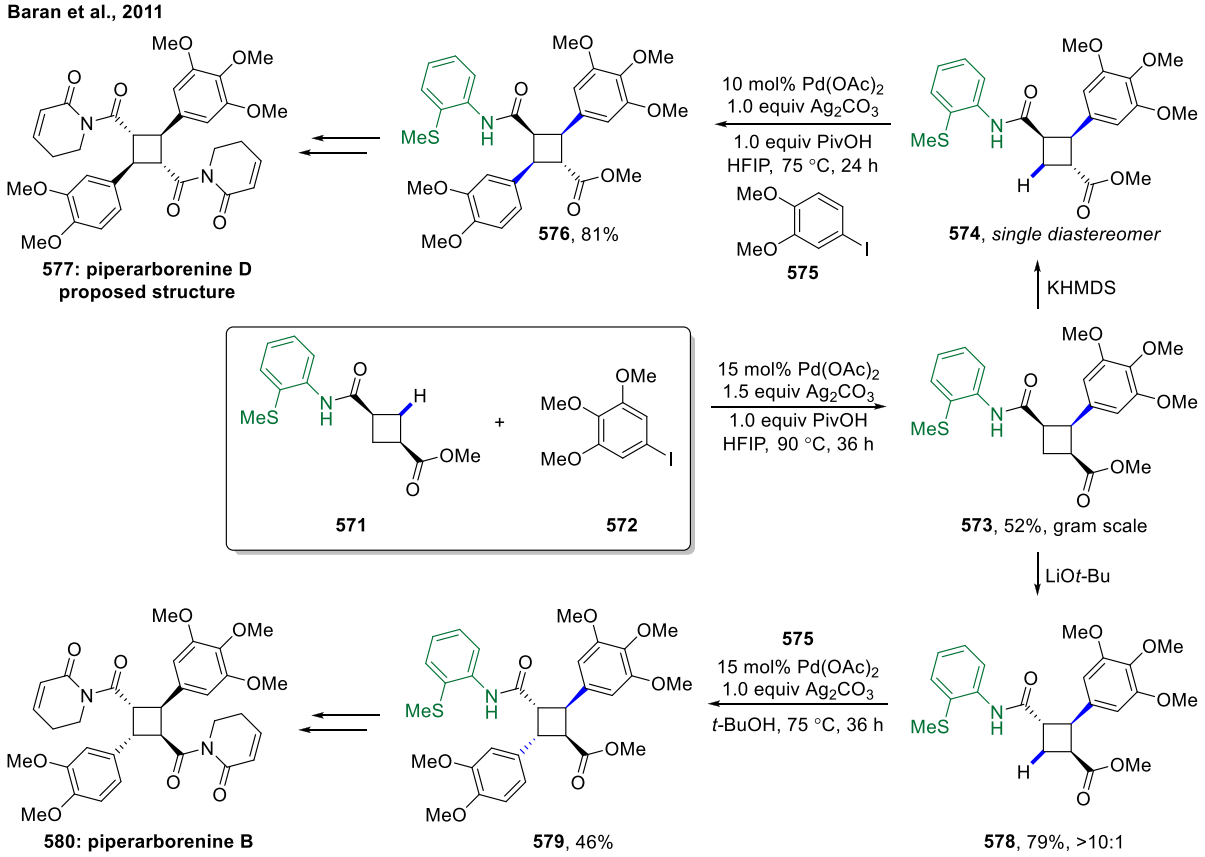
Scheme 93. 2-Thiomethylaniline-Directed Sequential C(sp^3)−H Arylation of Cyclobutane as a Key Step in the Total Synthesis of Piperarborenine Natural Products[273]



sites around the metal to coordinate a chiral ligand. The pioneering example of a Pd-catalyzed, 8-aminoquinoline-directed enantioselective methylene C(sp^3)−H arylation of aliphatic carboxylic amides using phosphoric amide **L70** as chiral ligand was reported by Duan et al. in 2015 (Scheme 95a).[277] The arylation of benzylic methylene C(sp^3)−H bonds was achieved in good yields with good enantioselectivities (up to 91:9 er). However, when this protocol was applied to more challenging unbiased methylene C(sp^3)−H bonds, both yield and ee value reduced dramatically (R = ^{n}Pr, 68%, 26% ee; R = ^{i}Pr, 20%, 28% ee). A series of mechanistic experiments indicated that the reaction rate is accelerated by the addition of chiral phosphoric amides or acids. They proposed that an enantioenriched intermediate, **591**, is formed by cleaving one of the two enantiotopic β-C−H bonds of **592** with the assistance of chiral phosphoric amide ligand **L70**. In 2018, the Chen group reported a Pd(0)-catalyzed enantioselective benzylic methylene C(sp^3)−H arylation of 3-arylpropanamides with the BINOL phosphoramidite (P^{III}) ligand **L71** (Scheme 95b).[278] This represented the first Pd(0)-catalyzed enantioselective C(sp^3)−H arylation reaction employing bidentate DGs.

In 2016, Chen and co-workers reported an enantioselective benzylic C−H arylation reaction directed by picolinamide (PA) (Scheme 96).[279] High enantioselectivity was enabled through the combination of the 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) phosphoric acid ligand and Cs_2CO_3 under neat conditions. Both yield and enantioselectivity were significantly influenced by the alkali cation. A nonlinear effect with respect to the enantiopurity of the ligand was also observed. Based on these mechanistic investigations, the authors proposed the interme-diacy of a Cs complex that contains two molecules of **L73** in the stereodetermining C(sp^3)−H palladation step.

While these examples demonstrated that significant progress has been made in the enantioselective functionalization of benzylic C(sp^3)−H bonds, realizing an analogous process at completely unactivated methylene positions directed by strongly coordinating bidentate DGs remains challenging and elusive. In 2018, the Shi group addressed this challenge by taking advantage of their own developed 2-(pyridine-2-yl)isopropyl (PIP) amine DG. They demonstrated the palladium(II)-catalyzed highly enantioselective arylation of unbiased β-methylene C(sp^3)−H bonds by the combination of PIP bidentate DG with a non-C_2-symmetric, monodentate chiral phosphoric acid (CPA) ligand (**L74**) (Scheme 97).[280] Investigation of a variety of structurally diverse ligands revealed that fluorine-containing substituents could improve the enantioselectivity. Aryl bromide electrophiles that contain either electron-donating or electron-withdrawing substituents are tolerated, generating enantioenriched, β-arylated carboxylic acid derivatives in good to excellent yields. Notably, this is the first time that more readily available and relatively nonactivated aryl bromides were used as aryl reagents in Pd(II)-catalyzed enantioselective C−H arylation. Examination of various directing auxiliaries other than the PIP group revealed that replacement of the *gem*-dimethyl substituents with longer chains or adding substituents on the pyridyl ring results in lower yield and enantioselectivity. The linear correlation between ee values of product and **L74** indicated that only one chiral ligand was involved in the stereodetermining C−H cleavage step. They hypothesized that the high stereoinduction compared with other bidentate auxiliaries might be attributable

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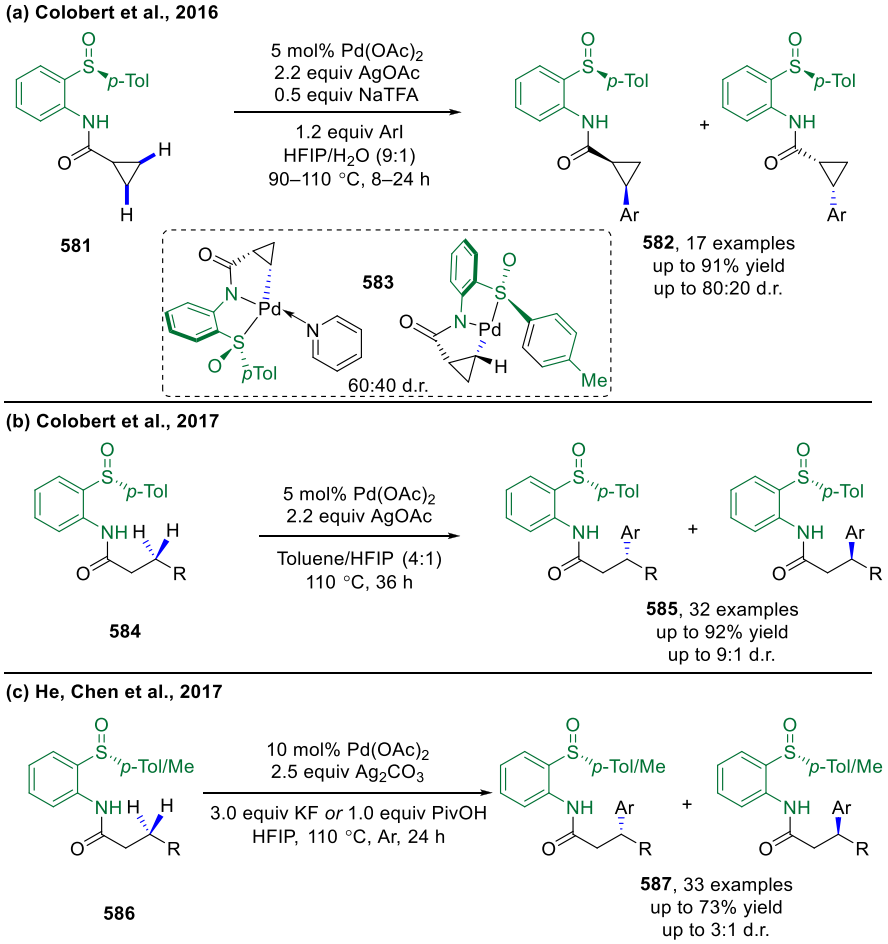
Scheme 94. Palladium-Catalyzed, Chiral 2-Methylsulfinyl Aniline-Directed Diastereoselective C(sp^3)−H Arylation of (a) Cyclopropane,[274] (b) Linear Aliphatic Carboxamides,[275] and (c) Palladium-Catalyzed, 2-Sulfinylaniline-Directed C(sp^3)−H Arylation with Sterically Hindered Aryl Iodides[276]



to steric communication between the *gem*-dimethyl unit and the ligand.

2.2.1.1.2. Palladium-Catalyzed C(sp^3)−H Arylation Using Transient DGs. While the introduction of a properly designed directing group can exhibit remarkable efficiency and chemoselectivity for C(sp^3)−H activation reactions, as described above in this review, the covalently attached mono- or bidentate directing groups must be used in stoichiometric amounts and necessitate concession steps for installation and removal. One approach to circumvent these limitations, as covered earlier, is through the use of a native chemical functional group in conjunction with an optimized catalyst or ligand. This approach, however, is neither universally successful nor universally applicable. Thus, an attractive complementary approach would involve a well-designed "transient DG" that can reversibly link to the substrate to direct the C−H functionalization and in situ deconstruction to release.[281] Thus, these so-called "transient DGs" (Figure 5) could be used in catalytic amounts as their addition and removal happens during the reaction typically through passive means, such as condensation.[282−287]

In 2016, Yu and co-workers pioneeringly reported a palladium-catalyzed C(sp^3)−H arylation with catalytic amounts of a transient DG (Scheme 98a).[288] On the basis of the development of mono-*N*-protected amino acid ligands and the earlier use of amino acids as bidentate DGs in the C−H functionalization of peptides,[261] they reasoned that catalytic quantities of the amino acid could be reversibly tethered to an aldehyde or ketone substrate via an imine linkage under the appropriate conditions. Once condensed, the imine moiety and the carboxylate could coordinate to the catalyst in a bidentate fashion to facilitate a subsequent C−H functionalization. The initially reported system uses glycine (40 mol %) as the transient DG, $Pd(OAc)_2$ (10 mol %) as the catalyst, and AgTFA (1.5 equiv) as the additive in a 9:1 solvent mixture of AcOH and H_2O at 90 °C for 36−48 h. In a control experiment, they found that when *N*-protected glycine was used, no conversion was detected. This result indicates that the formation of imine is essential for the reaction to proceed. Under the reaction conditions, the scope of aryl iodides and 2-methylbenzaldehyde was examined, and a variety of functional groups were found to be tolerated. The use of sterically hindered *ortho*-substituted aryl iodides leads to reduced yields. Aliphatic ketone substrates were investigated using the same strategy, and the optimal conditions for this transformation are as follows: glycine (50 mol %) and a 3:1 mixture of HFIP/AcOH as solvent at 110 °C for 36 h. A wide range of aryl iodides with electron-donating or -withdrawing substituents were well tolerated under the modified conditions. Notably, methylene C(sp^3)−H bonds in cyclic substrates could also be activated, producing the corresponding *syn* products with excellent diastereoselectivity. γ-C(sp^3)−H arylation was observed when β-C(sp^3)−H bonds were absent in aliphatic ketone. Unfortunately, aliphatic aldehydes were incompatible with this

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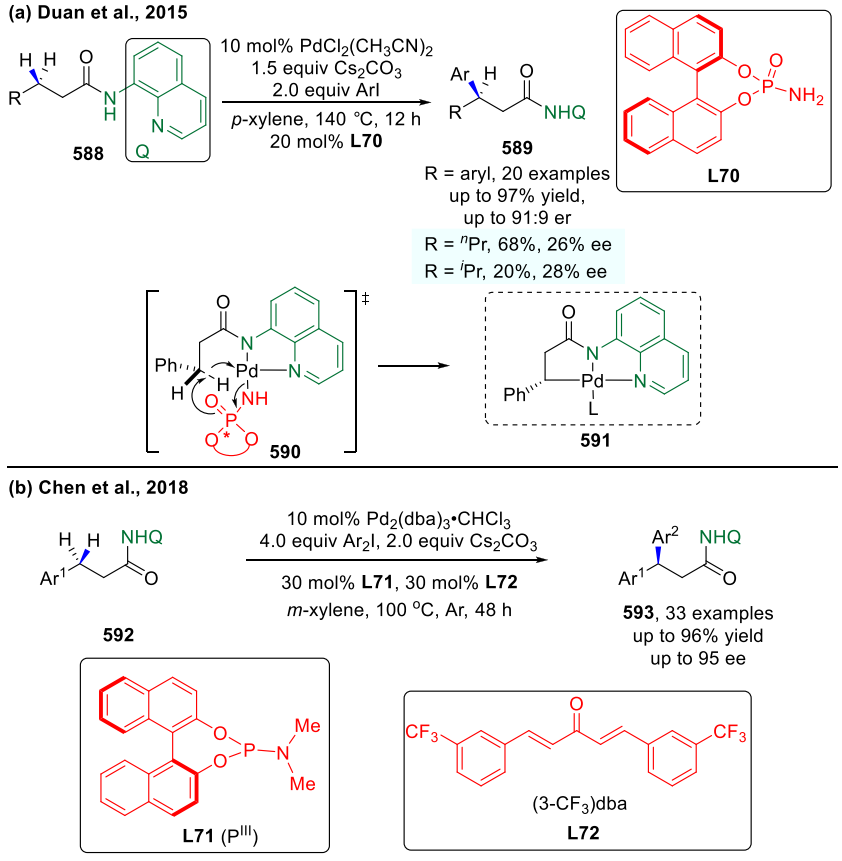
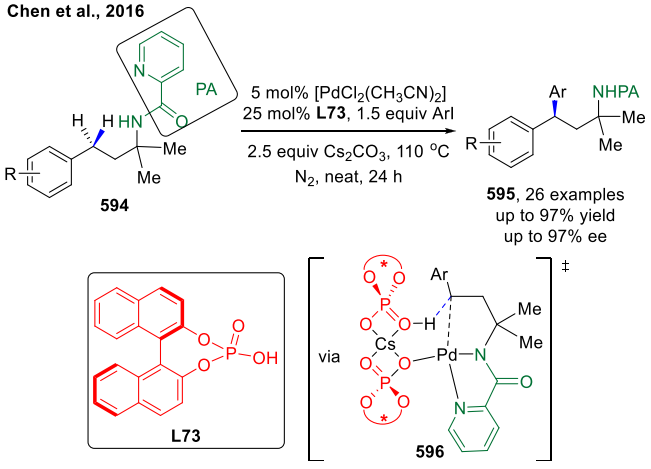
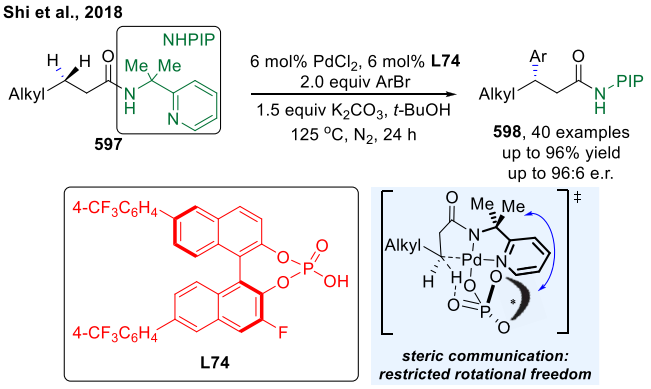
Scheme 95. (a) Pd(II)-Catalyzed, 8-Aminoquinoline-Directed Enantioselective Arylation of Methylene C(sp^3)−H Bonds Using Phosphoric Amide[277] and (b) Pd(0)-Catalyzed, 8-Aminoquinoline-Directed Enantioselective Benzylic C−H Arylation Using Phosphoramidite[278]



Scheme 96. Picolinamide-Directed Enantioselective Benzylic C(sp^3)−H Arylation[279]



Scheme 97. Pd(II)-Catalyzed, PIP-Directed Enantioselective Arylation of Unbiased Methylene C(sp^3)−H Bonds with Aryl Bromides[280]



protocol, due to the decomposition of the starting materials. Finally, benzaldehydes bearing methylene C(sp^3)−H bonds were investigated using a chiral amino acid as transient DG to carry out enantioselective C−H arylation. By use of L-*tert*-leucine in place of glycine, excellent enantioselectivity was achieved. Moreover, the yield of the arylated product was significantly improved by changing the ligand-to-Pd ratio from 4:1 to 2:1. Density functional theory calculations revealed that a six-membered transition state is favored in the benzylic C(sp^3)−H activation because of higher ring strain in the five-membered transition state for the alternative *ortho*-aryl C(sp^2)−H activation process.[289] The C(sp^3)−H activation step was found to take place via a concerted metalation−deprotonation mechanism. Later, primary benzylic C(sp^3)−H arylation using transient DGs was also disclosed by the groups of Hu (Scheme 98b)[290] and Li (Scheme 98c).[291]

In 2017, Pd-catalyzed β-methylene C(sp^3)−H arylation of aliphatic ketones using α-benzyl β-alanine (**TDG5**) as a catalytic TDG was reported by the Yu group (Scheme 99a).[292] β-Amino acid was used as a transient DG to generate a [5,6]-fused palladacycle, which promoted methylene C−H activation. In

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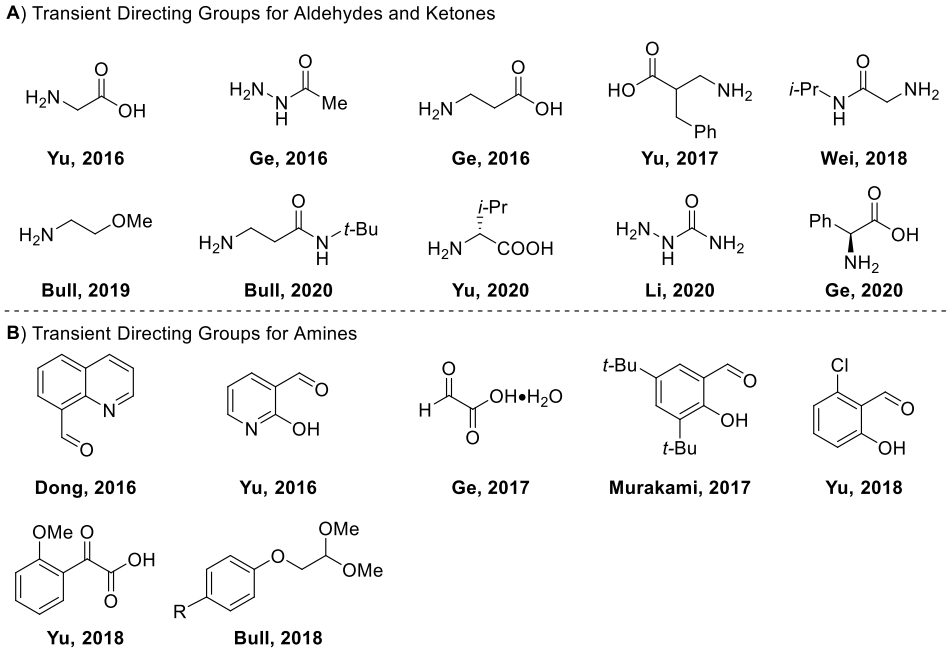

Figure 5. Bidentate transient DGs for C(sp^3)−H activation.

2018, Wei and co-workers reported primary β-C(sp^3)−H arylation of aliphatic ketones using 2-amino-*N*-isopropylacetamide (**TDG6**) as a transient DG (Scheme 99b).[293] β-Methylene C(sp^3)−H arylation of cyclic ketones was also amenable, giving the corresponding *syn*-products with excellent diastereoselectivity. The enantioselective β-methylene C(sp^3)−H arylation of cyclobutyl ketones was achieved by the Yu group in 2020 (Scheme 99c). D-Valine (**TDG7**) was used as the chiral transient DG and 5-nitropyridone (**L75**) was used as the ligand.[294] However, the substrate scope was limited to α-cyclobutyl ketones. When cyclopentyl ketone and linear aliphatic ketones were used, low enantioselectivity was obtained.

Palladium-catalyzed C(sp^3)−H arylation of aliphatic aldehydes enabled by a transient DG was reported by Ge and co-workers in 2016 (Scheme 100a). 3-Aminopropanoic acid (**TDG8**) was discovered as a novel catalytic transient DG for β-C(sp^3)−H arylation of aliphatic aldehydes.[295] All of the arylation reactions of aliphatic aldehydes discussed thus far are limited to β-C(sp^3)−H bonds. In 2020, Ge and co-workers developed the first example of γ-C(sp^3)−H arylation of aliphatic aldehydes with L-phenylalanine (**TDG9**) as a transient DG and 3-nitro-5-(trifluoromethyl)pyridin-2-ol (**L69**) as a ligand (Scheme 100b).[296] The Bull group also discovered examples of C(sp^3)−H arylation via the transient DG strategy, including intramolecular C(sp^3)−H arylation of tertiary aldehydes with 2-methoxyethan-1-amine (**TDG10**) (Scheme 101a)[297] and diarylation of cyclohexane carbaldehydes with *t*-Bu-amide (**TDG11**) (Scheme 101b).[298]

Meanwhile, the development of TDGs for C(sp^3)−H functionalization of aliphatic amines has also been reported. In 2016, Dong and co-workers reported the use of an *exo*-imine-based bidentate DG generated in situ from the reaction of an aliphatic amine substrate with stoichiometric amounts of 8-formylquinoline (**TDG12**) for facilitating γ-C(sp^3)−H functionalization (Scheme 102a).[299] The pyridine base (**L77**) was employed to neutralize the HBF_4 that is produced as the reaction proceeds. A γ-C(sp^3)−H activated palladacycle (**628**) was isolated and characterized by X-ray crystallography, which sheds light on the mechanism of the reaction.

In 2016, 2-hydroxynicotinaldehyde (**TDG13**) was reported as a catalytic transient DG for γ-C(sp^3)−H arylation of aliphatic amines by the Yu group (Scheme 103a).[300] It is noteworthy that when the reaction was conducted in 2 mmol scale, the loading of the transient DG could be lowered to 4%, showing the high efficiency and robustness of this protocol. Thus far, C(sp^3)−H activation of amine derivatives has been largely limited to the functionalization of the γ-position through a kinetically favored five-membered palladacycle intermediate. The Yu group successfully overcame these limitations to enable the switchable γ-C(sp^3)−H arylation of free amines using a transient DG. This transformation was then extended to γ-methylene and δ-methyl C(sp^3)−H bonds in 2018 through the development of new ligands and transient DGs (Scheme 103b).[301] The driving force for the switchable selectivity might be attributable to the preferred formation of a less strained [5,6]-bicyclic palladacycle containing a double bond rather than a [5,5]-bicyclic palladacycle.[267] Specifically, the 6-chloro-substituted hydroxybenzaldehyde (**TDG14**) favors six-membered coordination with the palladium(II) catalyst to enable γ-C(sp^3)−H cleavage, forming a [6,5]-bicyclic palladacycle intermediate with less strain, while 2-methoxy-substituted glyoxylic acid (**TDG15**) favors five-membered coordination with the palladium(II) catalyst to enable δ-C(sp^3)−H cleavage, forming a [5,6]-bicyclic palladacycle intermediate with a five-membered palladium complex. Notably, a broad range of medicinally important heteroaryl iodides were compatible with this protocol. The use of quinolone-based ligands significantly improved reaction efficiency. When using the combination of hydroxybenzaldehyde (**TDG13**) and pyridine ligand (**L76**), even typically unreactive heteroaryl bromides could be used as coupling partners in the heteroarylation of cyclohexylamine (**633a**).

In 2017, the $Pd(OAc)_2$-catalyzed C(sp^3)−H arylation of primary aliphatic amines enabled by a transient DG was reported by Ge and co-workers. Glyoxylic acid (**TDG16**) was developed as a novel catalytic transient DG for γ-C(sp^3)−H arylation of

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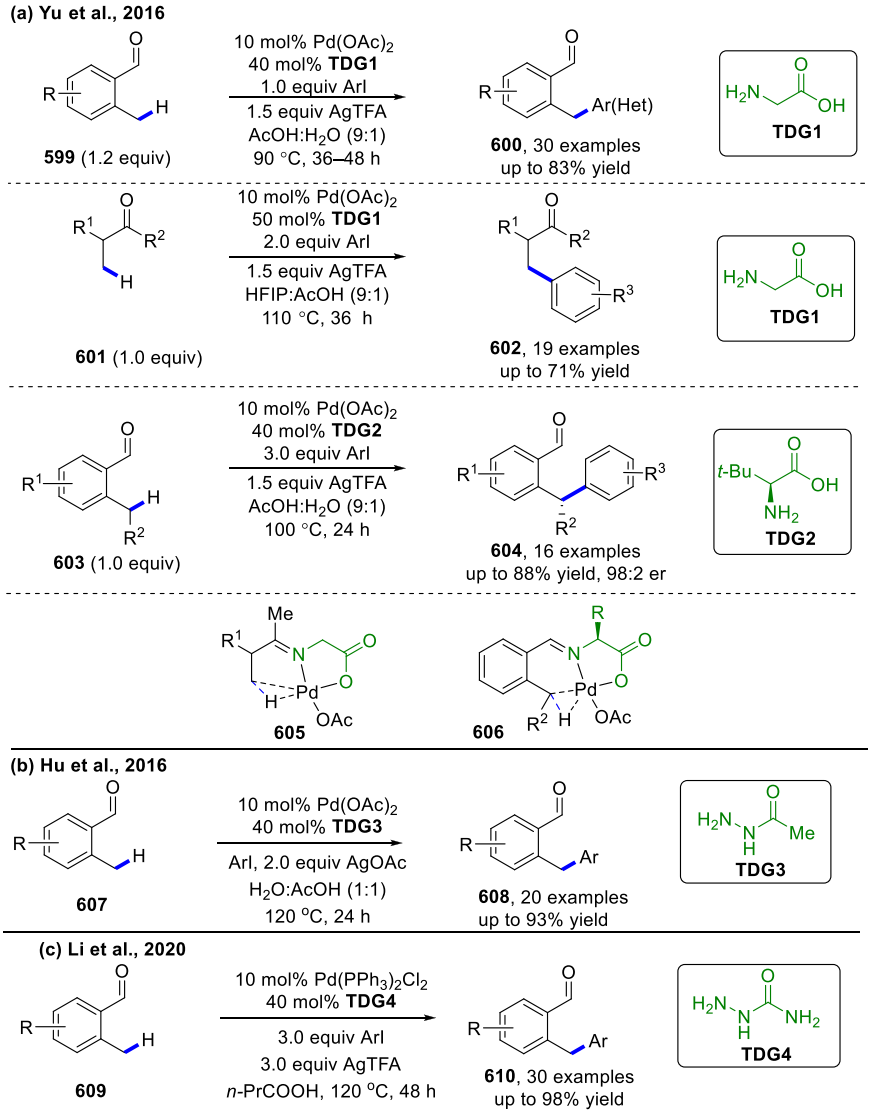
Scheme 98. Pd-Catalyzed C(sp^3)−H Arylation of 2-Alkylbenzaldehydes via Transient DG Strategy: (a) Glycine and L-*tert*-Leucine as TDGs;[288] (b) Acetohydrazone as TDG;[290] (c) Semicarbazide as TDG[291]



primary aliphatic amines (Scheme 104a).[302] By treatment of the *tert*-amylamine with glyoxylic acid (1 equiv), Pd(OAc)$_2$ (1 equiv), and pyridine (1 equiv) in HFIP at 100 °C, the cyclopalladated intermediate **640** was obtained. The palladacycle **640** could be transformed to the corresponding arylation product **638** under the standard conditions. A Pd(II)−Ag(I) heterodimeric complex was observed by Dang and co-workers, which emphasized the importance of silver(I) carboxylate additive in lowering the activation barrier of the C(sp^3)−H activation transition state (Scheme 104b).[303]

In 2017, the Murakami group used a sterically modified salicylaldehyde (**TDG17**) that could be conveniently condensed onto an aliphatic amine substrate to promote γ-C(sp^3)−H arylation and then be fully removed under acidic conditions after the reaction is complete (Scheme 105a).[304] While the Murakami group uses stoichiometric loadings of the modified salicylaldehyde TDG, they also demonstrate that a loading of 20 mol % provides their desired product, albeit in diminished yield but with around 3 turnovers of the TDG, suggesting that dual catalytic cycles with the Pd and TDG could be envisioned. In 2018, the Bull group reported a primary γ-C(sp^3)−H arylation of free amines using an alkyl acetal (2,2-dimethoxyethoxy)-benzene (**TDG18**) as a transient DG in catalytic amount (Scheme 105b).[305] γ-C(sp^3)−H arylation of free amino esters employing 2-hydroxynicotinaldehyde (**TDG13**) as a DG with an acid workup using $SOCl_2$ in EtOH to recover all of the products was reported by Kamenecka and co-workers in 2018 (Scheme 105c).[306]

2.2.1.1.3. C(sp^3)−H Arylation via Pd(II)/Pd(0) Catalysis. Palladium-catalyzed, bidentate group-directed C(sp^3)−H arylation reactions via Pd(II)/Pd(0) catalytic systems are relatively undeveloped. In 2018, Li and co-workers designed a weak *N,O*-bidentate DG for β-C(sp^3)−H arylation through a Pd(II)/Pd(0) catalytic cycle enabled by APAO ligand (**L37**) (Scheme 106).[307] Preliminary results on enantioselective β-C(sp^3)−H arylation via *gem*-dimethyl desymmetrization of isobutyramide have also been demonstrated by using **L37** as chiral ligand, giving monoarylated product in 43% yield with 73:27 er.

2.2.1.2. Alkenylation. A bidentate group-directed, palladium-catalyzed γ-C(sp^3)−H alkenylation was reported by He and Chen in 2011 in the functionalization of aliphatic amine

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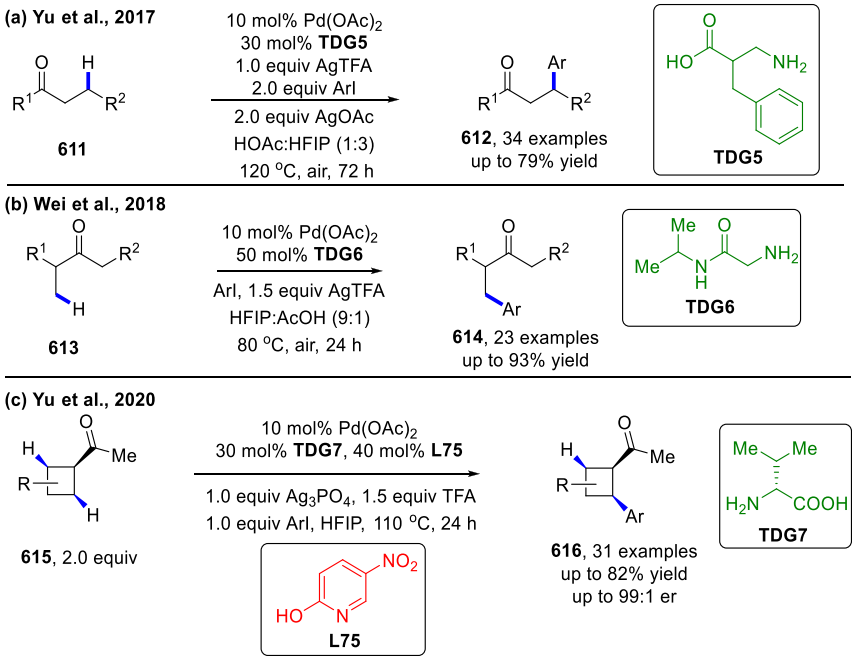
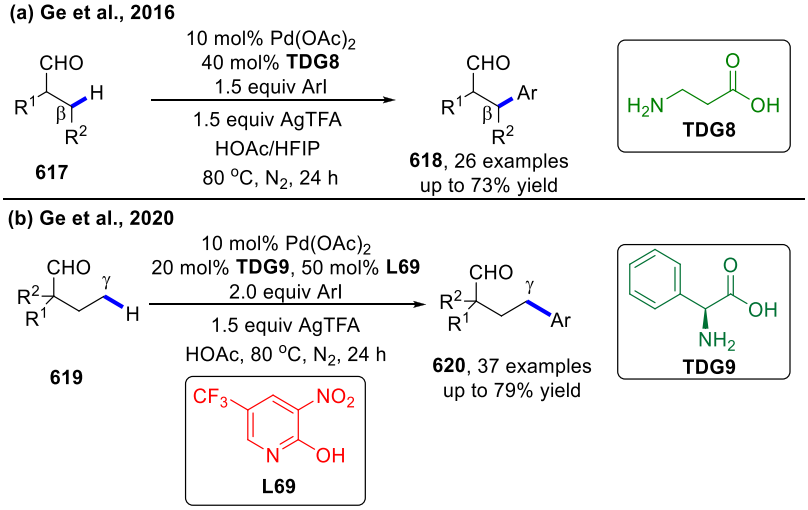
Scheme 99. Pd-Catalyzed β-C(sp^3)−H Arylation of Ketones via Transient DG Strategy: (a) Aliphatic Methylene C(sp^3)−H Arylation by α-Benzyl β-Alanine as TDG;[292] (b) Methyl and Cyclic Methylene C(sp^3)−H Arylation by 2-Amino-*N*-isopropylacetamide as TDG;[293] (c) Enantioselective C(sp^3)−H Arylation of Cyclobutyl Ketones by D-Valine as TDG[294]



Scheme 100. (a) Site-Selective β-C(sp^3)−H Arylation of Aliphatic Aldehydes[295] and (b) Site-Selective γ-C(sp^3)−H Arylation of Aliphatic Aldehydes[296]



derivatives (Scheme 107a).[221] The optimized reaction conditions were as follows: alkenyl iodide (1.5 equiv), Pd(OAc)$_2$ (10 mol %), and AgOAc (1.5 equiv) in *t*-BuOH at 110 °C for 20 h. The addition of benzoquinone led to a slight increase in yield. In 2015, Shi and co-workers used alkenyl bromide compounds as coupling partners in a C(sp^3)−H alkenylation reaction with the picolinimide DG (Scheme 107b).[237] Even in the presence of primary β-C(sp^3)−H bonds, alkenylation took place exclusively at the secondary C(sp^3)−H bonds on the cyclic ring system. Both electron-rich and electron-deficient alkenyl bromides gave the corresponding products in modest yields.

In 2012, the Baran group reported the use of an aminoquinoline-directed, palladium-catalyzed C(sp^3)−H alkenylation method to introduce an alkene moiety onto a cyclobutane core, thereby preparing a key intermediate in the synthesis of pipercyclobutanamide A (Scheme 108a).[192] In 2014, the synthesis of β-olefinated α-amino acid was reported by the Chen group via a palladium(II)-catalyzed, aminoquinoline carboxamide-directed γ-C(sp^3)−H alkenylation (Scheme 108b).[308] After extensive screening, the combination of 3 equiv of AgOAc and 2 equiv of TFA at room temperature in dioxane was found to give the desired products in good yields. Switching the solvent to a biphasic solvent system of TCE/H$_2$O (1:1) and elevating the reaction temperature to 65 °C led to improved yields. Alkenyl iodide electrophiles that bear various functional groups could be coupled to the alanine-derived substrate in a stereoretentive fashion at room temperature. Moreover, the olefinated products could be transformed to γ-lactams in excellent yield and with high diastereoselectivity (dr >

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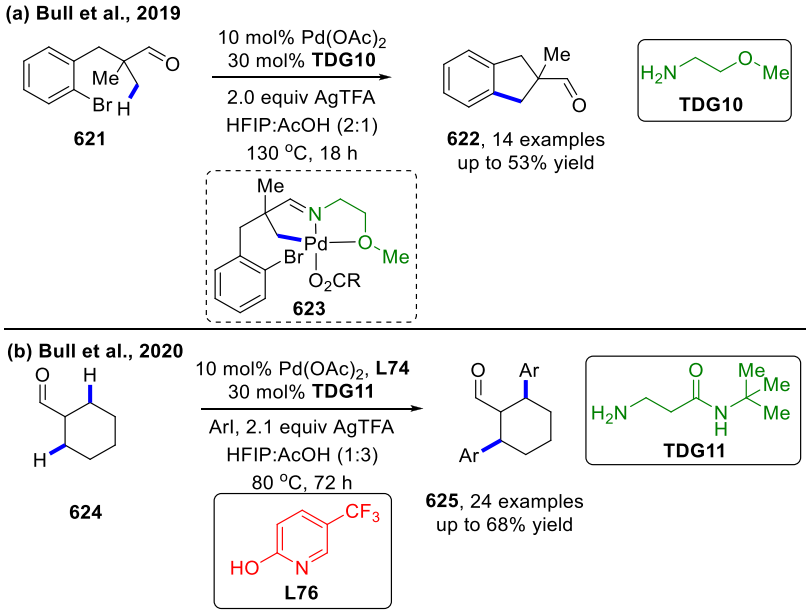
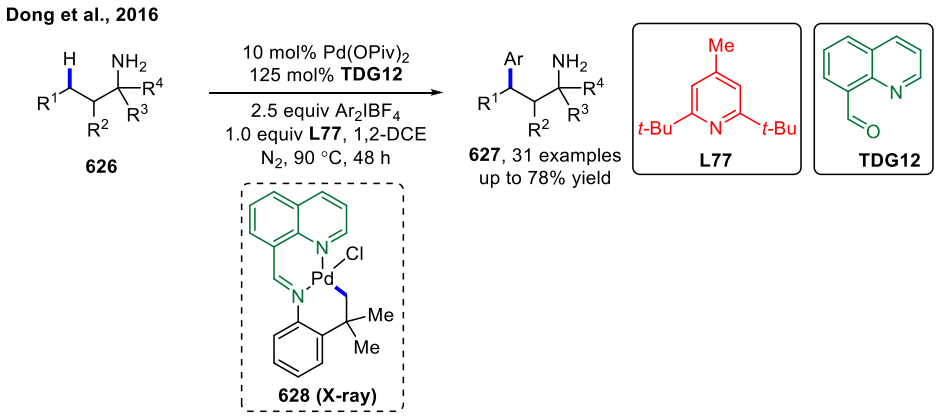
Scheme 101. (a) Intramolecular C(sp^3)−H Arylation of Tertiary Aldehydes[297] and (b) Methylene β-C(sp^3)−H Arylation of Cyclohexanecarbaldehydes[298]



Scheme 102. γ-C(sp^3)−H Arylation of Free Amines Enabled by Transient DG strategy and In Situ Formed *exo*-Imine-Based Bidentate DG[299]



15:1) upon treatment with 1.2 equiv of 4-dimethylaminopyridine (DMAP) in MeOH at room temperature for 4 h.

In 2015, a palladium-catalyzed, β-methylene C(sp^3)−H alkenylation of acyclic aliphatic amides was developed by Rao and co-workers (Scheme 108c).[309] A range of alkenyl iodides, such as 3-iodo-α,β-unsaturated ketones and (*E*)-β-aryl vinyl iodides, worked well under the optimized conditions. They also discovered that the product distribution was significantly affected by solvent effects. While toluene afforded solely the β-C(sp^3)−H alkenylation product, an additional δ-C(sp^2)−H alkenylation was observed when the reaction was performed in MeCN. In addition, *Z*/*E* isomerization occurred when (*Z*)-(2-iodovinyl)-benzene was employed as the alkene reagent, potentially via an allyl-type Pd(IV) intermediate. In 2016, the Reisman group employed 8-aminoquinoline-directed, palladium(II)-catalyzed C(sp^3)−H alkenylation as a key step in the total synthesis of (+)-psiguadial B (Scheme 108d).[310] Palladium(II)-catalyzed C(sp^3)−H alkenylation of cyclopropanes directed by the 8-aminoquinoline group was also reported by the Shuto group in 2019 (Scheme 108e).[311] In 2018, the Yu group reported a preliminary result on γ-C(sp^3)−H alkenylation of ketones by using the previously discussed 2,2-dimethyl aminooxyacetic acid auxiliary (Scheme 109).[266]

In 2020, both the Liu and the Ackermann groups took advantage of C(sp^3)−H alkenylation transformations to develop methods for palladium(II)-catalyzed β-C(sp^3)−H glycosylation of amino acids and peptides. 8-Aminoquinoline was employed by Liu and co-workers as a DG to enable the glycosylation of various *N*-phthaloyl α-amino acids (Scheme 110a).[312] The Ackermann group used triazolyldimethylmethyl (TAM) as their main DG and were also able to employ 8-aminoquinoline as a DG under slightly altered conditions to achieve the glycosylation of various *N*-phthaloyl α-amino acids (Scheme 110b).[313] In addition, an unprecedented late-stage glycosylation of internal peptides directed by TAM was also achieved. The silver salt Ag_2CO_3 was used by both groups. Notably, this is the first time glycals were used as coupling partners for β-C(sp^3)−H functionalization of amino acids and peptides.

2.2.1.3. Alkynylation. In 2011, the Chatani group demonstrated the first palladium(II)-catalyzed alkynylation of unactivated C(sp^3)−H bonds (Scheme 111a).[314] A variety of aliphatic carboxylic amide derivatives were successfully alkyny-

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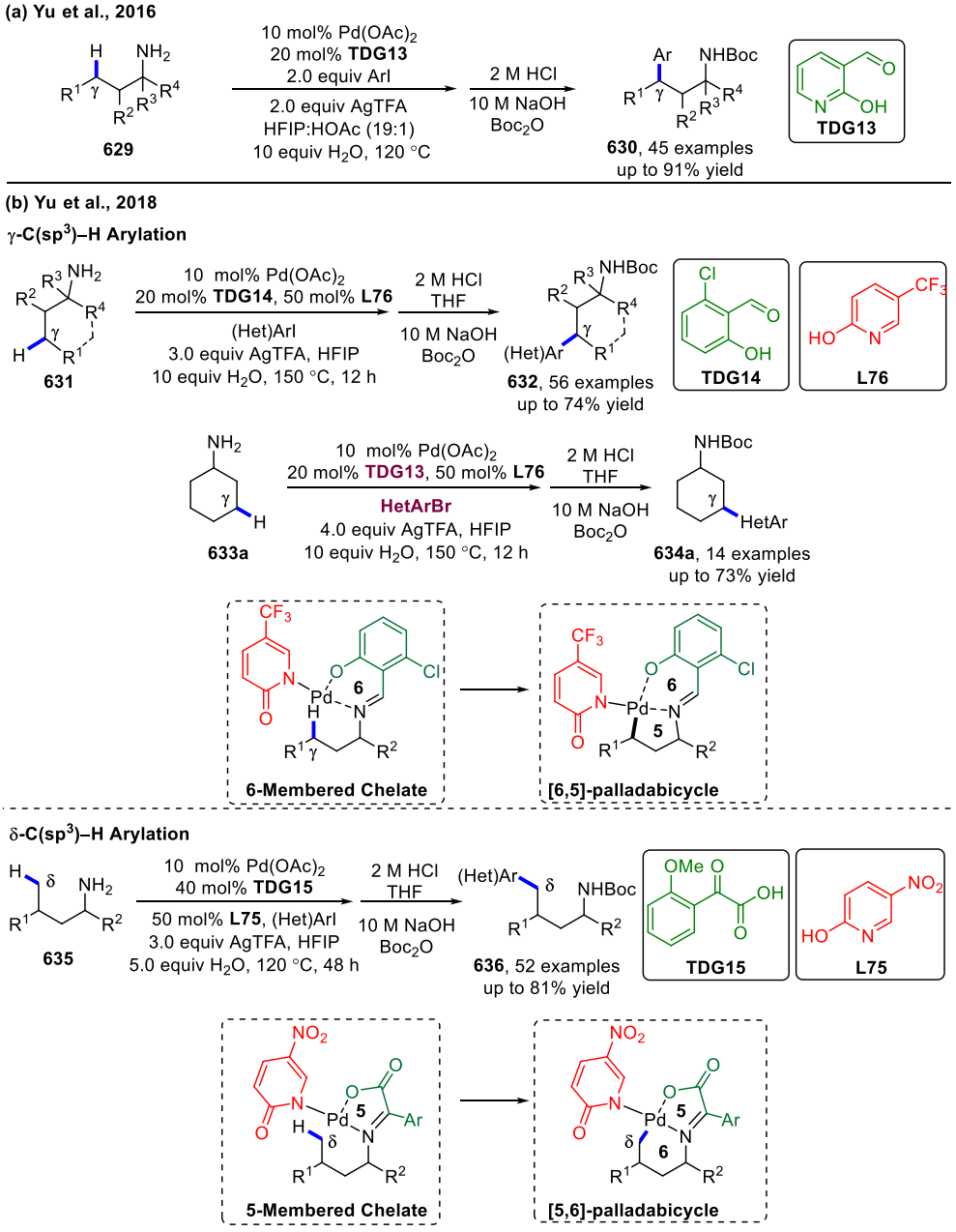
Scheme 103. (a) Pd-Catalyzed γ-C(sp^3)−H Arylation of Free Amines Using 2-Hydroxynicotinaldehyde as TDG[300] and (b) Ligand-Enabled Pd-Catalyzed γ- and δ-C(sp^3)−H (Hetero)arylation of Amines with TDGs[301]



lated with a TIPS-protected bromoalkyne electrophile directed by the 8-aminoquinoline group. In 2014, one example of palladium(II)-catalyzed, 8-aminoquinoline-directed β-C(sp^3)−H alkynylation of *N*-phthaloyl alanine was reported by the Chen group (Scheme 111b).[308] In 2015, an example of palladium(II)-catalyzed diastereoselective C(sp^3)−H alkynylation of cyclopropane was reported by the Hong group using an isoleucine-derived amide chiral bidentate DG (Scheme 111c).[247] The Shi group reported in 2016 a comprehensive study of a silver-free C(sp^3)−H alkynylation of *N*-phthaloyl amino acids and aliphatic acids directed by 1,2,3-triazole amine (TAM) (Scheme 111d).[315] In 2017, Yu and co-workers reported a palladium(II)-catalyzed C(sp^3)−H alkynylation of oligopeptides with various sterically bulky alkynyl bromides (Scheme 111e).[316] The addition of tetrabutylammonium acetate (NBu_4OAc) dramatically increased the yield. It was proposed that the acetate anion in NBu_4OAc enables the C−H activation, while the quaternary ammonium cation stabilizes the high-valent palladium intermediate during the C−H activation step.

In 2018, the Balaraman group reported a palladium-catalyzed, amide-directed γ-C(sp^3)−H alkynylation of aliphatic amines.[317] It is noteworthy that a variety of *N,N*-bidentate DGs related to picolinamide bearing pyrazine, quinoline, or isoquinoline heterocycles were found to be effective in promoting the reaction. Both cyclic and linear amine substrates could be successfully alkynylated in good yields (Scheme 112).

In 2019, the first Pd-catalyzed enantioselective alkynylation of unbiased methylene C(sp^3)−H bonds was reported by Shi and co-workers using 3,3′-fluorinated BINOL as the chiral ligand and PIP as DG (Scheme 113).[318] A broad range of aliphatic amides were well tolerated, giving the alkynylated products in good yields with high enantioselectivities (up to 96% ee).

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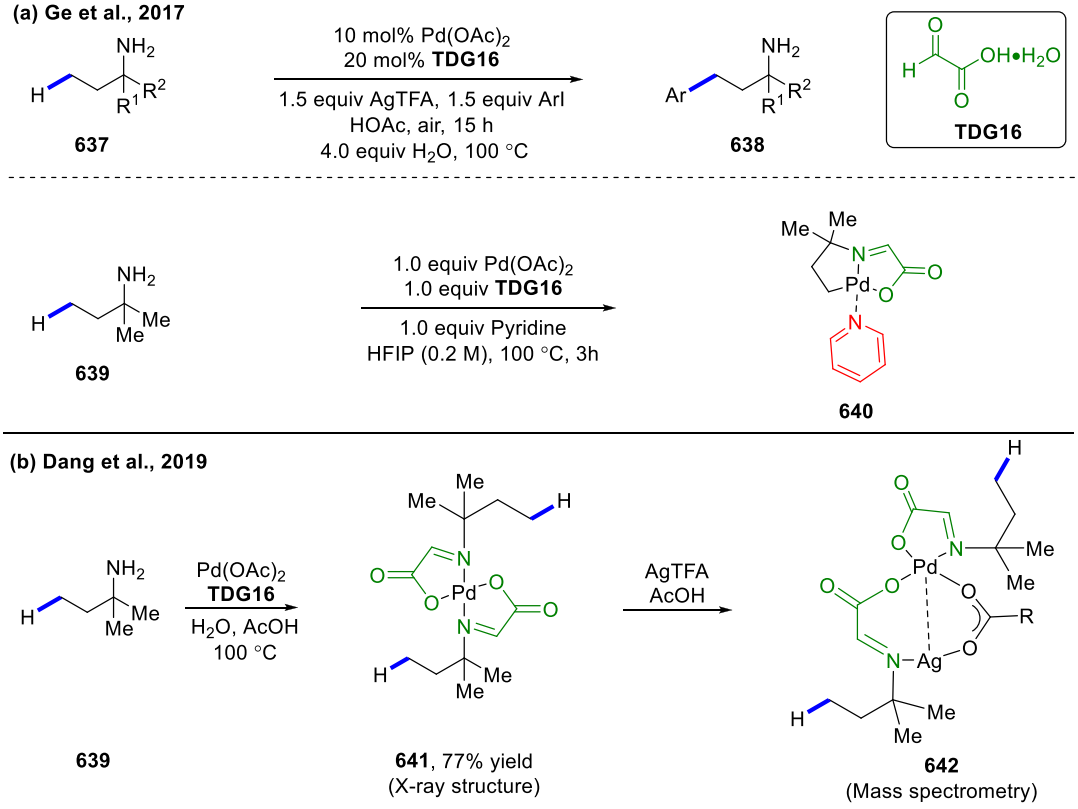
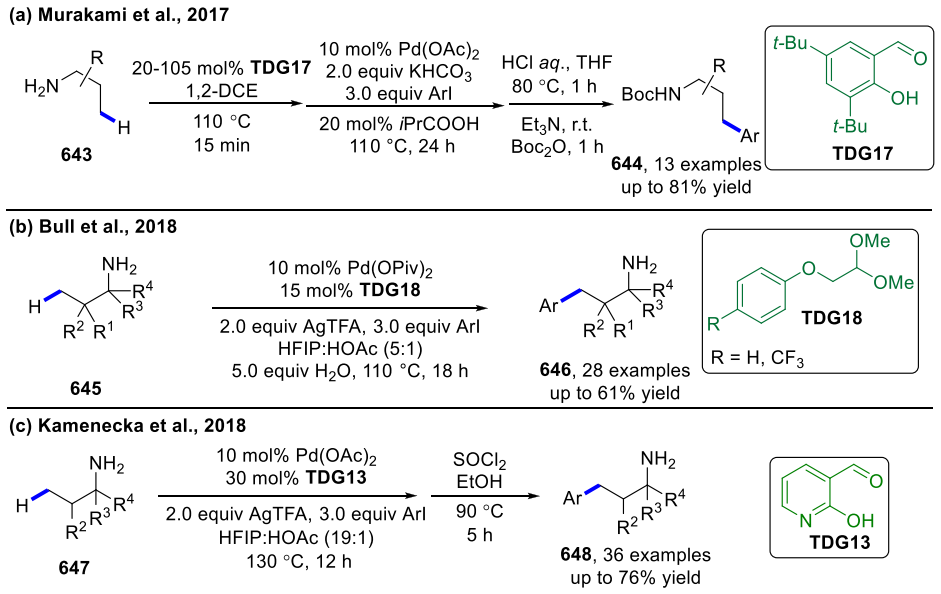
Scheme 104. (a) C(sp^3)−H Arylation of Free Amines Using Glyoxylic Acid as TDG[302] and (b) [5,5]-Fused Palladacycle Characterized by the Dang Group[303]



Scheme 105. (a) Sterically Modified Salicylaldehyde,[304] (b) Alkyl Acetal (2,2-Dimethoxyethoxy)benzene,[305] and (c) 2-Hydroxynicotinaldehyde[306]



Control experiments revealed that the use of the 8-aminoquinoline DG in place of PIP-NH$_2$ led to lower yield and enantioselectivity under identical conditions (36%, 48% ee). A positive nonlinear effect revealed that the stereodetermining C−H palladation step may be influenced by multiple ligands. A dramatic ligand acceleration was observed, which might be attributed to the unprecedented high stereocontrol.

2.2.1.4. Alkylation. Compared to aryl halides, alkyl halides are resistant to oxidative addition and susceptible to base-induced elimination. Provided that they are able to undergo oxidative addition, the resulting alkyl−metal intermediates are prone to β-hydride elimination. Thus, the alkylation of C(sp^3)−H bonds is an inherently challenging family of reactions to develop, and progress on this front is slow. Pioneering work on bidentate group-directed, palladium-catalyzed C(sp^3)−H bond alkylation

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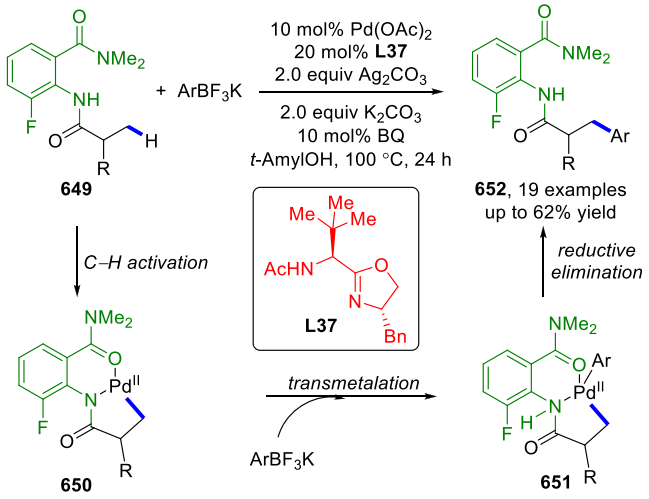
Scheme 106. Palladium-Catalyzed, *N,O*-Bidentate-Directed *β*-C(sp^3)−H Arylation with Aryltrifluoroborates[307]



was reported by Daugulis and co-workers in 2010 (Scheme 114a).[181] Two examples of alkylation of *β*-methyl C(sp^3)−H bonds of aminoquinolyl propanamide (**707**) were demonstrated with branched and linear primary alkyl iodides as coupling partners (e.g., *i*-butyl iodide and *n*-octyl iodide). 8-Aminoquinoline directed alkylation of amino-acid-derived substrates was also developed by the Daugulis group in 2012.[196]

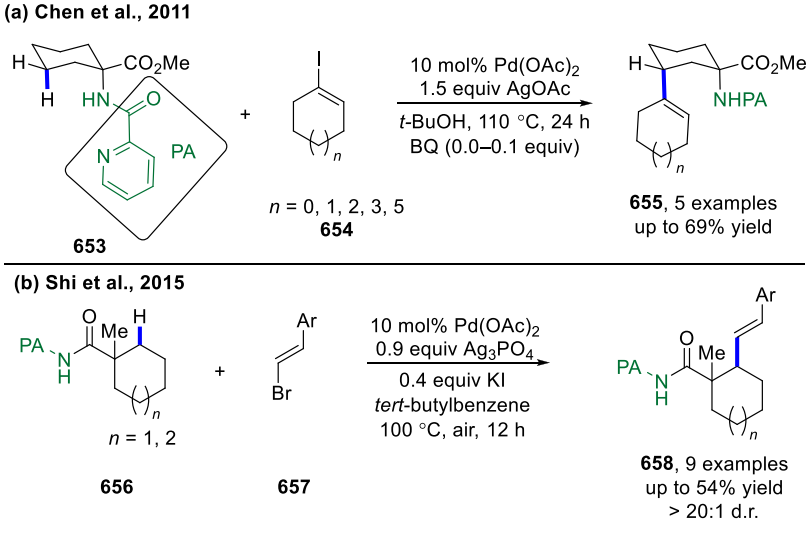
Subsequently, the Chen group expanded upon this Pd-catalyzed alkylation to functionalize unactivated *β*-methylene C(sp^3)−H bonds of aminoquinolyl aliphatic carboxamides with *α*-haloacetate and methyl iodide (Scheme 114b).[319] This protocol was applied to the alkylation of the *β*-methylene position of *N*-phthaloyl *α*-amino acids with 2 equiv of *α*-haloacetate or MeI in good to excellent yields and high diastereoselectivities. Deuterium-labeled methyl iodide was also employed to afford the isotopically enriched amino acids.

The Shi group independently reported the Pd-catalyzed C(sp^3)−H alkylation of *N*-phthaloyl *α*-amino acids directed by 8-aminoquinoline under mild conditions (Scheme 114c).[320] The alkylation of *N*-phthaloyl alanine with a wide range of primary alkyl iodides that encompass various length alkyl chains and synthetically useful functional groups was achieved, affording the desired alkylation products in good to high yields. Notably, this reaction also represented the first example of Pd-catalyzed alkylation of C(sp^3)−H bonds with alkyl bromide reagents, which are less expensive and more readily available than alkyl iodide reagents. As expected, the *β*-secondary C(sp^3)−H bonds of various amino acid derivatives were also alkylated with *α*-iodoacetate esters and *α*-bromoacetate esters. The *γ*-alkylation of C(sp^3)−H bonds could be achieved when no reactive *β*-C−H bonds are present. Finally, the significance of this palladium-catalyzed alkylation is further demonstrated by the synthesis of *β*-branched *α*-amino acids via several sequential functionalizations of C(sp^3)−H bonds.

Thus far, unactivated methylene C(sp^3)−H alkylation has been limited to the use of *α*-haloacetates and methyl iodide without *β*-hydrogen atoms. To overcome this limitation, the Shi group reported a palladium-catalyzed alkylation of unactivated methylene C(sp^3)−H bonds with an expanded scope of alkyl iodide reagents in 2014 (Scheme 115a).[321] Screening of various additives showed that the use of silver salts together with 4-Cl-$C_6H_4SO_2NH_2$ and NaOCN significantly improved the reaction yield. Linear and branched primary alkyl iodide coupling partners that bear *β*-hydrogen atoms worked smoothly under the optimized reaction conditions. In addition, 2-amino-butyric acid (Abu), norvaline (Nva), lysine (Lys), ornithine (Orn), and phenylalanine (Phe) derivatives were all compatible with the alkylation protocol. Furthermore, alkylation of the *γ*-methyl C(sp^3)−H bond of isoleucine was achieved. Importantly, a series of *β*,*β*-heterodialkylated *α*-amino acids could be prepared by sequential C(sp^3)−H functionalization of alanine. Additionally, both alkylation/arylation and arylation/alkylation sequences could be achieved to provide a variety of *β*-alkyl-*β*-aryl *α*-amino acids in good yields. In 2016, an efficient method for the synthesis of chiral *β*-alkyl-*α*-hydroxy acids via palladium-catalyzed C(sp^3)−H alkylation of lactic acid with the assistance of an 8-aminoquinoline DG with retention of chirality was also reported by the Shi group (Scheme 115b).[322]

Palladium-catalyzed, 8-aminoquinoline-assisted, site-selective cyanomethylation of unactivated C(sp^3)−H bonds with acetonitrile was reported by Ge and co-workers in 2016 (Scheme 116a).[323] The authors propose that this reaction

Scheme 107. (a) Picolinamide-Directed C(sp^3)−H Alkenylation[221] and (b) Picolinimide-Directed C(sp^3)−H Alkenylation[237]



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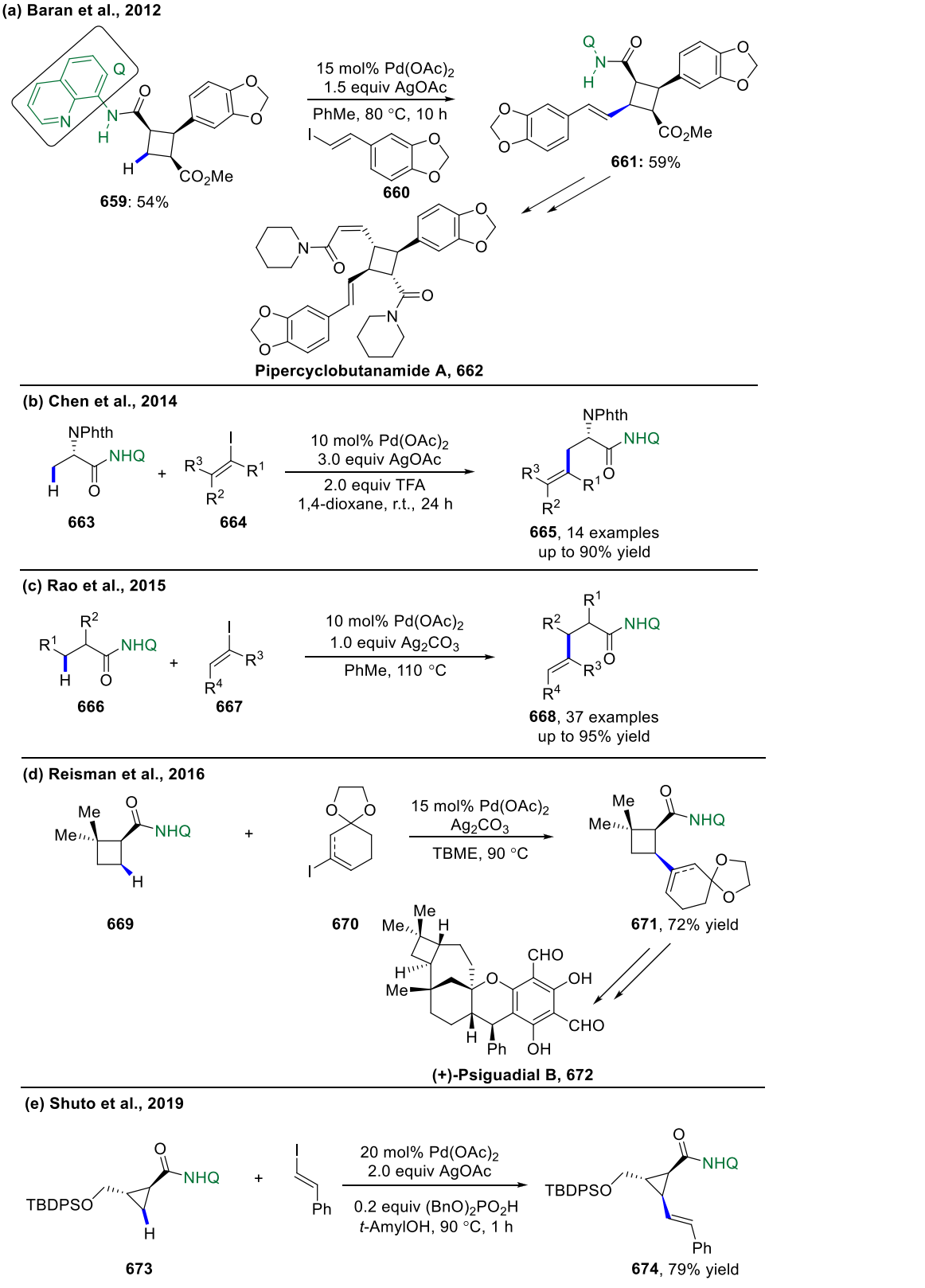
Scheme 108. 8-Aminoquinoline-Directed C(sp^3)−H Olefination (a) As a Key Step in the Total Synthesis of Pipercyclobutanamide A,[192] (b) As Phthaloyl Alanine with Alkenyl Iodide Reagents,[308] (c) As Acyclic Aliphatic Amides,[309] and (d) As a Key Step in the Total Synthesis of (+)-Psiguadial B,[310] and (e) Cyclopropanes[311]



proceeds through a Pd(II) species in which the Pd is coordinated to the DG, which can then perform an irreversible C(sp^3)−H bond activation under basic conditions to create a cyclometalated Pd(II) complex. This complex then undergoes transmetalation with a cyanomethyl Cu(II) species that is likely the result of a Ag-promoted reaction with the acetonitrile. Upon

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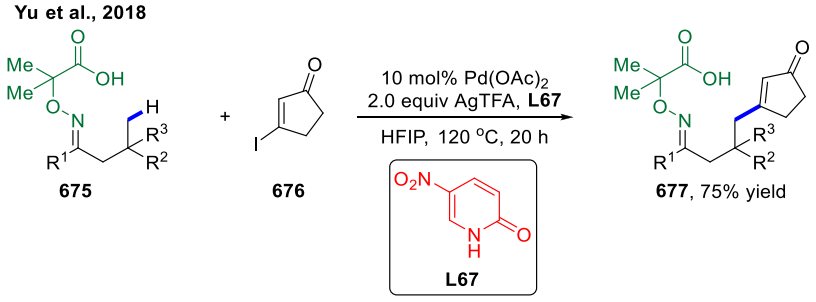
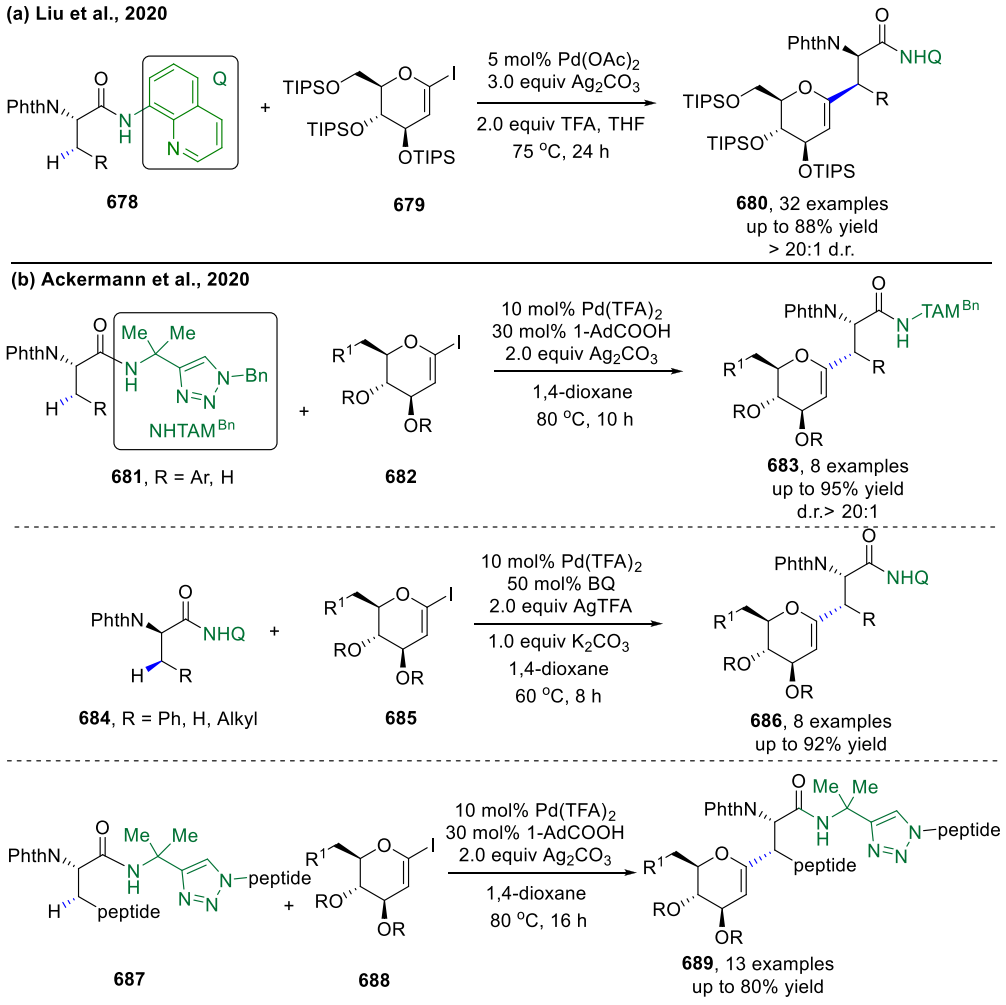
Scheme 109. γ-C(sp^3)−H Alkenylation of Aliphatic Ketones with Alkenyl Iodide[266]



Scheme 110. Bidentate Group-Directed C(sp^3)−H Glycosylation with 1-Iodoglycals: (a) *N*-Phthaloyl α-Amino Acids;[312] (b) *N*-Phthaloyl α-Amino Acids and Internal Peptides[313]



reductive elimination, the product is produced, and the Pd(0) is reoxidized by Cu(II) or Ag(I) to the Pd(II) species. In 2017, the Yang group developed a procedure for synthesizing chiral γ-phosphono-α-amino acids via 8-aminoquinoline-directed C-(sp^3)−H alkylation of α-amino acids (Scheme 116b).[324] Pd-catalyzed C(sp^3)−H alkylation of cyclopropanes directed by 8-aminoquinoline was developed by the Shuto group (Scheme 117).[311,325]

After achieving *ortho*-C(sp^2)−H alkylation with picolinamide-protected benzylamines using alkyl halide reagents,[326] the Chen group reported a picolinamide-directed, Pd-catalyzed alkylation of unactivated methyl C(sp^3)−H bonds with alkyl iodides in 2013 (Scheme 118a).[327] After extensive screening, a catalytic amount of dibenzyl phosphate $(BnO)_2PO_2H$ was found to promote the C−H alkylation reaction, and they proposed that it might act as a solid-to-solution phase-transfer catalyst (PTC) for Ag_2CO_3. In the presence of excess methyl iodide, *exo*- or *endo*-norbornene substrates undergo an initial addition of a methyl group at the γ-C(sp^3)−H that is followed by two sequential δ-C(sp^3)−H activations at the newly formed methylene position to give an isopropyl group in 77% and 88% yield, respectively. In 2018, Shi and co-workers reported a Pd(II)-catalyzed selective δ-methyol C(sp^3)−H alkylation of amino acids and peptides in the presence of γ-methyl C(sp^3)−H

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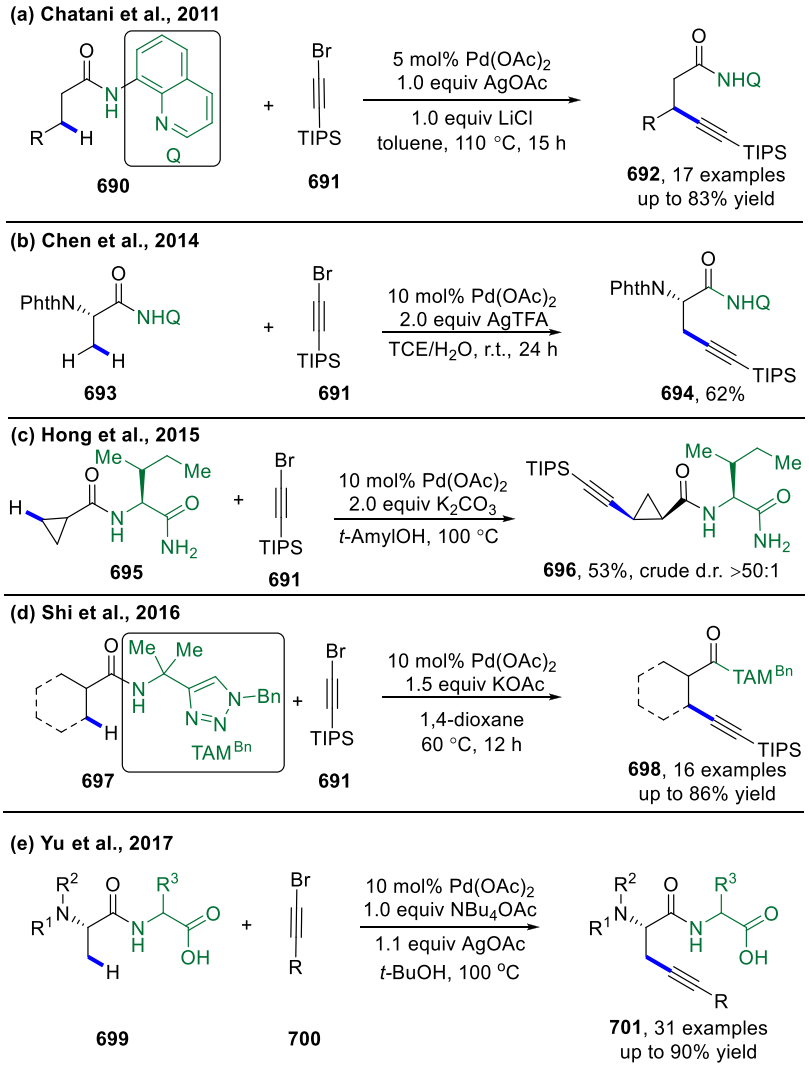
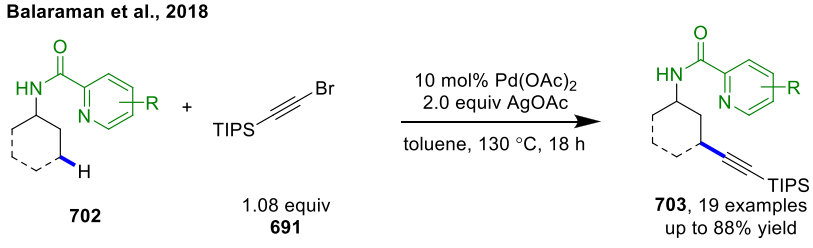
Scheme 111. Palladium-Catalyzed β-C(sp^3)−H Alkynylation: (a) Aliphatic Amides with 8-Aminoquinoline DG;[314] (b) *N*-Phthaloyl Alanine with 8-Aminoquinoline DG;[308] (c) Diastereoselective Alkynylation of Cyclopropane with an Isoleucine-Derived Amide Chiral DG;[247] (d) *N*-Phthaloyl Amino Acids and Aliphatic Acids Directed by 1,2,3-Triazole Amide;[315] (e) Alanine and Oligopeptides[316]



Scheme 112. Palladium-Catalyzed γ-C(sp^3)−H Alkynylation of Aliphatic Amines[317]



bonds using maleimides as alkylating reagents (Scheme 118b).[328] The authors invoke the Curtin−Hammett principle to suggest that both the five- and six-membered palladacycles are reversibly formed in this reaction and that the reaction proceeds faster through the thermodynamically less disfavored six-membered palladacycle intermediate.

2.2.1.5. Carbonylation. An *N*,*O*-bidentate DG-enabled, palladium-catalyzed γ-C(sp^3)−H carbonylation of aliphatic amines was reported by Zhao and co-workers in 2015 (Scheme 119a).[329] Oxalyl amide was used as an efficient DG, and 3-(trifluoromethyl)benzoic acid was found to be the most effective additive. Notably, amines bearing two β-substituents are more reactive compared to those bearing only one β-methyl group, providing the corresponding pyrrolidines in good to excellent yields. The oxalyl amide DG can be readily removed under basic conditions at 50 °C.

Another example of palladium-catalyzed γ-C(sp^3)−H carbonylation of aliphatic amines was reported by Wang and co-workers in the same year using picolinamide as the DG (Scheme 119b).[330] The success of this reaction relied on the judicious

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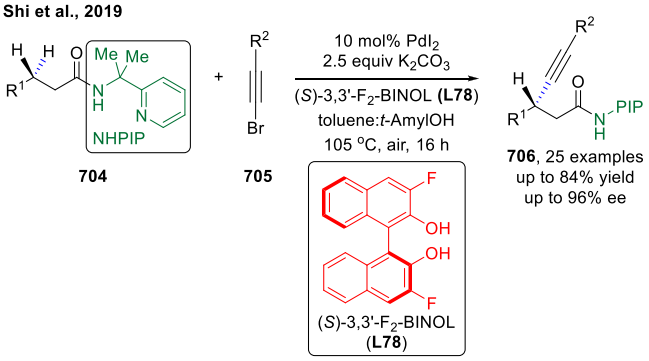
Scheme 113. Pd(II)-Catalyzed Enantioselective Alkynylation of Unbiased Methylene C(sp^3)−H Bonds[318]

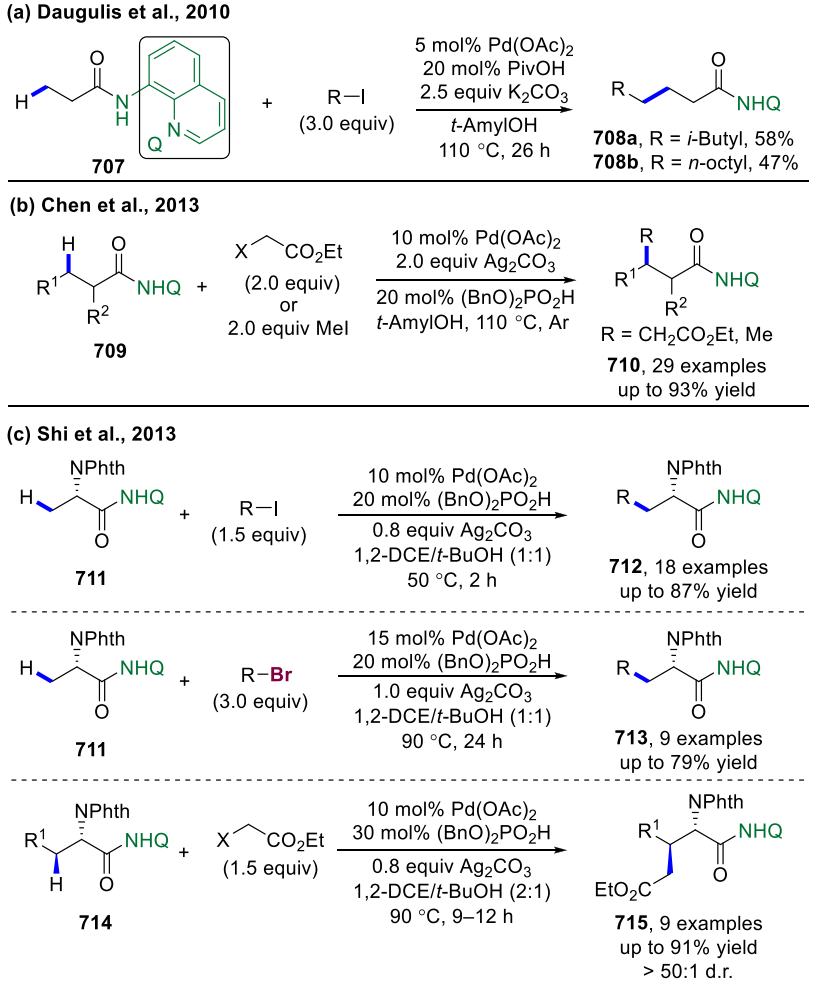


choice of TEMPO as a proper oxidant because classic oxidants, such as Cu(II), Ag(I), $PhI(OAc)_2$, DDQ, NFSI, CAN, and $K_2S_2O_8$, were found to be ineffective in this transformation. A range of commercial α-amino acids and amino alcohols were converted into the corresponding γ-lactams in good yield. Finally, a concise total synthesis of *rac*-pregabalin was achieved using this γ-C(sp^3)−H carbonylation protocol as the key step. In 2016, the Carretero group also reported a carbonylative cyclization of amines via Pd(II)-catalyzed γ-C(sp^3)−H activation with substoichiometric $Mo(CO)_6$ as the CO source directed by *N*-(2-pyridyl)sulfonyl auxiliary (Scheme 119c).[331] α-Amino acid and β-amino acid derivatives could also be used, affording the corresponding γ-lactams in good yields.

The C(sp^3)−H carbonylation of alcohol derivatives enabled by a DG containing an *N*-acetyl-protected aminoethylpyridine scaffold was first reported by the Yu group in 2019 (Scheme 120).[332] They proposed that the hemilabile ether was crucial for the transformation, in which it dissociated after the C−H activation step to allow the binding of carbon monoxide. Apart from the γ-C(sp^3)−H carbonylation, an unprecedented δ-C(sp^3)−H carbonylation was also achieved, giving the desired product (**751**) in 33% yield.

Up until now, palladium-catalyzed C(sp^3)−H carbonylation was limited to the functionalization of primary C−H bonds. The first Pd(II)-catalyzed alkoxycarbonylation of more unactivated secondary C(sp^3)−H bonds was achieved by the Shi group in 2016 with readily available and operationally simple alkyl chloroformates (Scheme 121a).[333] In their initial efforts to use carbon monoxide as the carbonylation source, they found that the corresponding CO−ligand palladacycle complex derived from *N*-phthaloyl phenylalanine bearing the 8-aminoquinoline DG was very stable under a variety of conditions, likely due to the difficulty of CO migratory insertion as well as the challenging CO reductive elimination. Thus, alkyl chloroformates were used

Scheme 114. 8-Aminoquinoline-Directed C(sp^3)−H Alkylation: (a) Pioneering Study;[181] (b) Methylene C(sp^3)−H Alkylation with α-Haloacetates and Methyl Iodide;[319] (c) C(sp^3)−H Alkylation of *N*-Phthaloyl α-Amino Acids[320]



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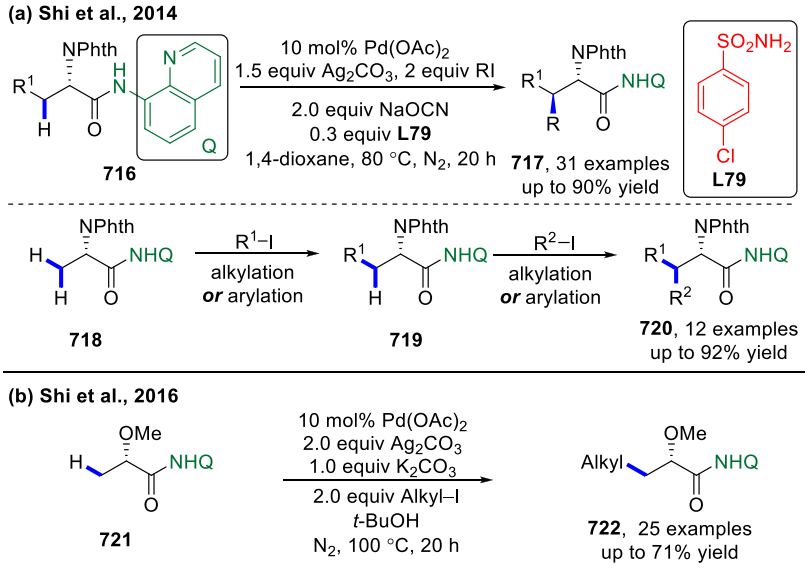
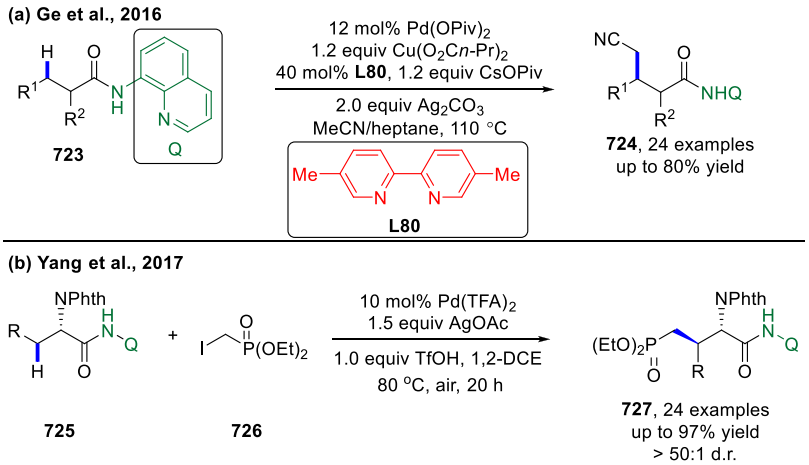
Scheme 115. 8-Aminoquinoline-Directed C(sp^3)−H Alkylation with Various β-Hydrogen Containing Alkyl Iodides: (a) Methylene C(sp^3)−H Alkylation of *N*-Phthaloyl α-Amino Acids;[321] (b) Methyl C(sp^3)−H Alkylation of Lactic Acid[322]



Scheme 116. (a) Cyanomethylation of Unactivated Methylene C(sp^3)−H Bonds with Acetonitrile[323] and (b) Methylene C(sp^3)−H Alkylation of Amino Acids with (Iodomethyl)phosphonate[324]



to oxidize the CH_3CN-bound palladacycle via a Pd(II)/Pd(IV) redox process, which then triggers a facile reductive elimination to generate the carbonylated product. The methylene C(sp^3)−H alkoxycarbonylation of a broad range of *N*-phthaloyl amino acids was achieved. The relative stability of CO−ligand palladacycle complexes has been extensively studied by Shi, Hong, Wang, and co-workers in 2019 (Scheme 121b).[334] Based on computational study, they found that the Gibbs free energy (ΔG) for ligand exchange with four different electrophiles is significantly higher with the CO-coordinated palladacycle than with the palladacycles coordinated with CH_3CN, DMSO, and pyridine (>3.2 kcal/mol). It was also observed that the CO-coordinated palladacycle is extremely stable under a variety of conditions.

2.2.2. Carbon−Heteroatom Bond Formation. *2.2.2.1. Carbon−Oxygen Bond Formation.* The first C(sp^3)−H acetoxylation of protected amino acids was reported by the Corey group in 2006 (Scheme 122a).[188] A number of *N*-phthaloylamino acids with various carboxylate-based directing auxiliaries, such as *N*-methoxyamide, Weinreb amide, oxazoline, picolinamide (PA), pyridin-2-ylmethanamine, and 8-aminoquinoline, were investigated. Promising results were only observed when the 8-aminoquinoline group was used. Screening of various additives showed that the use of $Mn(OAc)_2$ led to critical improvement of the yield. Corey and co-workers postulated that the stereochemistry of the β-functionalization can be understood in terms of a preference for forming the sterically favored *trans*-palladacycle intermediate (**764**). In 2012, the Daugulis group also described a method for C−H acetoxylation of amino acid derivatives using $PhI(OAc)_2$ as the oxidant and Ac_2O as the solvent.[196] In 2015, an improved synthesis of *anti*-β-hydroxy-α-amino acids via Pd(II)-catalyzed arylation or alkylation of C(sp^3)−H bonds followed by β-acetoxylation was developed by Shi and co-workers.[335]

In 2012, the alkoxylation of unactivated C(sp^3)−H bonds with broad scope of PA DG-containing substrates was reported by the Chen group (Scheme 122b).[336] A wide range of primary alcohols, such as MeOH, *n*-PrOH, BnOH, CF_3CH_2OH, and *n*-octyl alcohol, can be used, giving the desired products in good to excellent yields. In addition, secondary alcohols, such as *i*-PrOH and cyclohexanol provided the corresponding products in good yields after prolonged reaction time. Even *t*-BuOH afforded the

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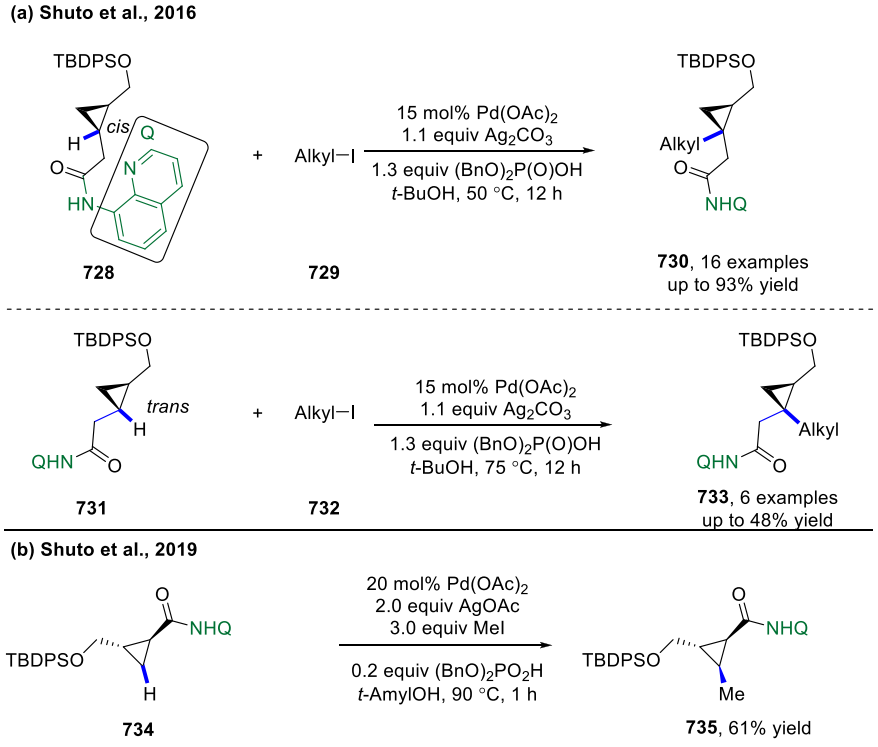
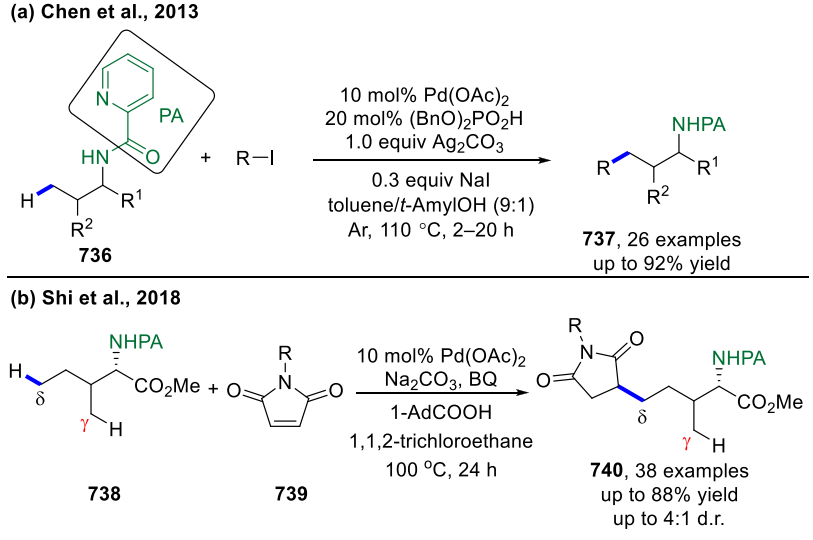
Scheme 117. 8-Aminoquinoline-Directed C(sp^3)−H Alkylation of Cyclopropane[311,325]



Scheme 118. (a) Picolinamide-Directed Alkylation of Unactivated Methyl C(sp^3)−H Bonds with Alkyl Iodides[327] **and (b) Remote Selective δ-C(sp^3)−H Alkylation of Amino Acids and Peptides with Maleimides**[328]



tert-butyl ether product in 63% yield. Aliphatic amine substrates bearing primary γ-C(sp^3)−H bonds with or without α-substituents can be methoxylated under the standard reaction conditions.

In 2012, Sahoo and co-workers described a process for selective acetoxylation of unactivated β-C(sp^3)−H bonds using $PhI(OAc)_2$ as the oxidant with the assistance of *S*-methyl-*S*-2-pyridylsulfoximine (MPyS) at room temperature (Scheme 123a).[337] Control experiments indicated that the carboxylic acid solvent participated in C−O bond formation, while the $PhI(OAc)_2$ oxidant turned over the catalytic cycle. Thus, a variety of carboxylic acids, CD_3CO_2H, $EtCO_2H$, *n*-$PrCO_2H$, and *iso*-$PrCO_2H$, could be incorporated into the oxygenated products. Finally, the DG can be easily removed by simple acid hydrolysis and can be recycled after recovery, which improves the practical utility of this method. Over the next few years, a number of additional directing groups were employed in successful C(sp^3)−H acetoxylation. In 2013, 2-*N*-pyridine-1,2,3-triazole-4-amide-directed, methyl C(sp^3)−H acetoxylation was reported by the Shi group (Scheme 123b).[338] In 2014, palladium-catalyzed γ-C(sp^3)−H acetoxylation of *N*-alkylpicolinamide substrates using $PhI(OAc)_2$ oxidant was developed by the Chen group (Scheme 123c).[339] In 2015, palladium-catalyzed oxygenation of C(sp^3)−H bonds with the assistance of the oxalyl amide DG was reported by the Zhao group (Scheme 123d).[340]

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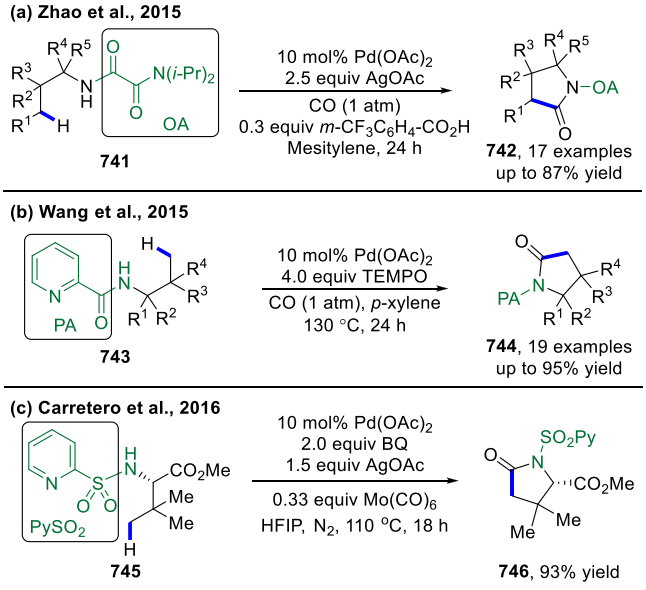
Scheme 119. Pd-Catalyzed γ-C(sp³)−H Carbonylation: (a) Oxalyl Amide DG;[329] (b) Picolinamide DG;[330] (c) *N*-(2-Pyridyl)sulfonamide DG[331]

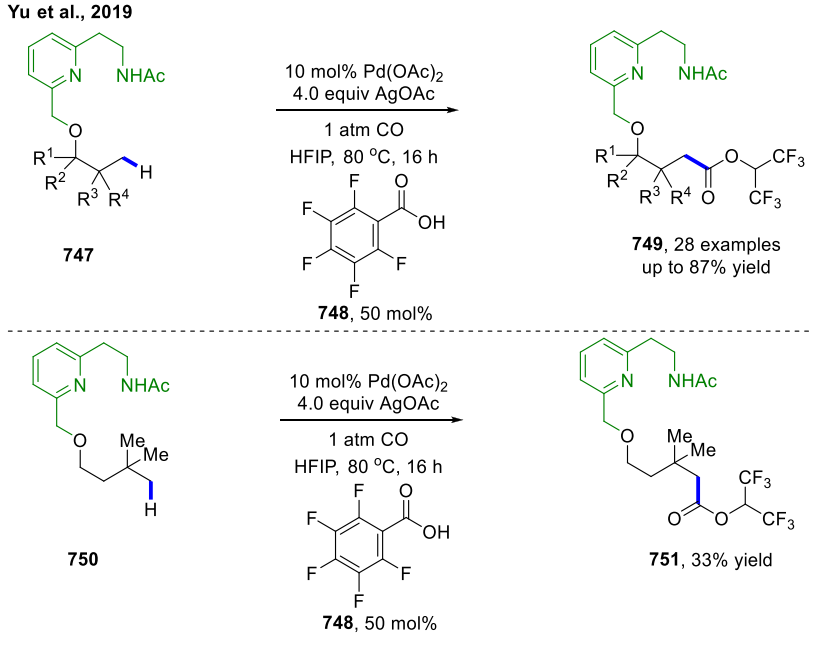


Methylene C(sp³)−H bond alkoxylation, which is more challenging compared to the methyl C(sp³)−H bond alkoxylation due to high steric hindrance, was achieved by the Shi group in 2013 (Scheme 124).[341] Inspired by the early efforts of Daugulis, the authors designed and reported the first use of a novel 2-(pyridine-2-yl)isopropyl (PIP) DG, which proved most efficient for this transformation. Optimization revealed that the use of recrystallized $PhI(OAc)_2$ (from HOAc and hexane) significantly improved the yield. This reaction protocol was very sensitive to steric hindrance; substrates with linear chains gave high yields, while substrates bearing sterically demanding groups at the α position failed. A large number of alcohols, such as linear or branched primary alcohols, were found to be compatible with the reaction protocol. Additionally, secondary alcohols could be applied in the alkoxylation reaction, albeit in slightly lower yields. Later, C−H alkoxylation of unactivated methylene using cyclic hypervalent iodine (I^{3+}) oxidants with the aid of 8-aminoquinoline was reported by the Rao group.[342−344]

Palladium-catalyzed β-C(sp³)−H acetoxylation of tripeptides via *N*,*N*-bidentate coordination of the peptide backbone was demonstrated by Yu and co-workers in 2014 (Scheme 125).[261] Currently, the acetoxylation of the tripeptide N-terminus is limited to alanine.

In 2012, Dong and co-workers developed a Pd-catalyzed, oxime-directed functionalization of unactivated β-C(sp³)−H bonds via a five-membered *exo*-palladacycle (Scheme 126a).[345] The substrate scope of primary, secondary, and tertiary alcohol derivatives was examined, and the corresponding vicinal dioxygenated products were isolated in good yields. Notably, in substrates that lack methyl groups at the β-positions, C−H activation can take place at methylene positions. Additionally, the methine tertiary C−H bonds of norborneol-derived substrates could also be oxidized. In 2015, the Dong group further expanded this protocol to an analogous intramolecular version for the synthesis of cyclic ethers (Scheme 126b).[346] In the same year, the Dong group developed a Pd-catalyzed, 8-quinolinecarboxaldehyde oxime-directed sulfonyloxylation of a nonactivated C(sp³)−H bond at the β-position, providing a convenient and efficient approach for the synthesis of β-sulfonyloxylated alcohols (Scheme 126c).[347] Remarkably, both methyl and unactivated methylene C−H bonds could be sulfonyloxylated in moderate yields. The tosyl group could be used as a late-stage intermediate to prepare complex molecules via nucleophilic substitution (S_N2) reactions. In 2016, Dong and co-workers extended this strategy to a hydrazone-based DG for the β-C(sp³)−H oxidation of aliphatic amines (Scheme 126d).[348] Inspired by these precedents, the C(sp³)−H acetoxylation of alcohol derivatives that bear a monoanionic *N*,*N*-bidentate DG was disclosed by Xu and co-workers in 2019 (Scheme 126e).[270] The potential application of this reaction was

Scheme 120. Palladium-Catalyzed γ-C(sp³)−H Carbonylation of Aliphatic Alcohols[332]



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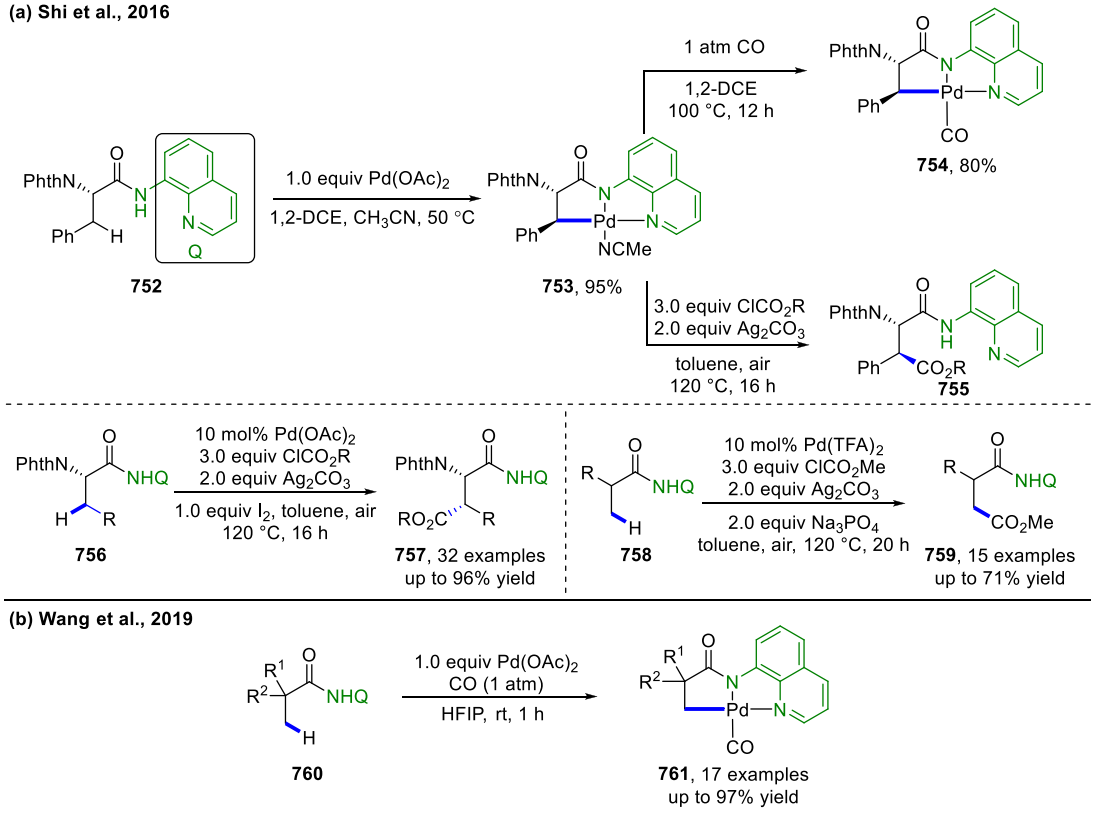
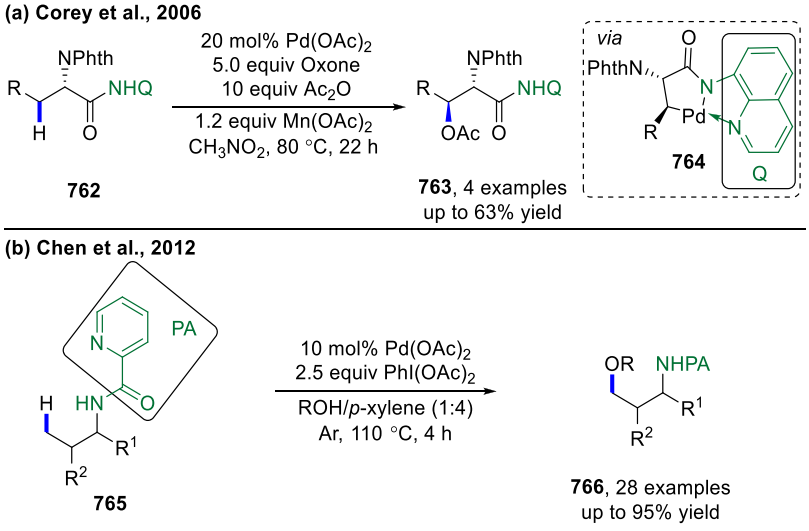
Scheme 121. (a) Palladium-Catalyzed Alkoxycarbonylation of Unactivated β-Methylene C(sp^3)−H Bonds with Alkyl Chloroformates[333] and (b) Synthesis of Stable CO-Coordinated Palladacycles and Mechanistic Studies[334]



Scheme 122. (a) 8-Aminoquinoline-Directed β-Methylene C(sp^3)−H Acetoxylation of *N*-Phthaloylamino Acids[188] and (b) Picolinamide-Directed γ-Methyl C(sp^3)−H Alkoxylation[336]



demonstrated by removing the DG and Ac group to generate 1,2-diols in good yields.

All the aforementioned bidentate DGs proceed through five- or six-membered metallacycle intermediates. Transition-metal-catalyzed C(sp^3)−H activation via four-membered metallacycle intermediates is less developed. Two notable examples covered earlier were monodentate-directed, Pd-catalyzed C(sp^3)−H carbonylation and Pd-catalyzed C(sp^3)−H activation of aliphatic amines, both reported by Gaunt in 2014.[145] In 2015, the Zhang group reported 1-aminoanthraquinone-directed, α-C(sp^3)−H acetoxylation of aliphatic carboxamides via a four-membered palladacycle intermediate (Scheme 127a).[349] In 2020, the Hartwig group reported primary β-C(sp^3)−H acetoxylation of aliphatic amines via a four-membered palladacycle by using salicylaldimine as the DG (Scheme 127b).[350] However, isolation of the four-membered palladacycle was unsuccessful. DFT calculations indicated that formation of the four-membered palladacycle is endergonic, in contrast to formation of the corresponding five-membered palladacycle,

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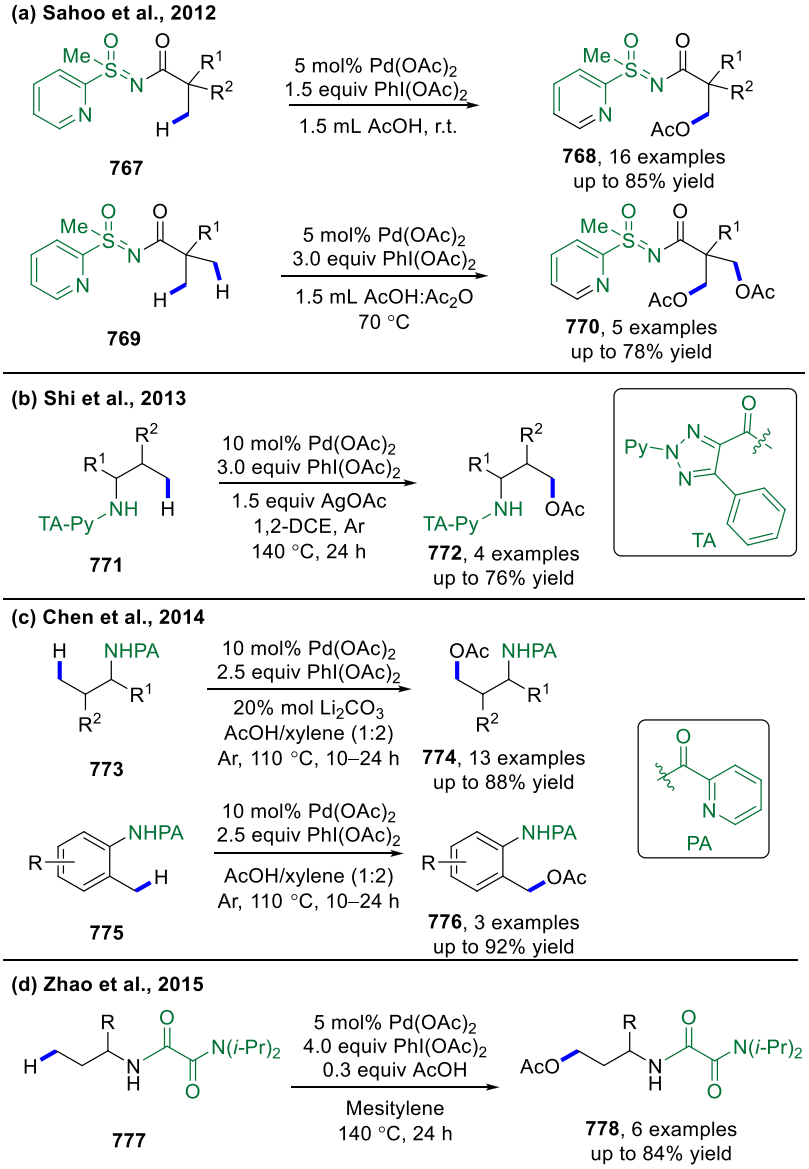
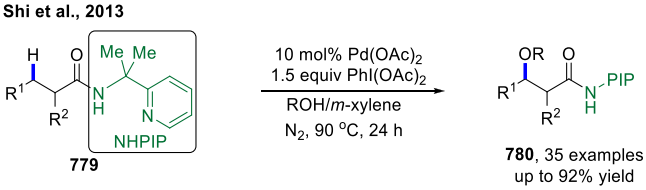
Scheme 123. (a) MPyS-*N*-Amide-Directed Primary β-C(sp^3)−H Acetoxylation,[337] (b) 1,2,3-Triazole-4-Amide-Directed Methyl C(sp^3)−H Acetoxylation,[338] (c) Picolinamide-Directed γ-C(sp^3)−H Acetoxylation,[339] and (d) Oxalyl-Amide-Directed γ-C(sp^3)−H Acetoxylation[340]



Scheme 124. PIP-Directed Unactivated Methylene C(sp^3)−H Alkoxylation[341]



which is exergonic. These results explain the challenge of isolating the former.

2.2.2.2. Carbon−Nitrogen Bond Formation. In 2012, the Chen group reported a Pd-catalyzed, picolinamide-directed, and $PhI(OAc)_2$-mediated intramolecular amination of unactivated γ- and δ-C(sp^3)−H bonds of amine substrates, leading to the formation of azetidines and pyrrolidines (Scheme 128a).[351] Chen and co-workers found that the selective intramolecular amination of primary δ-C(sp^3)−H bonds in the leucine-derived substrate in the presence a sterically less accessible tertiary γ-C(sp^3)−H bond was achieved, giving the pyrrolidine product. In addition, no pyrrolidine products were isolated in the cyclization reactions of substrates that bear primary C(sp^3)−H groups at both γ and δ positions, which can be explained by preferential formation of the kinetically favored five-membered palladacycle over the six-membered palladacycle. In order to improve the synthetic utility of this protocol, a modified picolinic acid (PAre) was introduced as an auxiliary since PAre can be removed under mild conditions, such as in 1 M HCl at room temperature for 24 h, unlike PA, which traditionally requires significantly harsher conditions. Contemporaneously, the Daugulis group reported a similar method to achieve the same transformation (Scheme 128b).[352] In 2013, Shi and co-workers reported an example of intramolecular amination of primary C(sp^3)−H bonds with a triazole-derived DG (Scheme 128c).[338] An oxalyl-amide-assisted, intramolecular δ-C(sp^3)−H/N−H cyclization used in

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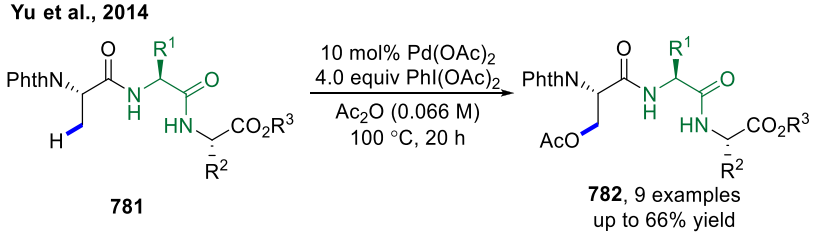
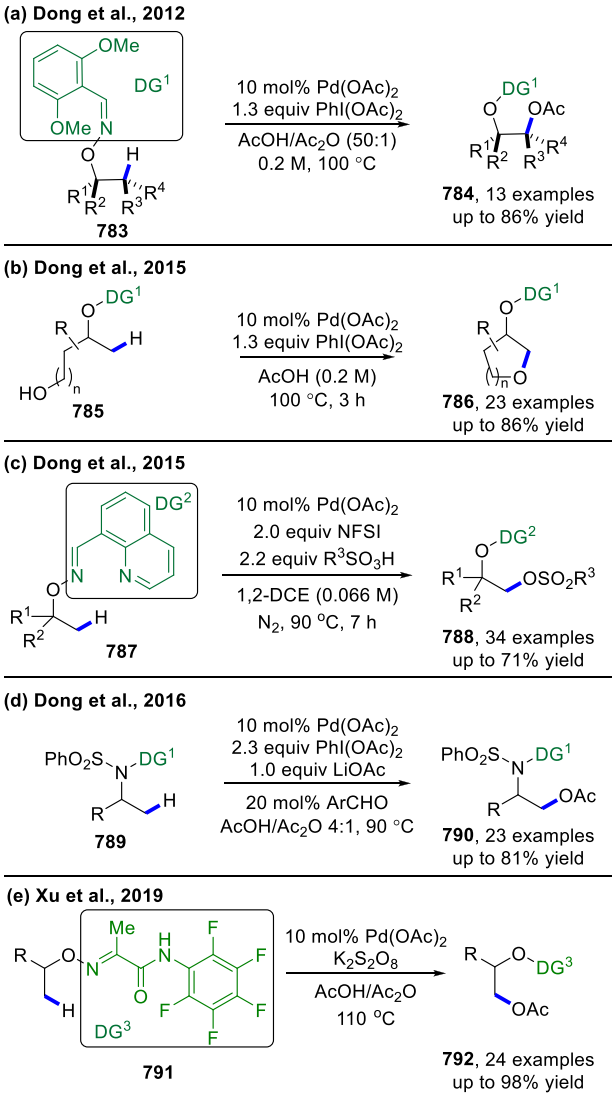
Scheme 125. Amino Acid-Directed C(sp^3)−H β-Acetoxylation of Dipeptides[261]



Scheme 126. *exo*-Oxime-type DG Enabled C(sp^3)−H Oxygenation: (a) Intermolecular Acetoxylation;[345] **(b) Intramolecular Etherification;**[346] **(c) Tosyloxylation;**[347] **(d) β-Acetoxylation of Aliphatic Amines;**[348] **(e) Monoanionic *N,N*-Bidentate DG**[270]



the synthesis of pyrrolidones was reported by Zhao and co-workers in 2014 (Scheme 124d).[353]

In 2013, Chen and co-workers developed a method for the synthesis of pyrrolidones via the Pd-catalyzed, carboxamide-directed, intramolecular amidation of unactivated γ-methyl C(sp^3)−H bonds (Scheme 129a).[354] When the reaction was attempted with a substrate that required formation of the kinetically more favorable five-membered palladacycle intermediate, no desired lactam product was observed, likely due to the ring strain inherent in four-membered β-lactams. Chen and co-workers, therefore, proceeded to explore a starting material that could access the kinetically unfavorable six-membered palladacycle intermediate that did indeed react readily with $PhI(OAc)_2$ to afford the γ-lactam products with high selectivity. Notably, this intramolecular γ-C(sp^3)−H amination reaction could be applied in conjunction with other aminoquinoline-directed C(sp^3)−H functionalization reactions. However, the cleavage of the DG is difficult with respect to this intramolecular C−H lactamization method. After evaluating modified auxiliary groups, 8-amino-5-methoxyquinoline (MQ) was found to be installed readily on carboxylic acid substrates and removed smoothly in the presence of ceric ammonium nitrate (3 equiv) in CH_3CN/H_2O at room temperature for 5 h.

The Shi group developed a robust protocol for the stereoselective synthesis of α-amino-β-lactams through Pd(II)-catalyzed sequential C(sp^3)−H monoarylation/amidation (Scheme 129b).[233] After extensive screening, the optimized reaction conditions were reported as $Pd(OAc)_2$ (10 mol %), $NaIO_3$ (0.3 mmol) as the oxidant, and Ac_2O (1.5 mmol) as the additive in MeCN (3 mL) under N_2 atmosphere at 70 °C for 48 h. The *N,N*-bidentate PIP amide DG was found to be effective both in controlling selectivity in the monoarylation step and in enhancing reactivity in the amination step. In 2017, they reported an improved synthesis of α-amino-β-lactams by employing MQ as a removable bidentate DG.[355]

In 2014, the Wu group also developed an efficient method to synthesize β-lactams with high regioselectivity through a Pd-catalyzed, intramolecular β-C(sp^3)−H amination of 8-amino-quinoline carboxamides (Scheme 129c).[356] They explored numerous aryl iodides with electron-withdrawing substituents and found that C_6F_5I could act as an efficient oxidant to enable the desired C−N reductive elimination rather than C−C reductive elimination, leading to the formation of desired β-lactams in high yield and selectivity. In 2014, during their endeavors to synthesize aryltetralin lignan natural products, the Maimone group was also able to isolate β-lactams produced by palladium-catalyzed intramolecular amidation of benzylic C-(sp^3)−H bonds using electron-deficient aryl iodides as oxidants.[193]

In 2020, Chen and co-workers demonstrated the synthesis of chiral β-lactams via Pd-catalyzed, 8-aminoquinoline-directed, enantioselective benzylic methylene C(sp^3)−H amidation using 3,3′-fluorinated BINOL (**L78**) as a chiral ligand (Scheme 130a).[357] A sterically hindered aryl iodide oxidant was found to promote C−N reductive elimination. Unfortunately, the amidation of aliphatic secondary C(sp^3)−H bonds using various 5-substituted 8-aminoquinoline DGs failed to give any promising results. At the same time, the Shi group successfully reported the palladium-catalyzed, enantioselective amidation of both benzylic and aliphatic secondary β-C(sp^3)−H bonds using

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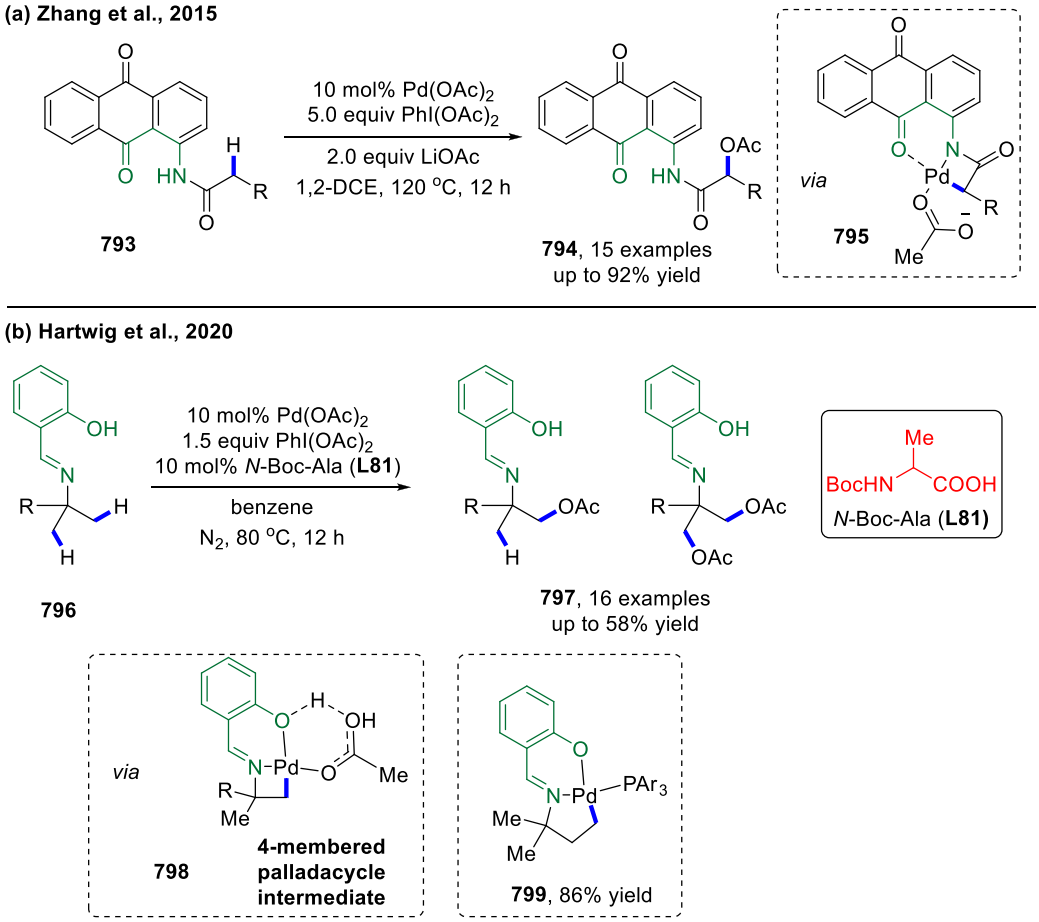
Scheme 127. Palladium-Catalyzed Intermolecular Acetoxylation of C(sp^3)−H Bonds via a Four-Membered Palladacycle[349,350]



PIP as bidentate DG (Scheme 130b).[358] The C−N reductive elimination product is the main product observed when using electron-deficient aryl iodide compounds, which is proposed to inhibit the undesired C−C reductive elimination. The amidation products via β-benzylic methylene C(sp^3)−H bond activation were obtained in high yields and ee in the presence of a 3,3′-dichlorinated BINOL ligand (**L82**). By switching 3,3′-dichlorinated BINOL to (*S*)-3,3′-fluorinated H_8-BINOL, they obtained chiral β-lactams via aliphatic secondary C(sp^3)−H amidation in good yields and ee (**L83**).

In 2015, a Pd(II)-catalyzed intermolecular amination of unactivated methyl C(sp^3)−H bonds using 2-(methylthio)-aniline as a bidentate DG was reported by the Qin group (Scheme 131a).[359] The reaction conditions were reported as $PdCl_2$ (10 mol %) as catalyst with Cs_2CO_3 (2 equiv) as base in benzene at 110 °C for 24−34 h. Kinetic isotope experiments revealed that the β-C(sp^3)−H bond cleavage step was the turnover-limiting step. In 2017, the Zhang group reported the 2-(pyridin-2-yl)isopropyl (PIP)-directed, intermolecular amination of methylene C(sp^3)−H bonds with diisopropylazodiformate (DIAD) as the amination reagent (Scheme 131b).[360] In the same year, Dong and Liu reported an intermolecular methyl C(sp^3)−H sulfonamidation of aliphatic alcohol derivatives with *N*-fluorobenzenesulfonimide (NFSI) (Scheme 131c).[361]

2.2.2.3. Carbon−Halogen Bond Formation. In 2014, the Sahoo group reported a palladium-catalyzed halogenation of unactivated primary C(sp^3)−H bonds with the assistance of the *S*-methyl-*S*-2-pyridylsulfoximine DG (Scheme 132a).[362] *N*-Bromophthalimide and *N*-chlorophthalimide were used as halogen sources. However, only primary C(sp^3)−H bonds that are adjacent to quaternary carbon centers could be transformed into C−Cl and C−Br bonds. In 2017, Yu and co-workers developed an aminooxyacetic acid auxiliary-directed β-C(sp^3)−H iodination of ketones catalyzed by $Pd(TFA)_2$ (Scheme 132b).[363] A wide range of ketones underwent β-iodination in good to excellent yields. Interestingly, a C−H insertion intermediate was isolated, which provided evidence for the L,X-type coordination mode of the oxime-carboxylic acid DG. In 2020, the Polyzos group reported a creative method for the halogenation of β-C(sp^3)−H bonds with alkyl halides (Scheme 133).[364] By visible light excitation of the palladacycle, an electron transfer to the alkyl halide produces a palladium(III) intermediate, which can either undergo disproportionation or be oxidized by Oxone to generate a palladium(IV) complex. Reductive elimination from the palladium(IV) complex affords the halogenation product in moderate to good yields.

In 2015, the first bidentate group-directed, palladium-catalyzed C(sp^3)−H fluorination of aliphatic carboxamides to synthesize β-fluoro α-amino acids was reported by the Shi group (Scheme 134a).[365] A broad range of substituted phenylalanine derivatives were fluorinated using Selectfluor as the F^+ source. Gratifyingly, when 2-methylbenzoic anhydride (**L84**) was used as an additive, fluorination of aliphatic methylene C(sp^3)−H bonds was also achieved. A wide range of protected natural and unnatural amino acid derivatives containing the PIP DG were compatible with this fluorination protocol, providing the desired products in moderate yields. Notably, a gram-scale reaction was performed, and the fluorinated product **850** was obtained in

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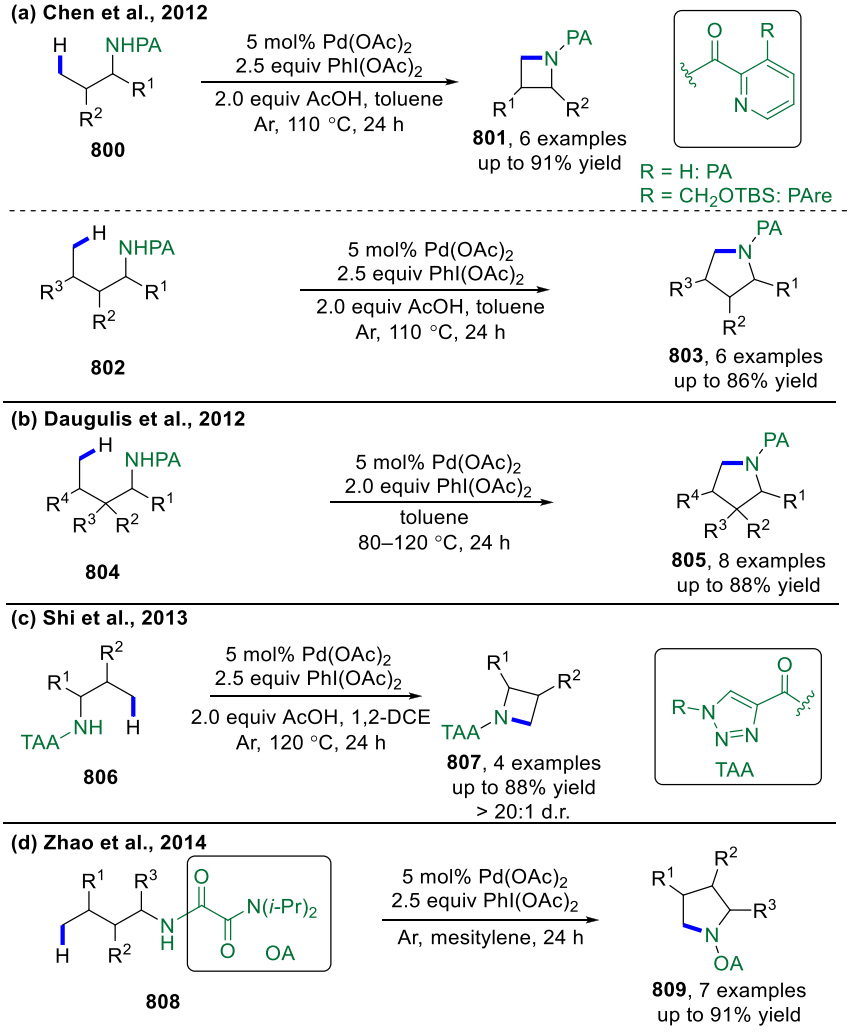
Scheme 128. (a, b) Picolinamide-Directed Intramolecular Amination of Unactivated C(sp^3)−H Bonds,[351,352] (c) 1,2,3-Triazole-4-Amide-Directed Intramolecular γ-(sp^3)−H Amination,[338] (d) Oxalyl-Amide-Directed Intramolecular δ-(sp^3)−H Amination[353]



69% yield. To further demonstrate the synthetic utility of this fluorination method, removal of the PIP DG was carried out, and the corresponding products were obtained in good yields with retention of configuration. Palladacycle intermediate **853** was isolated in 86% yield when **849** was allowed to react with 1 equiv of $Pd(OAc)_2$ in DCM at room temperature overnight. A stoichiometric reaction of **853** with 1.05 equiv of Selectfluor in d_3-MeCN was also conducted, which led to the formation of **853** in 78% yield within 5−10 min. Treatment of **854** with an aqueous solution of NH_4Cl and Na_2S provided the fluorinated product **850** in 86% yield with retention of configuration, consistent with direct C−F reductive elimination from the palladium center. Finally, they found that **853** was a viable precatalyst for the C−H fluorination of **849**. Palladium-catalyzed cyclic methylene C(sp^3)−H fluorination of alcohol derivatives directed by a 8-formylquinoline-derived oxime DG was also observed by the Dong group in 2015 (Scheme 134b).[347] During their investigation of alcohol β-C(sp^3)−H sulfonyloxylation, they found that a competitive β-C(sp^3)−H fluorination occurred when a set of cyclohexanol derivatives, such as *cis*-4-(*tert*-butyl)cyclohexanol, *trans*-4-(*tert*-butyl)-cyclohexanol, menthol, and cholesterol, were used as substrates. The tosyloxylation−fluorination ratios were determined by the substrate configurations and C−H functionalization predominantly occurred at the equatorial position. The production of sterically hindered product is indicative of a plausible concerted reductive elimination mechanism. It is noteworthy that the cholesterol derived substrate (**855d**) has also been converted to the mixture containing mesylated (OMs) and fluorinated products at the equatorial positions of C2 (**856d**) and C4 (**856d′**).

Soon afterward, the Ge group also developed a highly site-selective, PIP-directed, palladium-catalyzed C(sp^3)−H fluorination of aliphatic acid and α-amino acid derivatives (Scheme 135a).[366] The reaction conditions reported on 0.30 mmol scale were $Pd(OAc)_2$ (10 mol %), Selectfluor (2.5 equiv), $Fe(OAc)_2$ (0.3 equiv), Ag_2CO_3 (2.0 equiv), and 300 μL *i*-PrCN in 1,2-DCE (3.0 mL) at 150 °C for 14 h. The substrate scope was investigated, and the authors noted a large preference for functionalization of the unactivated β-C(sp^3)−H bond over the relatively reactive benzylic γ-C(sp^2)−H bond. After the fluorination reaction, the PIP auxiliary could be removed, and the desired products were isolated in good yields. Contemporaneously, 8-aminoquinoline-directed, Pd(II)-catalyzed fluorination of unactivated methylene and methyl C(sp^3)−H bonds at the β-position of carboxylic acids was developed by the Xu group (Scheme 135b).[367] Huang and co-workers later observed a significant difference between 8-aminoquinoline and 8-amino-

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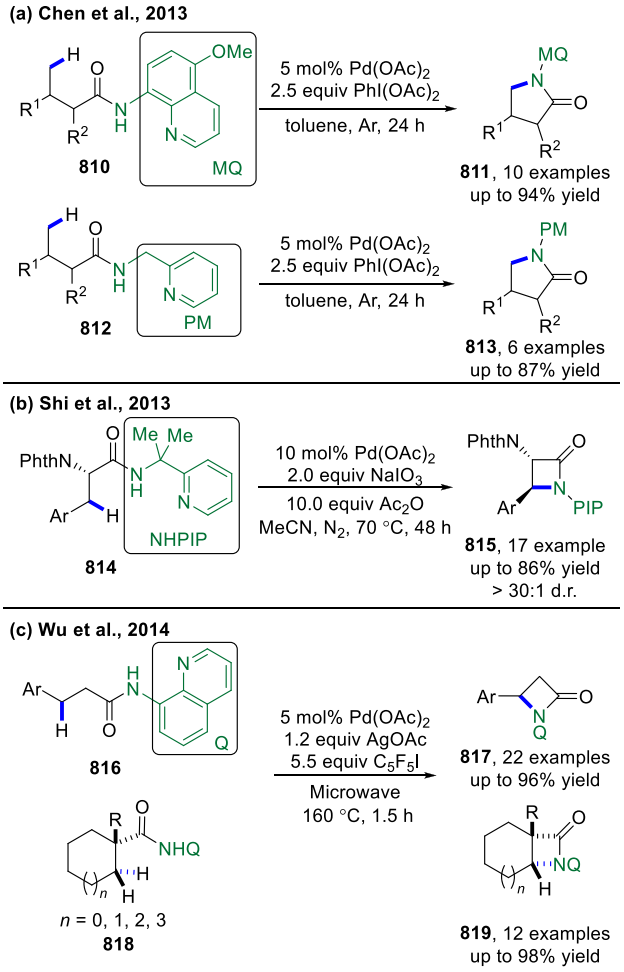
Scheme 129. (a) Synthesis of Pyrrolidones via the Pd-Catalyzed Intramolecular γ-Methyl C(sp^3)−H Amidation,[354] (b) Synthesis of β-Lactams via PIP-Directed Intramolecular β-Methylene C(sp^3)−H Amidation,[233] and (c) 8-Aminoquinoline-Directed Intramolecular β-C(sp^3)−H Amidation for the Synthesis of β-Lactams[356]



quinoxaline DGs for C(sp^3)−H fluorination reactions, with the latter providing the desired product in greater yield (Scheme 135c).[368] Experimental and computational studies revealed that the Pd(II)/Pd(IV) oxidation step was significantly affected by changes of the DG structure. In 2018, Xu and co-workers developed a method for the β-C(sp^3)−H fluorination of simple aliphatic alcohol derivatives using a novel exo-type DG (Scheme 136).[369] Both methyl C(sp^3)−H bonds and methylene C(sp^3)−H bonds could be functionalized in this transformation.

In 2018, the Yu group discovered that a bulky amino amide substrate could be used as a catalytic transient DG for palladium(II)-catalyzed, enantioselective C(sp^3)−H fluorination (Scheme 137).[370] When simple glycine was used as the transient DG, the corresponding C(sp^3)−H acetoxylation product was obtained as the major product. The authors had to consider how to promote the desired reductive elimination step, so they tested a series of amino acid transient DGs and found that selectivity for formation of the fluorinated product increased with increasing steric bulk on the side chain. They further found that switching to an amino amide transient DG further improved fluorination selectivity, with the *N*,*N*-diethyl amide proving optimal. Deuterium incorporation experiments indicated that the C(sp^3)−H insertion process is irreversible. The Yu group proposed that the C(sp^3)−F bond formation proceeds via an inner-sphere reductive elimination pathway with retention of configuration while the C(sp^3)−O bond formation occurs through an S_N2-type mechanism, consistent with the observation that the fluorinated and acetoxylated products have opposite absolute stereochemical configuration, as determined by X-ray crystallography.

2.2.2.4. Carbon−Sulfur and −Selenium Bond Formation. Although sulfonylation through a Pd(II)/Pd(IV) catalytic cycle was demonstrated early by the Dong group, this type of reaction is generally limited to C(sp^2)−H bonds.[371,372] In 2015, Shi and co-workers reported a Pd-catalyzed sulfonylation of unactivated C(sp^3)−H bonds with sodium sulfinates, which provides a method for the synthesis of diverse aryl alkyl sulfones (Scheme 138a).[373] $MesCO_2H$, a sterically bulky benzoic acid, was the best carboxylic acid additive for this protocol. A wide range of sodium arylsulfinates that bear electron-donating or -withdrawing groups were tolerated and gave the desired sulfonylated products in good yields. Finally, the potential utility of this C(sp^3)−H sulfonylation protocol was demonstrated by removal of the 8-aminoquinoline auxiliary in a representative product and through late-stage sulfonylation of β-citronellol, (−)-santonin, and cholic acid.

Among sulfur-containing functional groups, the trifluoromethylthiol functional group has recently attracted attention in medicinal chemistry, and in 2015, the first example of a palladium-catalyzed trifluoromethylthiolation of unactivated C(sp^3)−H bonds was disclosed by Besset and co-workers (Scheme 138b).[374] However, the highest yield of the desired product was 53%. In 2018, the Maiti group reported an 8-aminoquinoline-directed, γ-C(sp^3)−H chalcogenation of α-amino acids using disulfides or diselenides enabled by 2-chloroquinoline (**L85**) ligand (Scheme 138c).[375]

2.2.2.5. Carbon−Boron, −Silicon, and −Germanium Bond Formation. In 2014, Shi and co-workers reported the direct transformation of unactivated primary γ-C(sp^3)−H bonds of amino acid derivatives into C(sp^3)−B bonds using B_2pin_2 as the borylating reagent with the assistance of picolinamide as DG (Scheme 139).[376] Notably, oxygen was the sole oxidant in this transformation. A variety of amine substrates, such as amino acids and alkyl amines, were converted to desired alkyl boron species in good yields.

While studying the Pd-catalyzed silylation of *ortho*-C(sp^2)−H bonds with hexamethyldisilane in 2014, Kanai and co-workers also explored a limited substrate scope in which Pd catalyzed the silylation of unactivated C(sp^3)−H bonds, albeit with the highest yield under the reported reaction conditions being only 39% (Scheme 140a).[377] In 2016, the Shi group reported an 8-aminoquinoline-directed, palladium(II)-catalyzed β-C(sp^3)−H silylation of amino acids (Scheme 140b).[378] Both primary and secondary β-C(sp^3)−H could be silylated in moderate to good yields. Contemporaneously, Zhang and co-workers reported the silylation of unactivated β-C(sp^3)−H bonds (Scheme 140c).[379] In 2018, Liu and co-workers extended the reaction conditions developed by the Shi group[378] to the synthesis of β-germyl-α-amino acids (Scheme 140d).[380] In 2019, the Shi group described a procedure for γ-C(sp^3)−H silylation of peptides using picolinamide (PA) as the DG (Scheme 140e).[381] A variety of α-amino acids, α-amino alcohols, and oligopeptides were transformed to the corresponding silylated products in good yields. In 2017, Maiti and co-workers developed reaction conditions for the silylation and germylation of unactivated γ-

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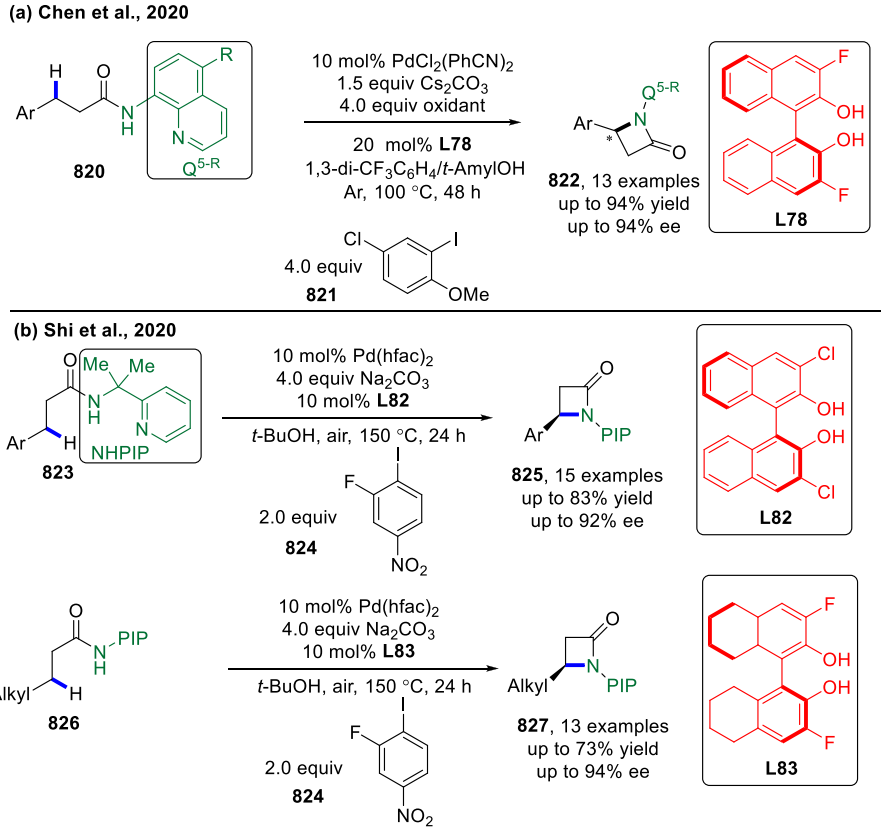
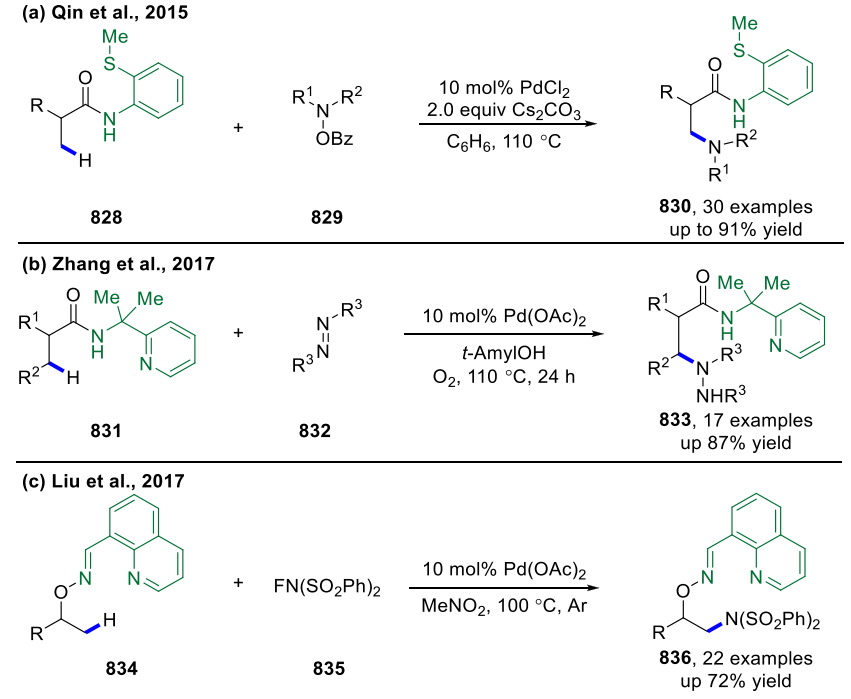
Scheme 130. Synthesis of Chiral *β*-Lactams (a) via 5-Subsituted 8-Amioquinoline-Directed Enantioselective Benzylic C(sp^3)−H Amidation[357] and (b) via PIP-Directed Enantioselective Amidation of Both Benzylic and Unbiased Methylene C(sp^3)−H Bonds[358]



Scheme 131. (a) Intermolecular Methyl C(sp^3)−H Amination Directed by 2-Thiomethylaniline,[359] (b) Intermolecular Amination of Unactivated Methylene C(sp^3)−H Bonds Directed by PIP,[360] and (c) Intermolecular Sulfonamidation of Methyl C(sp^3)−H Bonds of Aliphatic Alcohols[361]



C(sp^3)−H bonds of aliphatic acids via six-membered palladacycles through the blocking of *β*-positions (Scheme 141).[382]

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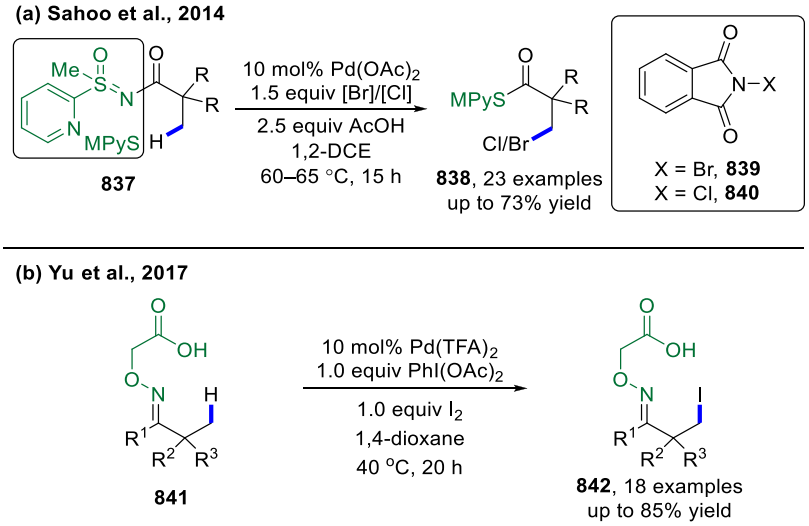
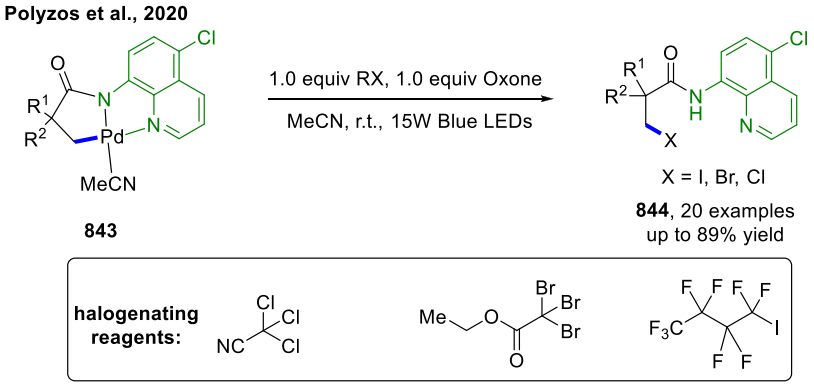
Scheme 132. (a) Sulfoximine-Directed Bromination and Chlorination of Primary β-C(sp^3)−H Bonds[362] and (b) β-C(sp^3)−H Iodination of Ketones[363]



Scheme 133. 5-Chloro-8-aminoquinoline-Directed Light-Induced β-C(sp^3)−H Halogenations[364]



3. NICKEL-CATALYZED, COORDINATION-ASSISTED FUNCTIONALIZATION OF C(sp^3)−H BONDS

While palladium has proven to be a privileged metal in C−H functionalization, its expense and scarcity have driven the development of earth-abundant nickel catalysts as competent alternatives in certain cross-coupling reactions. Compared to palladium, nickel offers increased access to alkyl coupling partners because it is frequently able to engage in single electron transfer (SET) processes and it undergoes a sluggish β-hydride elimination from alkylnickel species.[383−390] Three general catalytic cycles involving different redox processes have been proposed for nickel-catalyzed C(sp^3)−H activation reactions (Scheme 142). In particular, both Ni(II)/Ni(IV) and Ni(II)/Ni(III) catalytic cycles have been invoked in a number of reports on C(sp^3)−H arylation and alkylation, whereas a Ni(II)/Ni(II) catalytic cycle is thought to be operative in reaction involving C(sp^3)−H activation followed by alkyne/alkene insertion. The first example of Ni-catalyzed, coordination-assisted functionalization of C−H bonds using an *N,N*-bidentate DG involved the oxidative annulation of aromatic amides with internal alkynes for the synthesis of isoquinolones as reported by the Chatani group in 2011.[391] Since then, tremendous progress has been made in the field of Ni-catalyzed C(sp^2)−H bond functionalization using *N,N*-bidentate DGs.[392−395]

Nickel-catalyzed C(sp^3)−H bond activation reactions usually require high temperatures, and to the best of our knowledge, 8-aminoquinoline is the only *N,N*-bidentate DG that has been used for Ni-catalyzed C(sp^3)−H bond functionalization. Nevertheless, the first nickel(II)-catalyzed β-arylation of unactivated C−H bonds of aliphatic amides was reported by the Chatani group in 2014, using the 8-aminoquinoline moiety as the bidentate DG and iodoarenes as coupling partners (Scheme 143a).[396] $Ni(OTf)_2$ was applied as the catalyst with the aid of a sterically bulky carboxylic acid ($MesCO_2H$) and a base (Na_2CO_3), which are proposed to facilitate a concerted metalation−deprotonation step during the C−H cleavage step. It is worth noting that the reaction proceeds smoothly with either $Ni(OAc)_2$ or $Ni(COD)_2$ as the precatalyst.

The Chatani group also demonstrated the first example of a Ni(II)-catalyzed arylation of C(sp^3)−H bonds in aliphatic amides with diaryliodonium salts (Scheme 143b).[397] In this case, the desired products were isolated in good yields even in the absence of a carboxylic acid additive. Since diaryliodonium salts could undergo decomposition under heat or basic conditions to generate aryl iodides or aryl triflate, a control experiment was conducted to confirm that diaryliodonium salts are the main arylation reagent (76% yield) in the system; 4-$MeOC_6H_4I$ (37% yield) might have a small contribution, while 4-$MeOC_6H_4OTf$ (0% yield) has no contribution to this arylation process.

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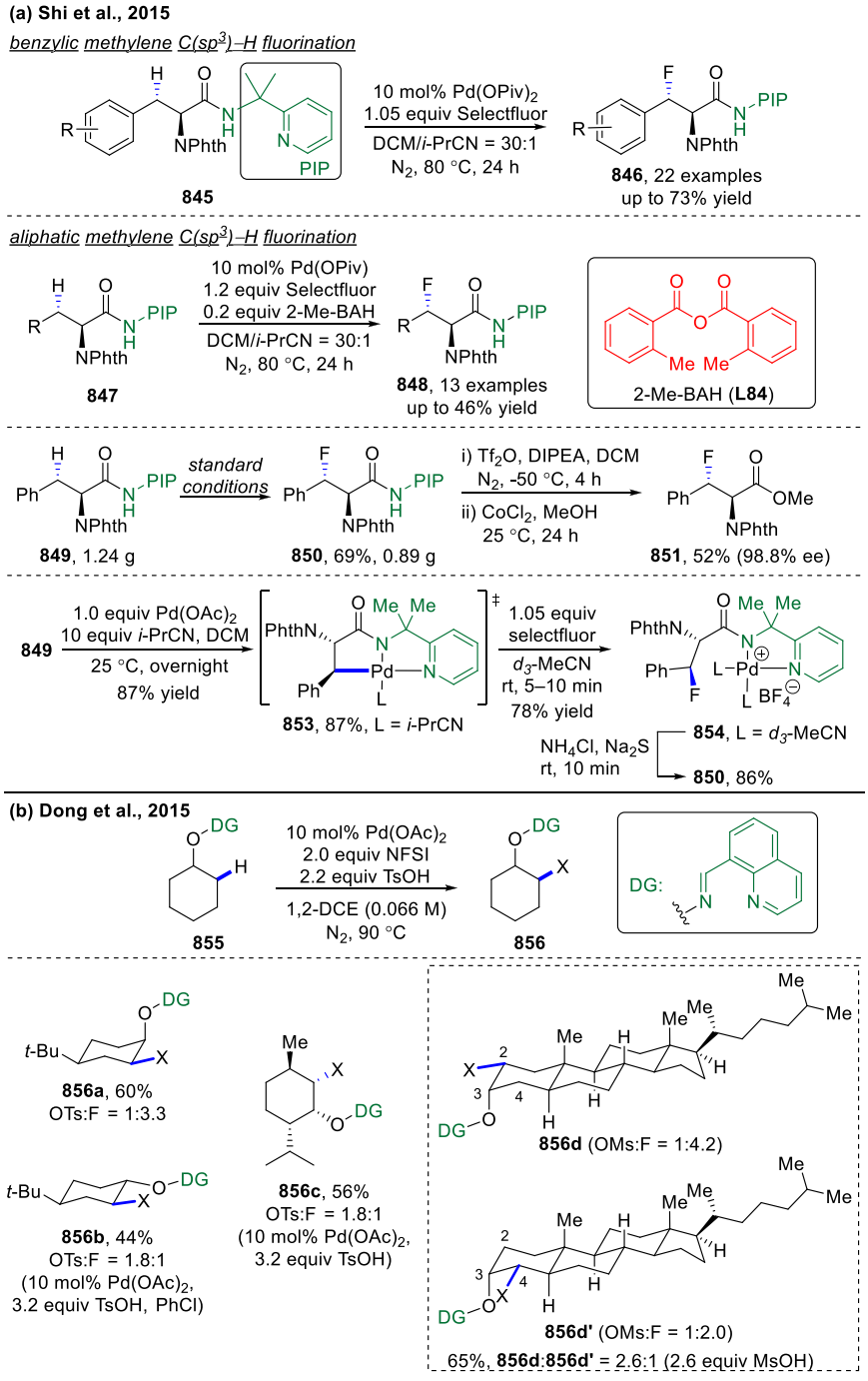
Scheme 134. (a) PIP-Directed Fluorination of Unactivated Methylene C(sp^3)−H Bonds of α-Amino Acids[365] and (b) Cyclic Methylene C(sp^3)−H Fluorination of Alcohol Derivatives Directed by an 8-Formylquinoline-Derived Oxime DG[347]



A similar system for the nickel(II)-catalyzed arylation of C(sp^3)−H bonds in aliphatic amides using 8-aminoquinoline as the bidentate DG was independently achieved by the You group (Scheme 143c).[398] $Ni(OTf)_2$ was used as the catalyst precursor, Na_2CO_3 (2 equiv) was the base, and PivOH (20 mol %) was the sterically bulky carboxylic acid. Moreover, using PPh_3 (20 mol %) and DMSO (3.5 equiv) as additives was found to be essential to promote the cross-coupling in high yields when run in 1,4-dioxane at 160 °C for 24−36 h. Both aryl iodides and bromides were successful arylating reagents. In this system, various functional groups, such as Ac, CO_2Me, $CONEt_2$, CN, and CHO, were well tolerated. In 2015, the nickel-catalyzed, directed C(sp^3)−H arylation of aliphatic amides with bromothiophenes was reported by the Qiu group.[399] In 2017, Yin and co-workers reported a $Ni(OTf)_2$-catalyzed C(sp^3)−H/C(sp^2)−H cross-coupling of thiophenes directed by 8-aminoquinoline.[400]

Omer and Liu recently explored the mechanism of Ni-catalyzed C(sp^3)−H activation through DFT calculations.[401] Compared to the analogous palladacycle intermediate formed after oxidative addition, the nickelacycle intermediate formed via C(sp^3)−H activation is thermodynamically less favorable, which makes the C−H metalation process generally reversible. The mechanism for subsequent elementary steps involving the nickelacycle depends on the coupling partners, and both Ni(III)

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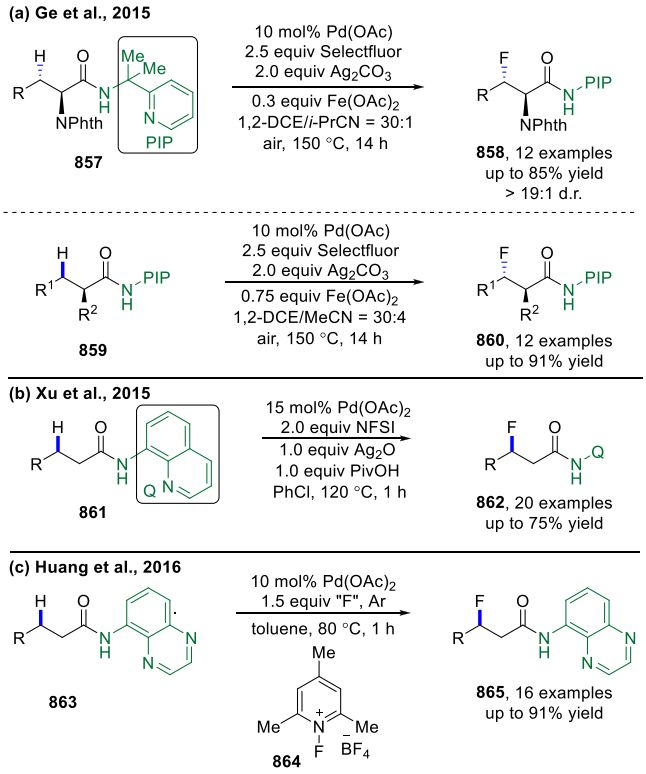
Scheme 135. Palladium-Catalyzed Fluorination of Unactivated Methylene C(sp^3)−H Bonds of Aliphatic Carboxamides: (a) with PIP DG;[366] (b) with 8-Aminoquinoline DG;[367] (c) with 8-Aminoquinoxaline DG[368]



and Ni(IV) intermediates were computed to be viable. A computational study by Sunoj and co-workers also shows that the oxidative insertion step is rate-limiting.[402] Interestingly, experimental evidence reported by Love, Schafer, and co-workers showed that the rate-determining step in a model substrate in which C(sp^3)−H activation occurred alpha to an amide nitrogen was the C(sp^3)−H activation.[403] The Love group also made a seminal contribution by isolating the first example of an 8-aminoquinoline-directed nickelacycle intermediate formed via C(sp^3)−H activation (Scheme 144). A similar nickelacycle intermediate was synthesized by Sanford and co-workers through decarbonylation.[404]

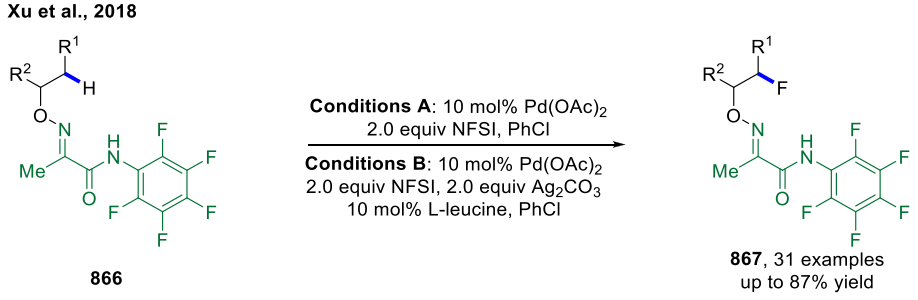
The first example of nickel(II)-catalyzed β-alkylation of aliphatic amides with linear alkyl halides (iodides, bromides, and chlorides) with the assistance of the 8-aminoquinoline DG was reported by the Ge group in 2014 (Scheme 145).[405] In this case, Ni(acac)$_2$ was employed as the precatalyst with 1,2-bis-(diphenylphosphino)benzene (dppbz) (10 mol %) as the ligand. However, this transformation gave exclusive alkylation at the β-methyl C−H bonds in preference to β-methylene, β-benzylic, γ-methyl, and γ-benzene C−H bonds, thereby limiting use of the method to aliphatic amides bearing a quaternary α-carbon and containing at least one β-methyl group. Notably, the addition of TEMPO resulted in decreased yield of this reaction and the observation of an alkyl−TEMPO adduct, suggesting the formation of a carbon-centered radical via alkyl−X homolysis. These results also support a plausible Ni(II)/Ni(III) cycle and exclude the Ni(II)/Ni(IV) cycle that was described earlier for the arylation and alkylation of C(sp^3)−H and C(sp^2)−H bonds, respectively.

In 2015, You and co-workers used 2,2-disubstituted propanamides containing the bidentate 8-aminoquinoline auxiliary in nickel-catlayzed coupling with either symmetrical or unsymmetrical alkynes to give a range of alkenylated products (Scheme 146a).[406] Ni(II) complexes were the preferred precatalysts, and the optimized reaction conditions were Ni(OAc)$_2$ (30 mol %) and PPh$_3$ (60 mol %) in a mixture of *i*-PrOH and toluene (1:5) at 170 °C for 24 h. The system was also highly site-selective, favoring C−H bond alkenylation at β-methyl positions over β-methylene, γ-methyl, or aryl sites. Deuterium-labeling experiments indicated that the hydrogen source in protonolysis might come from the generated AcOH in the reaction system. Moreover, the kinetic isotope effect (KIE) value was found to be k_H/k_D = 1.0, indicating that the cleavage of the methyl C−H bond with a nickel species was not involved in the turnover-determining step. Notably, treatment of the alkenylated products with pyridinium chlorochromate (PCC) in CH_2Cl_2 at 100 °C triggered an oxidative O-cyclization process, ultimately leading to cleavage of the 8-aminoquinoline moiety to furnish γ-butyrolactones in moderate to high yield.

The Maiti group reported a similar system for the nickel(II)-catalyzed insertion of alkynes into unactivated C(sp^3)−H bonds using 8-aminoquinoline as the bidentate auxiliary (Scheme 146b).[407] The optimized reaction conditions were Ni(OAc)$_2$·4H$_2$O (10 mol %) in DMF at 140 °C for 24 h. The authors succeeded in using both symmetrical and unsymmetrical internal alkynes. Terminal alkynes are also compatible coupling partners, affording the desired product with excellent regio- and stereoselectivity, albeit in low yields. After minor modifications to the reaction conditions, electron-deficient olefins were also found to be compatible, providing access to C(sp^3)−H alkylated products.

Another nickel-catalyzed protocol to effect alkenylation of unactivated C(sp^3)−H bonds was reported by the Shi group. In this method, styrenyl iodides were used as electrophiles with aliphatic carboxamides that contain a bidentate 8-aminoquinoline DG (Scheme 147).[408] After extensive screening, the

Scheme 136. Palladium-Catalyzed C(sp^3)−H Fluorination of Alcohol Derivatives[369]



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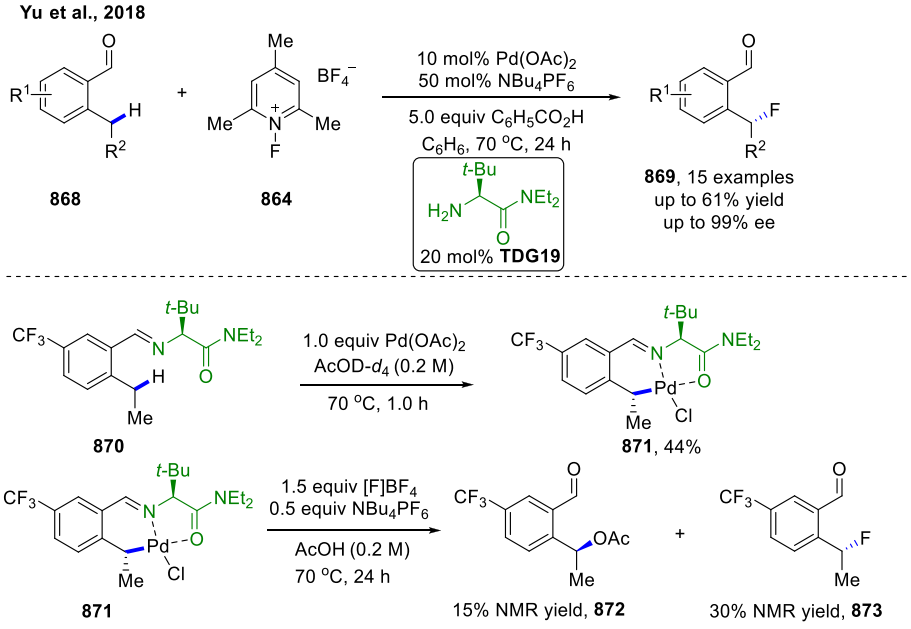
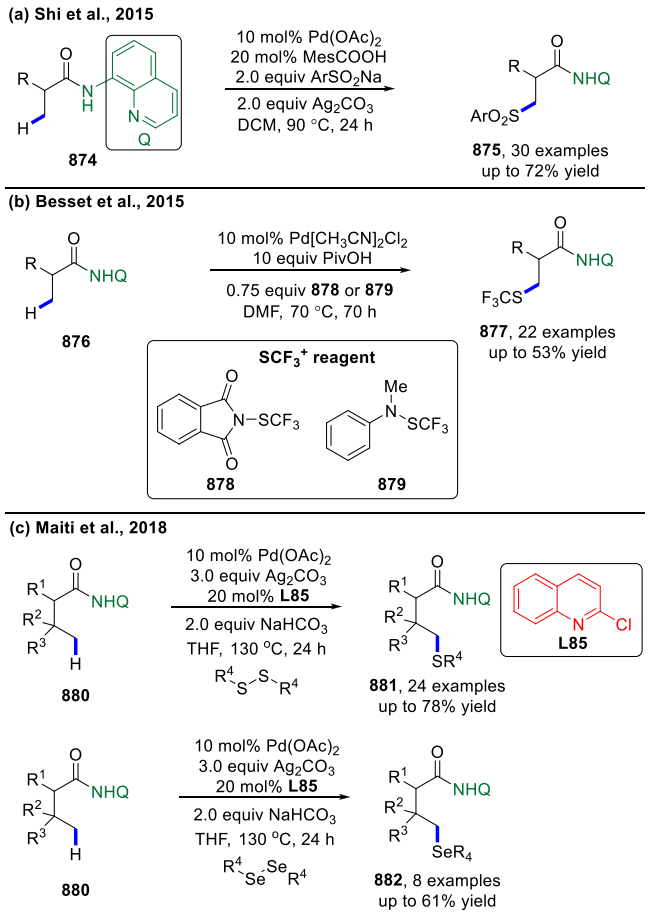
Scheme 137. Pd-Catalyzed Enantioselective C(sp^3)−H Fluorination Using a Transient DG[370]



Scheme 138. Palladium-Catalyzed, 8-Aminoquinoline-Directed C(sp^3)−H Chalcogenation: (a) β-C(sp^3)−H Sulfonylation;[373] **(b) β-C(sp^3)−H Trifluoromethylthiolation;**[374] **(c) γ-C(sp^3)−H Chalcogenation**[375]



optimized reaction conditions were determined to be Ni(acac)$_2$ (10 mol %) as precatayst, BINOL (40 mol %) as a ligand, and Li_2CO_3 (2 equiv) and KTFA (2 equiv) as inorganic bases in DMSO at 140 °C for 8 h. Both electron-deficient and electron-rich (*E*)-β-iodostyrenes reacted smoothly with a wide variety of carboxamides that bear both linear and cyclic chains to give exclusively the (*E*)-isomers **889** in moderate to good yields.

In 2016, Zhang and co-workers developed a method to access a range of γ-lactams from terminal alkynes and aliphatic amides via nickel-catalyzed C(sp^3)−H bond activation.[409] Shi and co-workers reported an 8-aminoquinoline-directed C(sp^3)−H alkynylation of aliphatic amides with terminal alkynes (Scheme 148b).[410] While $NiBr_2$ was found to be the best nickel catalyst, the addition of Me_2S·CuBr cocatalyst and DavePhos ligand greatly enhance reactivity.

The Ge group reported a Ni(dme)$_2I_2$-catalyzed, intramolecular, dehydrogenative cyclization of aliphatic amides via C(sp^3)−H amination with TEMPO (3 equiv) as the single-electron oxidant (Scheme 149a).[411] The presence of K_2HPO_4 (2 equiv) as the base and a catalytic amount of TBAI (10 mol %) promoted the dehydrogenative cyclization in a solvent mixture of butyronitrile and benzonitrile in a 3:2 ratio at 150 °C for 24 h. Under these reaction conditions, reaction at the β-methyl group took place selectively in the presence of γ-methyl, β-methylene, and aromatic C−H bonds. Ge and co-workers achieved a direct carbonylation of C(sp^2)−H and C(sp^3)−H bonds with DMF as the CO source (Scheme 149b).[412] With a novel Ni/Cu synergistic catalysis system, succinimide derivatives were prepared from the corresponding aromatic or aliphatic amides under oxygen atmosphere. The authors observed a preference for functionalizing the methyl group over methylene groups, including relatively reactive benzyl positions, when aliphatic amides were used as substrates.

Nickel-catalyzed thiolation of β-methyl C(sp^3)−H bonds of aliphatic carboxamides with disulfides was independently reported by the Shi, Zhang, and Yin groups in 2015.[413−416] The Shi group demonstrated nickel-catalyzed thiolation of β-methyl C(sp^3)−H bonds of a broad range of aliphatic carboxamides with various disulfides (Scheme 150a).[413] The

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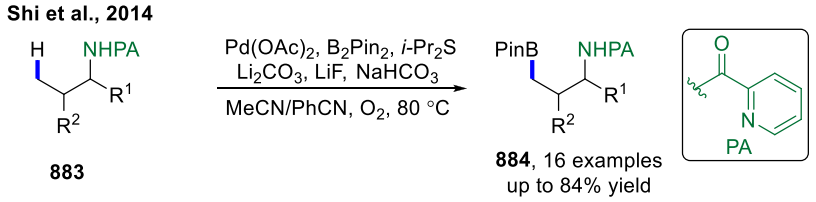
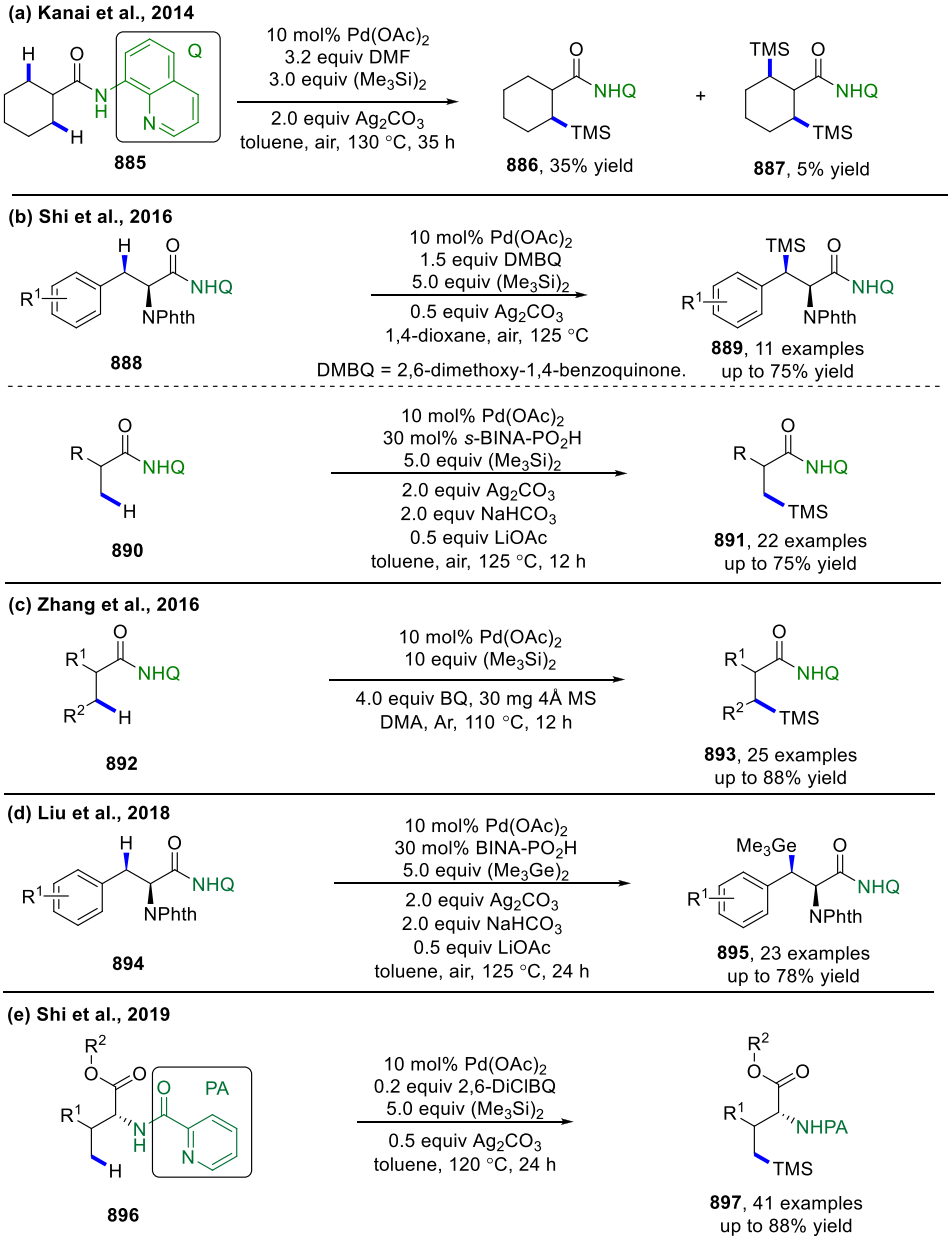
Scheme 139. Picolinamide-Directed C(sp^3)−H Borylation[376]



Scheme 140. (a−c) 8-Aminoquinoline-Directed C(sp^3)−H Silylation (Kanai et al.,[377] **Shi et al.,**[378] **Zhang et al.**[379]**), (d) 8-Aminoquinoline-Directed C(sp^3)−H Germylation,**[380] **and (e) Picolinamide-Directed C(sp^3)−H Silylation of Peptides**[381]



reaction conditions were determined to be (dppp)$NiCl_2$ (10 mol %) as the precatalyst, BINOL (20 mol %) as ligand, KTFA (2 equiv) as base, and Ag_2O (1 equiv) in DMSO (1 mL) at 140 °C for 12 h. A wide variety of aliphatic acid derivatives and disulfides are tolerated in the reaction. An approach for thiolation of C(sp^3)−H bonds that necessitates only Ni(OTf)$_2$ (20 mol %) and LiO*t*-Bu (5 equiv) in DMF (0.5M) at 120 °C along with the disulfide or thiol was also developed (Scheme 150b).[414]

The Zhang group demonstrated the thioetherification of *β*-C(sp^3)−H bonds of aliphatic amides by using Ni(OTf)$_2$ (10 mol %) as the catalyst, Ac-Gly-OH (20 mol %) as the ligand, Na_2CO_3 (2 equiv) as the base, and TBAI (4 equiv) as the additive in DMF at 140 °C for 12 h (Scheme 150c).[415] 1,2-Diphenyl diselenide was also found to be reactive under the

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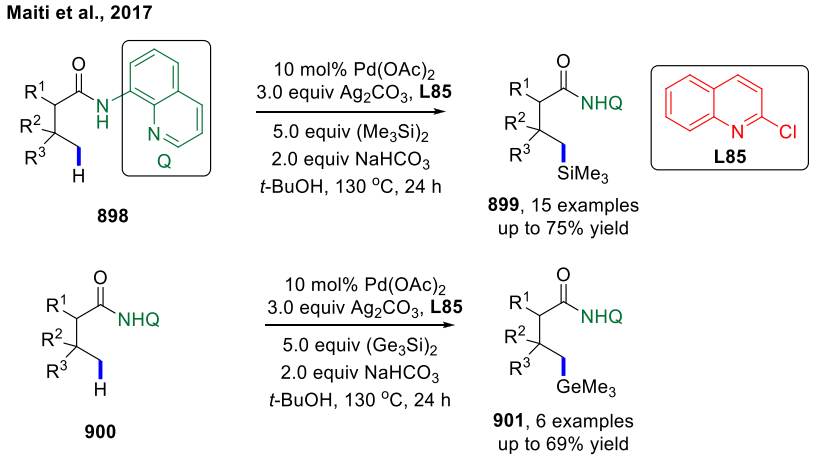
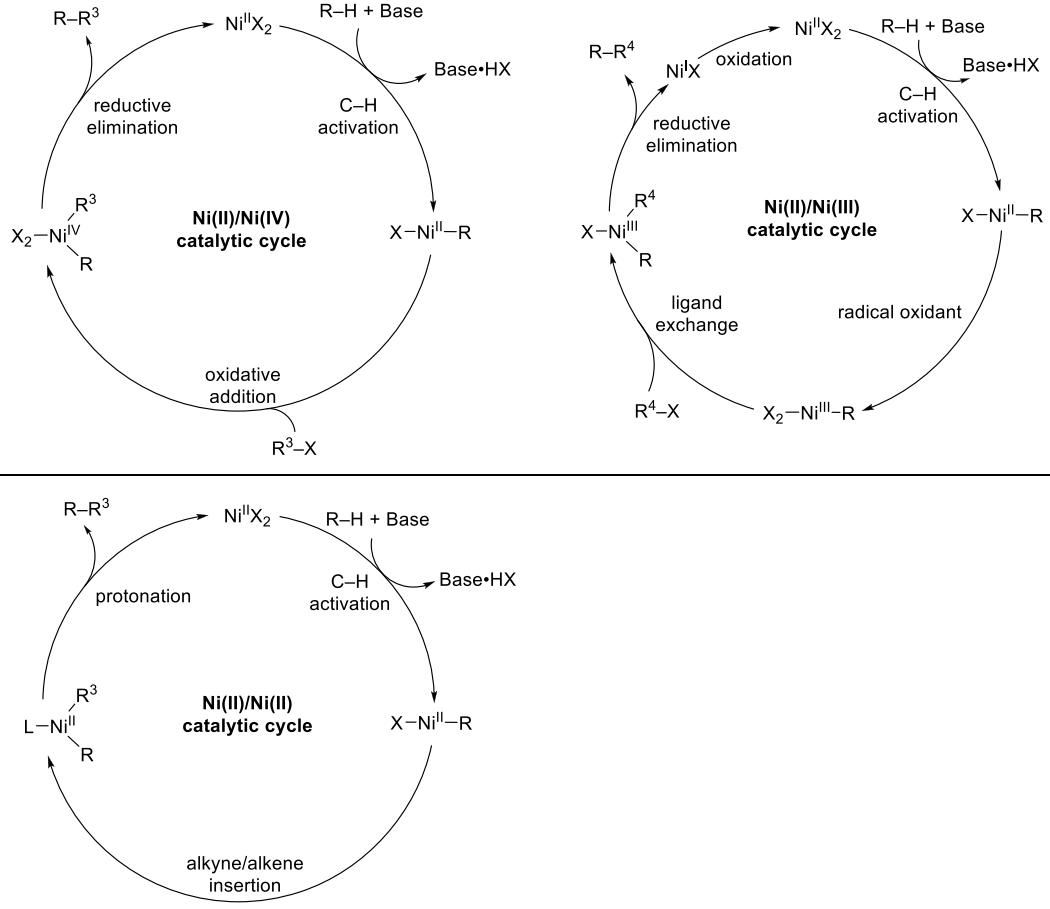
Scheme 141. 8-Aminoquinoline-Directed γ-C(sp^3)−H Silylation and Germylation[382]



Scheme 142. Catalytic Cycles of Nickel-Catalyzed C(sp^3)−H Functionalization Reactions



standard conditions. The nickel-catalyzed thiolation of C(sp^3)−H bonds in aliphatic amides using 8-aminoquinoline as the bidentate auxiliary DG was also described by the Yin group in 2015 (Scheme 150d).[416] In 2017, You and co-workers developed a protocol to prepare various *N*-alkoxyamine derivatives via nickel-catalyzed aminoxylation of an unactivated C(sp^3)−H bond using stable nitroxyl radicals (Scheme 146e).[417]

4. COPPER-CATALYZED, COORDINATION-ASSISTED FUNCTIONALIZATION OF C(sp^3)−H BONDS

Copper salts have been widely used to facilitate carbon−carbon and carbon−heteroatom bond formation in organic reactions. Use of copper as a catalyst offers practical advantages due to its abundance, lower cost, and nontoxic nature.[418] While copper-promoted C(sp^3)−H functionalization through outer-sphere mechanisms, such as bioinspired oxidations and oxygenations and those involving radical or Cu-nitrene species, have been well-studied,[418−423] copper-promoted inner-sphere C(sp^3)−H bond activation reactions are rare.[3,424−426] A typical catalytic

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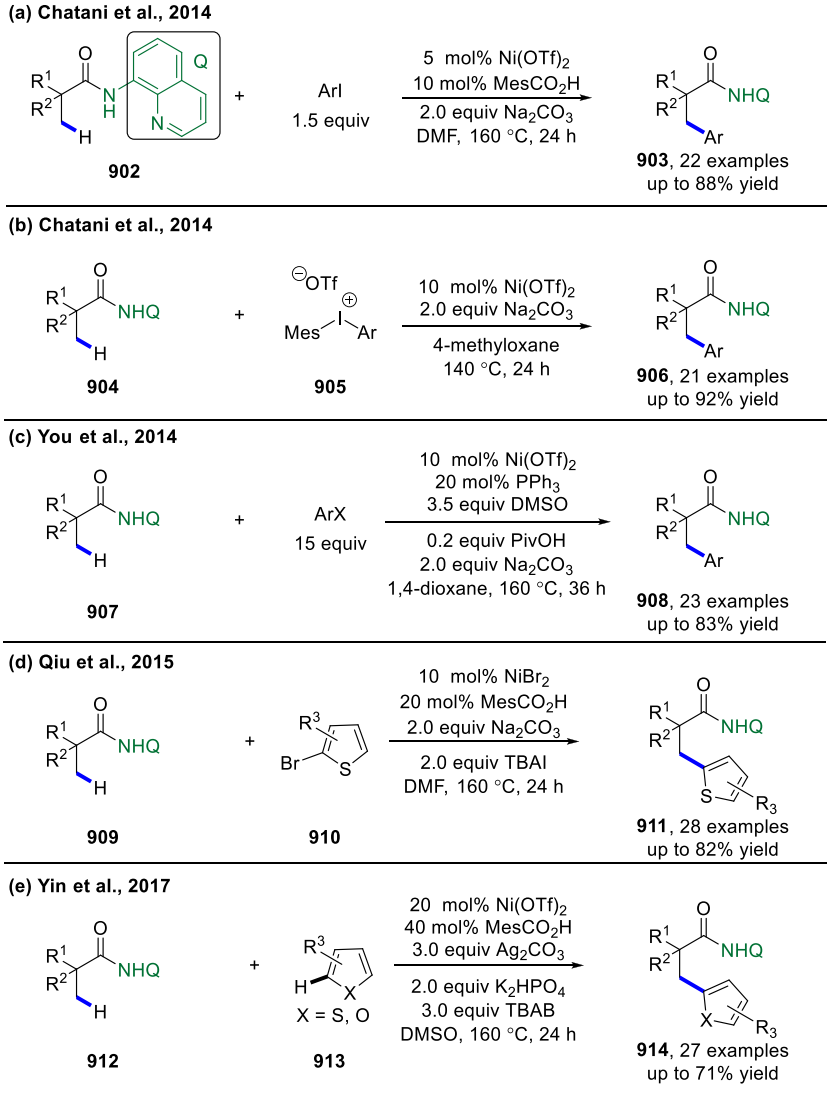
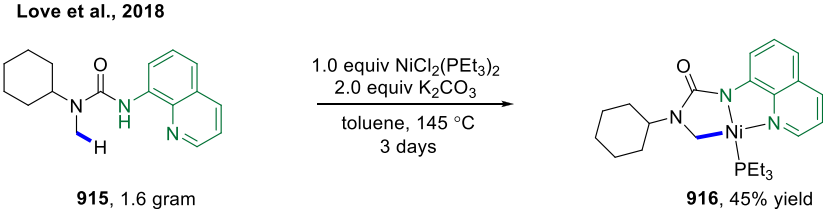
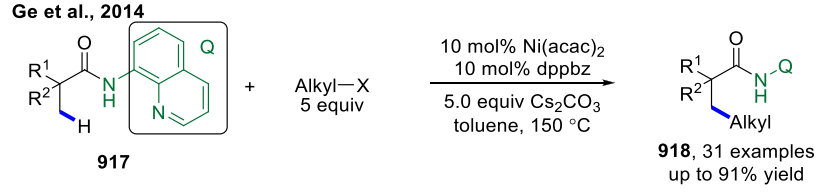
Scheme 143. Nickel-Catalyzed, 8-Aminoquinoline-Directed β-C(sp^3)−H Arylation of Aliphatic Amides: (a) with Aryl Iodides;[396] (b) with Diaryliodonium Triflate Salts;[397] (c) with Aryl Iodides or Bromides;[398] (d) with Bromothiophenes;[399] (e) via C(sp^3)−H/C(sp^2)−H Cross-Coupling with Heteroarenes[400]



Scheme 144. Nickelacycle Intermediate via C(sp^3)−H Activation[403]



Scheme 145. Nickel-Catalyzed β-C(sp^3)−H Alkylation of Aliphatic Amides[405]



cycle for inner sphere, Cu-promoted C(sp^3)−H activation is proposed to proceed as follows (Scheme 151): The initial C(sp^3)−H bond activation occurs through cyclocupration to form an alkyl−Cu(II) species **954**, which is oxidized either by

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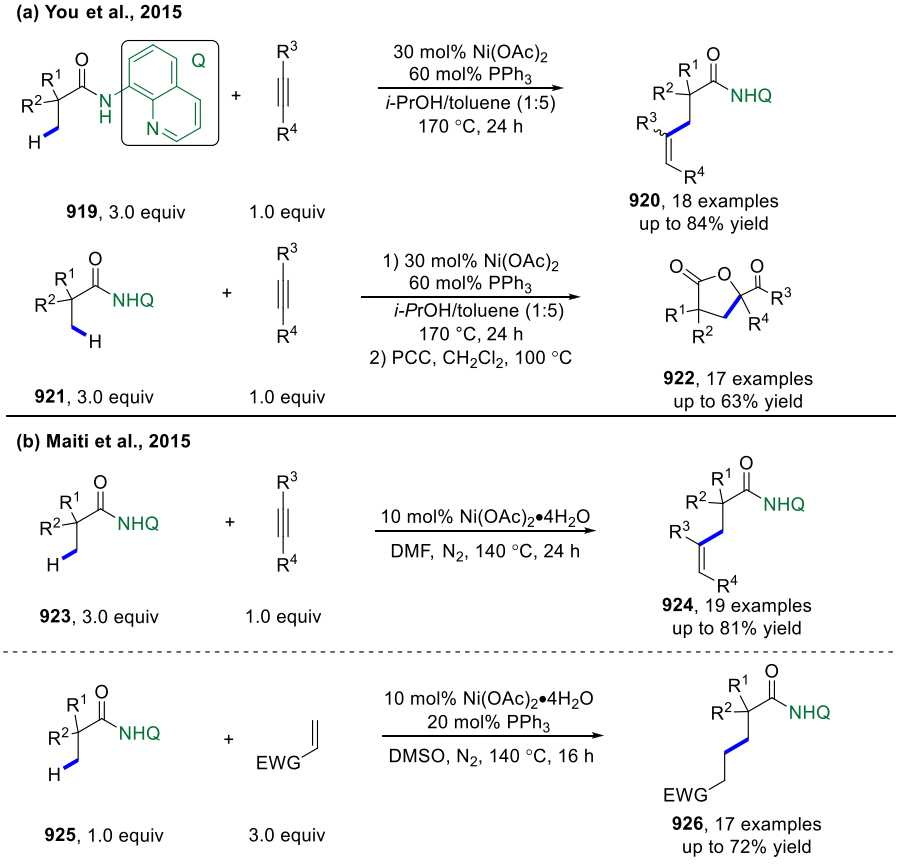
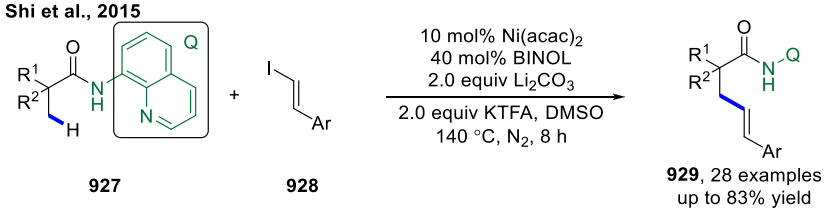
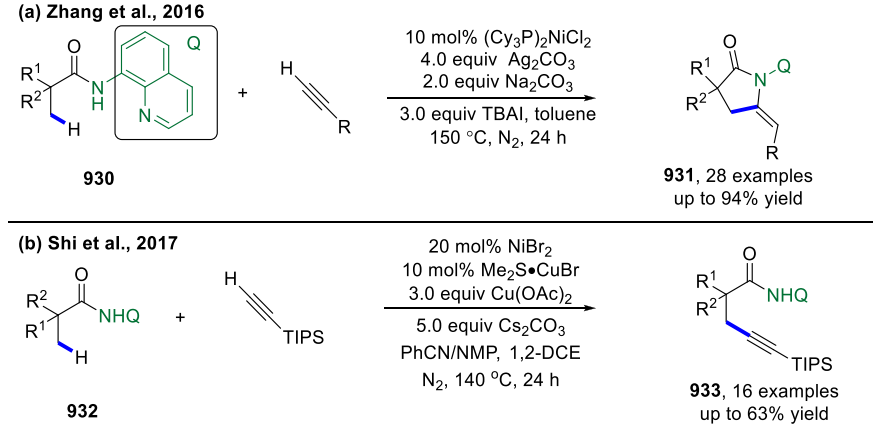
Scheme 146. (a) Nickel-Catalyzed β-C(sp^3)−H Alkenylation of Aliphatic Amides with Alkynes[406] and (b) Nickel-Catalyzed Insertion of Alkynes and Electron-Deficient Alkenes into β-C(sp^3)−H Bonds[407]



Scheme 147. Nickel-Catalyzed β-C(sp^3)−H Alkenylation of Aliphatic Amides with Styrenyl Iodides[408]



Scheme 148. Nickel-Catalyzed Oxidative Coupling of Unactivated C(sp^3)−H Bonds in Aliphatic Amides with Terminal Alkynes: (a) Alkynylation/Cyclization To Access γ-Lactams;[409] (b) Alkynylation[410]



another Cu salt or a silver salt, to form an alkyl−Cu(III) species **955**. Often, ligand exchange will then occur, followed by reductive elimination to give the final product **960** with concomitant generation of a Cu(I) species, which must be

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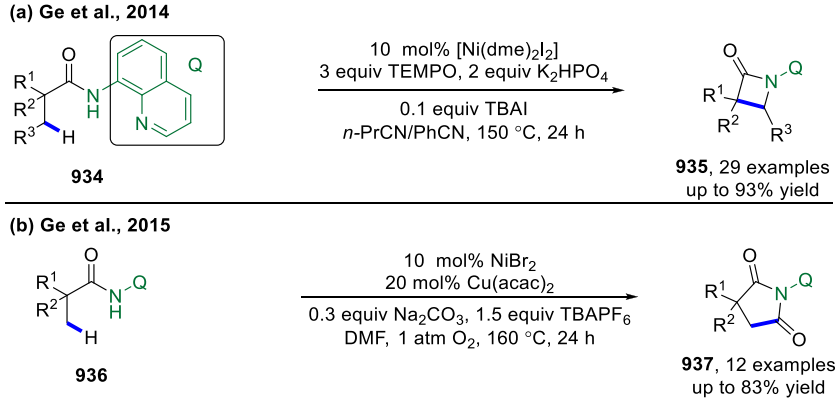
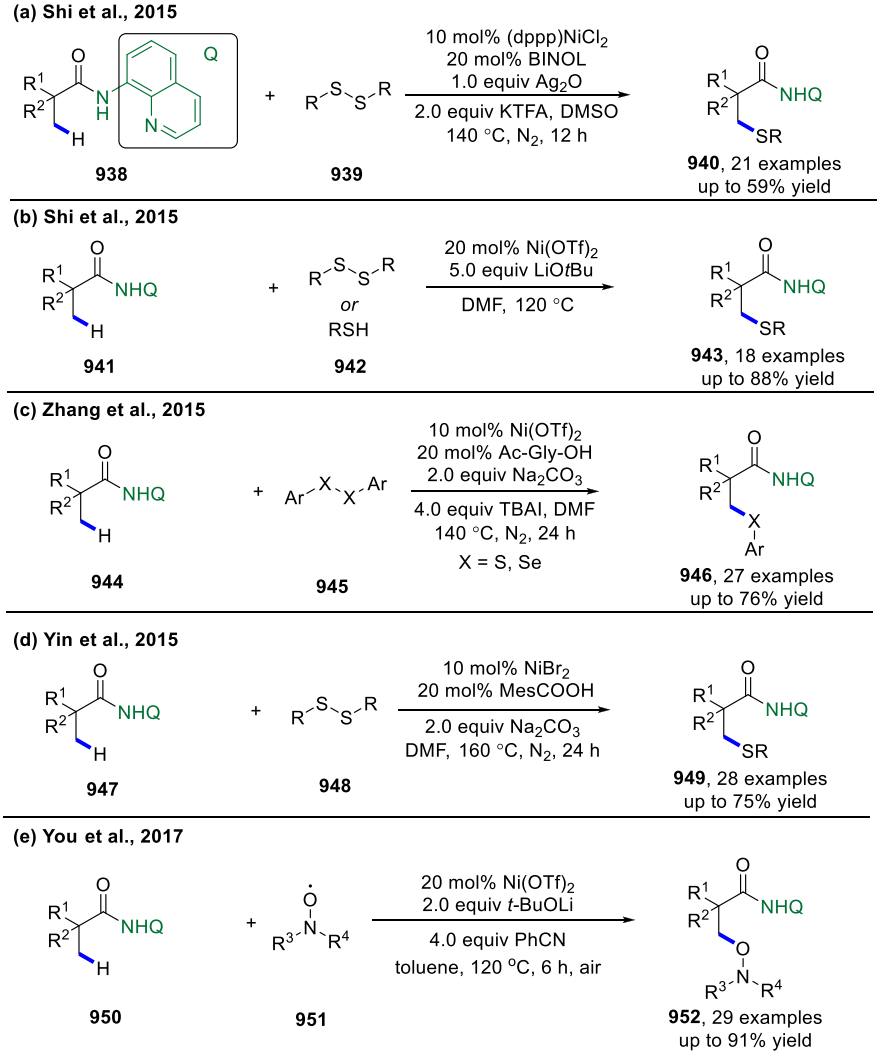
Scheme 149. (a) Nickel-Catalyzed Intramolecular Amidation of Aliphatic Amides[411] and (b) Nickel-Catalyzed β-C(sp^3)−H Carbonylation of Aliphatic Amides with DMF[412]



Scheme 150. Nickel-Catalyzed β-C(sp^3)−H Thiolation of Aliphatic Amides: (a) Shi et al.;[413] (b) Shi et al.;[414] (c) Zhang et al.;[415] (d) Yin et al.[416] (e) Nickel-Catalyzed C(sp^3)−H Aminoxylation of Aliphatic Amides[417]



reoxidized to Cu(II), often with a silver salt (Scheme 147, path I).[428−435,437] In some circumstances, Cu(II) is thought to coordinate to the DG first to form **957**, which can be oxidized to Cu(III) and then perform C(sp^3)−H bond activation to give an alkyl−Cu(III) species **959** (Scheme 151, path II).[427,436] One difficulty in using copper to functionalize C(sp^3)−H bonds is that accessing the Cu(III) species is energetically challenging and often requires high temperature and high loading of copper salts. Thus far, copper-mediated C(sp^3)−H activation reactions are limited to systems using the 8-aminoquinoline bidentate DG, and the most successful examples are intramolecular amidation and intermolecular acetoxylation reactions.

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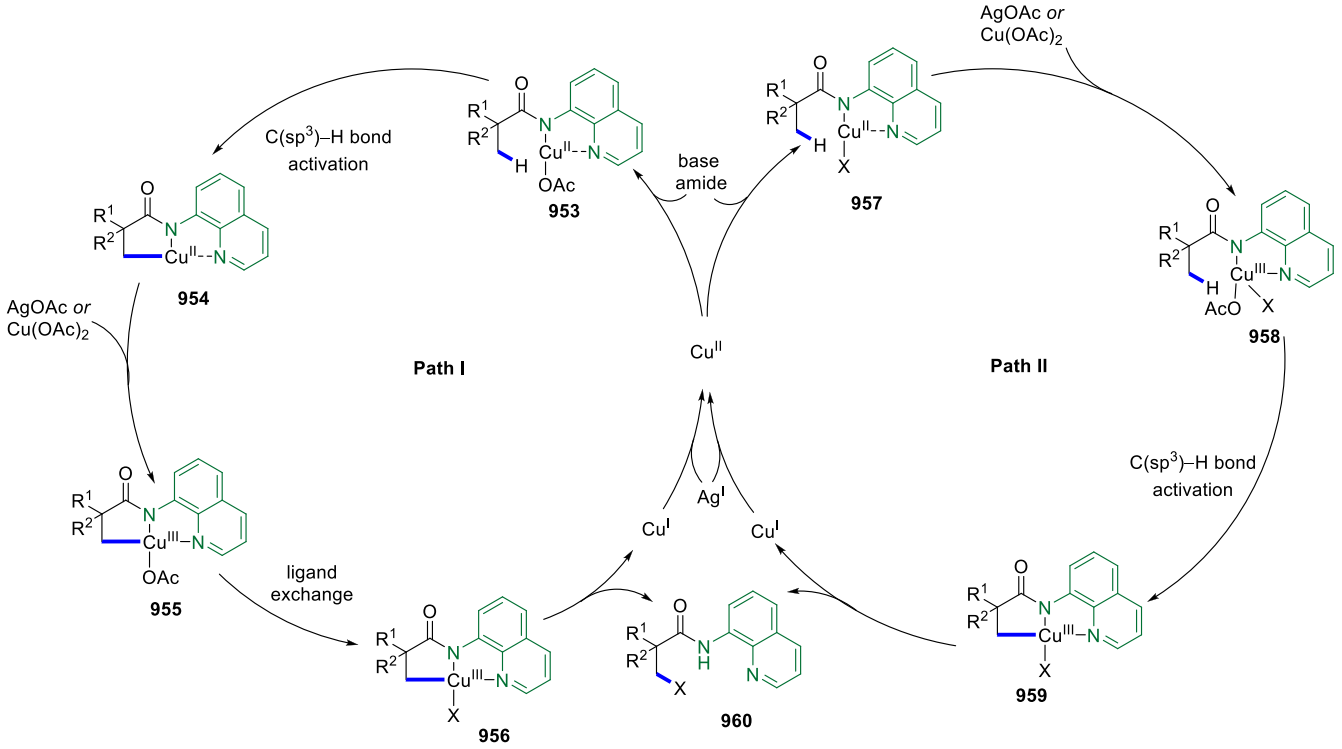
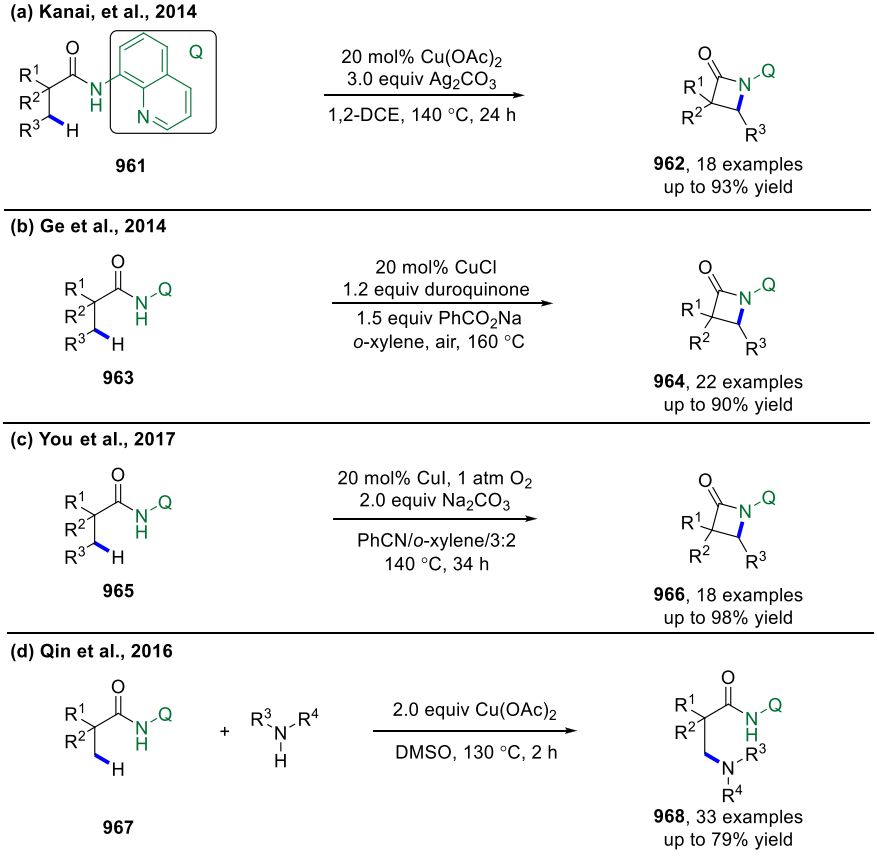
Scheme 151. Plausible Catalytic Cycles for Copper-Catalyzed C(sp^3)−H Functionalization Reactions



Scheme 152. Cu-Catalyzed Intramolecular β-C(sp^3)−H Amidation: (a) Kanai et al.;[427] (b) Ge et al.;[428] (c) You et al.[429] (d) Cu-Promoted Intermolecular β-C(sp^3)−H Amination[430]



In 2014, the Kuninobu and Kanai groups (Scheme 152a)[427] and the Ge group (Scheme 152b)[428] independently reported examples of Cu-catalyzed intramolecular amidation of C(sp^3)−H bonds, which provided efficient methods for the synthesis of

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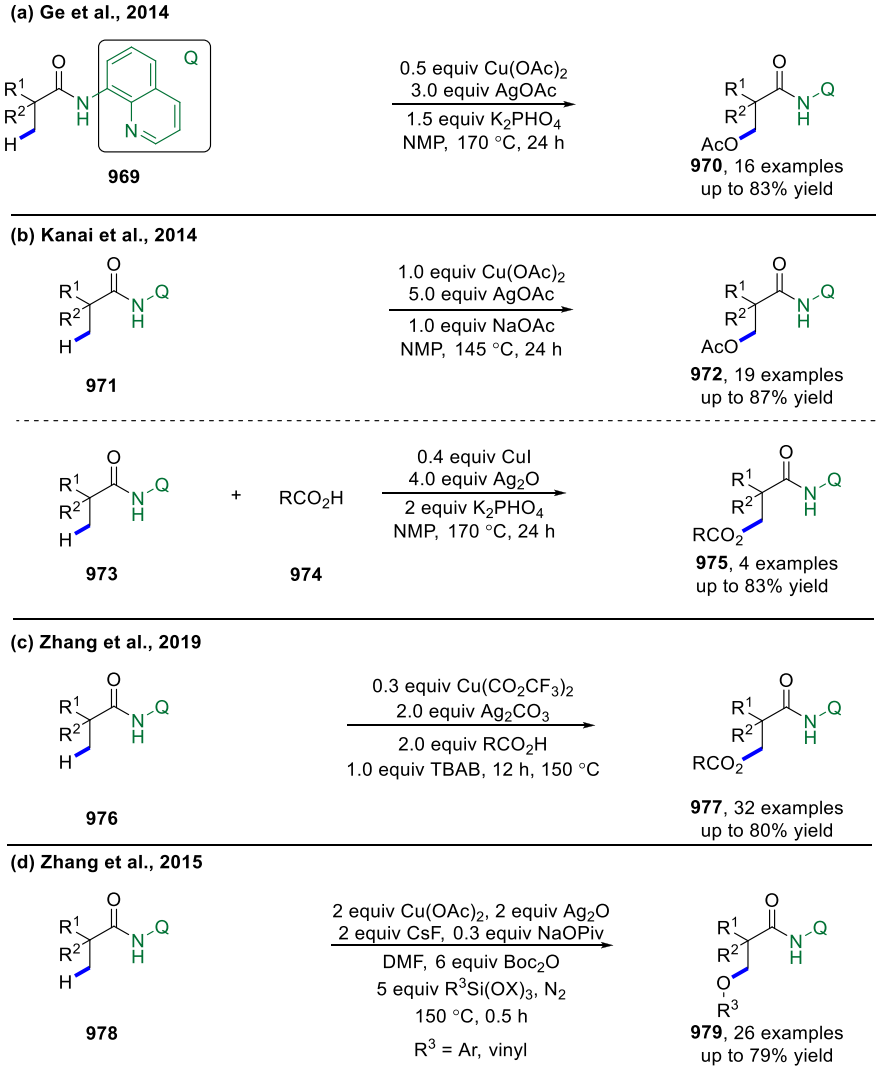
Scheme 153. (a) Cu-Catalyzed β-C(sp^3)−H Acetoxylation of Aliphatic Amides,[431] (b) Cu-Mediated β-C(sp^3)−H Acetoxylation of Aliphatic Amides,[432] (c) Copper-Catalyzed C(sp^3)−H Acyloxylation,[433] and (d) Cu-Mediated β-C(sp^3)−H Aryloxylation and Vinyloxylation of Aliphatic Amides with Organosilanes[434]



β-lactams. The protocol reported by the Kuninobu and Kanai groups involving $Cu(OAc)_2$ with Ag_2CO_3 as oxidant, while CuCl and duroquinone were employed as the catalyst and oxidant, respectively, by the Ge group. In 2015, You and co-workers described a more economical and practical protocol that uses oxygen as the sole oxidant in the production of β-lactam compounds (Scheme 152c).[429] An intermolecular version was disclosed by Qin and co-workers in 2016 (Scheme 152d).[430] The potential utility of this method was further demonstrated in the synthesis of CNS disorder modulator HY-2901.

Copper-catalyzed, 8-aminoquinoline-directed β-methyl C-(sp^3)−H acyloxylation of aliphatic amides was reported by Ge and co-workers in 2014 (Scheme 153a).[431] $Cu(OAc)_2$ (50 mol %) was employed as catalyst, and AgOAc (3 equiv) was added as an acetate source and oxidant. However, the reaction must be run at a high temperature (170 °C). At the same time, Kanai and co-workers reported a copper-mediated C(sp^3)−H acetoxylation of unactivated methyl groups using the 8-aminoquinoline DG. The use of 1.0 equiv of $Cu(OAc)_2$ as catalyst and 5.0 equiv of AgOAc as the oxidant was a requisite (Scheme 153b).[432] Copper-catalyzed, TBAB-accelerated C(sp^3)−H acyloxylation with carboxylic acids was demonstrated by Zhang and co-workers (Scheme 153c).[433]

In the same year, Zhang and co-workers reported a copper-mediated oxidation of β-C(sp^3)−H bonds of propionamides with organosilanes (Scheme 153d).[434] They observed that the desired products could not be isolated when phenol was employed under the standard conditions, which excluded a pathway involving C−O coupling of the C(sp^3)−H bond with phenol generated from trimethoxy(phenyl)silane. O^{18}-labeling experiments showed that $Cu(OAc)_2$ served as the source of the oxygen in the aryloxylation product. The proposed catalytic cycle starts with C(sp^3)−H bond activation and oxidation to an alkyl−Cu(III) species that then undergoes C−O reductive elimination between the alkyl group and an acetate ligand to provide the newly formed ester oxygen and a Cu(I) species ligated to the DG. Oxidation of Cu(I) to Cu(II), presumably with Ag_2O and HOAc, then allows the acetate ligand to hydrolyze to give a Cu(II) species bound to the DG and a terminal alcohol arising from the acetate ligand. Oxidation via disproportionation and subsequent transmetalation is followed by reductive elimination of the alcohol and the aryl or alkenyl group to provide the desired products. An oxidative

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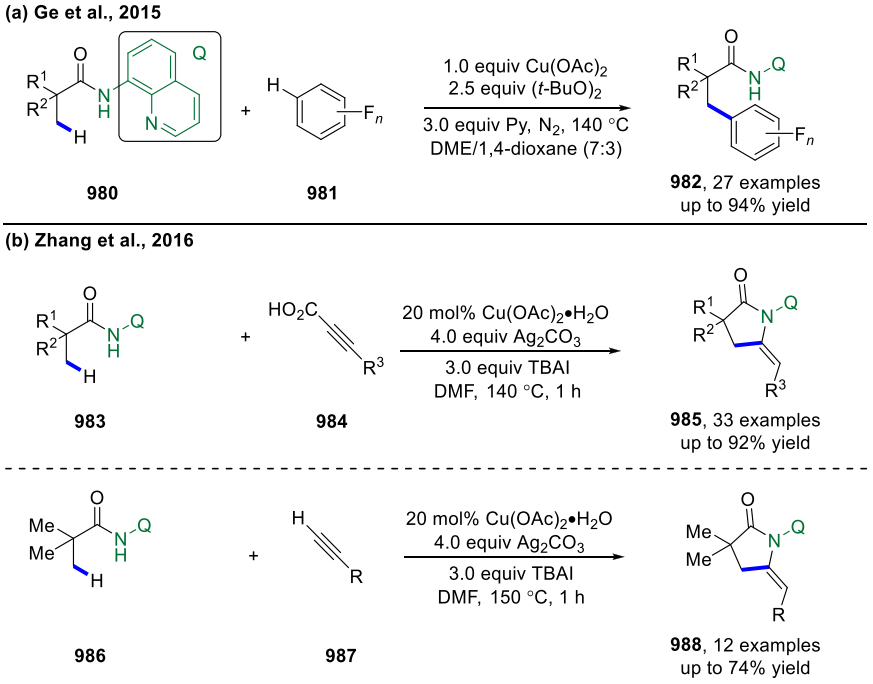
Scheme 154. (a) Cu-Mediated β-C(sp^3)−H Cross-Dehydrogenative Coupling of Aliphatic Amides with Polyfluoroarenes[436] and (b) Copper-Catalyzed C(sp^3)−H Alkynylation/Annulation of Aliphatic Amides and Alkynyl Carboxylic Acids or Terminal Alkynes[437]



demethylation of propionamides that might proceed via a similar mechanism of initial C(sp^3)−H acetoxylation followed by subsequent oxidative decarboxylation was reported by the Fu group.[435]

In 2015, the Ge group demonstrated that polyfluoroarenes were effective coupling partners in the copper-promoted, cross-dehydrogenative coupling of unactivated C(sp^3)−H bonds of aliphatic amides (Scheme 154a).[436] It was found that pyridine was essential for this transformation and di-*tert*-butyl peroxide was the best oxidant. However, stoichiometric $Cu(OAc)_2$ is needed in this reaction. Deuterium-labeling experiments show that an arylcopper intermediate may be involved in the C(sp^3)−H bond cleavage step of the amide and that cyclometalation of the amide is not the turnover-limiting step.

In 2016, Zhang and co-workers demonstrated a copper-catalyzed C(sp^3)−H alkynylation/annulation reaction between aliphatic amides and alkynyl carboxylic acids or terminal alkynes (Scheme 154b).[437] The authors postulated that the decarboxylation process may be promoted by the copper or silver salts to form phenylacetylide species.

Ge and co-workers observed a $Cu(OAc)_2$-promoted carbonylation of β-C(sp^3)−H bonds with nitromethane as the carbonyl source (Scheme 155).[438] They posit that the expected product arises from C(sp^3)−H bond activation of the $MeNO_2$ followed by reductive elimination at the β-position to provide the standard reductive elimination product **995**. The nitro-group then coordinates with Lewis acid to provide iminium ion **996**, which then undergoes an intramolecular cyclization with the amide nitrogen of the DG to form **997**. Lewis-acid-promoted loss of oxygen results in the formation of a nitroso group that is subsequently eliminated in the formation of a cyclic imine **999**. Upon treatment with water and subsequent oxidation, the desired product **1001** is generated.

5. COBALT-CATALYZED, COORDINATION-ASSISTED FUNCTIONALIZATION OF C(sp^3)−H BONDS

Co(III)-catalyzed functionalization of electronically activated C(sp^3)−H bonds, such as benzylic C(sp^3)−H bonds in 8-methylquinolines, has been well studied.[439−446] In all these cases, Co(III) is proposed to first coordinate to the nitrogen of the quinoline before performing benzylic C(sp^3)−H bond insertion, which allows a number of possible elementary steps to take place: alkene[439−442] or alkyne[443] coordination followed by migratory insertion, transmetalation followed by reductive elimination,[444] carbene formation followed by migratory insertion,[445] or nitrene formation via decarboxylative ring opening followed by migratory insertion.[446] However, the use of cobalt catalysts in the transformations of nonactivated C(sp^3)−H bonds is relatively underdeveloped.[447−450]

The first example of Co(III)-catalyzed nonactivated C(sp^3)−H activation was not reported until 2015. Ge and co-workers disclosed a cobalt-catalyzed intramolecular amination of non-activated β-C(sp^3)−H bonds of aliphatic amides directed by 8-aminoquinoline (Scheme 156).[451] A wide range of 2,2-disubstituted propanamides bearing either linear or cyclic substituents at the α-position were successfully functionalized catalyzed by $Co(OAc)_2$ in the presence of Ag_2CO_3 and $PhCO_2Na$, providing a rapid access to various β-lactams. Direct intermolecular amination of C(sp^3)−H bonds catalyzed by $Co(acac)_3$ (20 mol %) was also reported in the same communication. Radical intermediates were shown not to be involved in the catalytic cycle for the formation of β-lactams. However, in the case of γ-lactams, the addition of TEMPO dramatically reduces the yield, suggesting that a single electron oxidation produces an alkyl radical species that leads to the γ-lactams.

In 2017, Seayad, Dixon, and co-workers reported a thioamide-directed, cobalt-catalyzed amidation of C(sp^3)−H bonds with (hetero)aryl- and alkyl-substituted dioxazolones (Scheme

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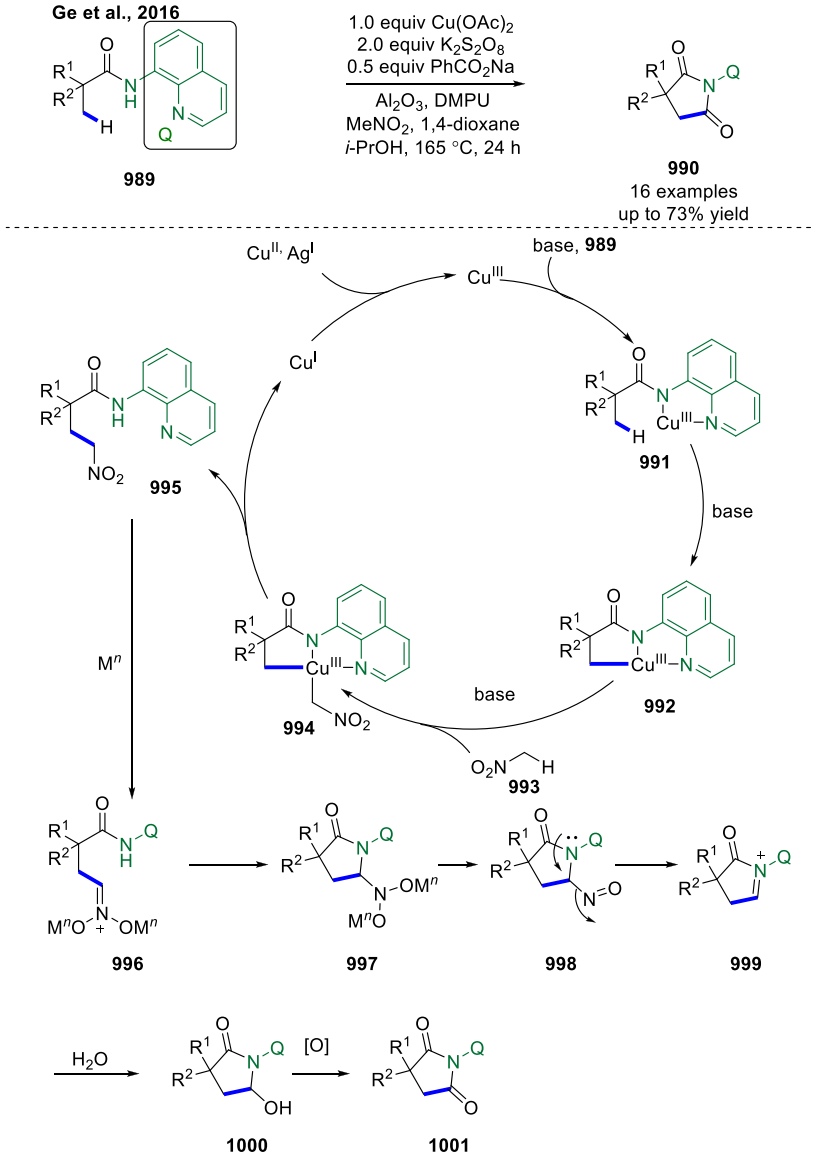
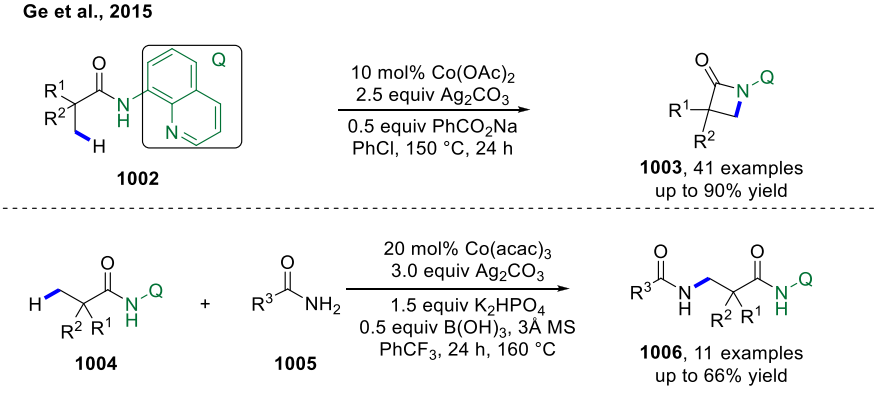
Scheme 155. Cu-Mediated β-C(sp^3)−H Carbonylation of Aliphatic Amides with Nitromethane[438]



Scheme 156. Cobalt-Catalyzed β-C(sp^3)−H Intra- and Intermolecular Amidation of Aliphatic Amides[451]



157a).[452] A wide range of thioamides with *N*-containing heterocycles, such as piperazine, morpholine, and tetrahydroisoquinoline, were all tolerated and afforded the corresponding products in good yields. In 2019, the Matsunaga group uncovered a Cp*Co/chiral carboxylic acid (CCA) system for the enantioselective C(sp^3)−H amidation of thioamides (Scheme 157b).[453] Imide-protected amino acids were screened, and **CCA-1** showed high enantioselectivity. The reactivity and selectivity were further improved by combining sterically hindered cobalt catalyst (**1013**) with the MS13X zeolite. In

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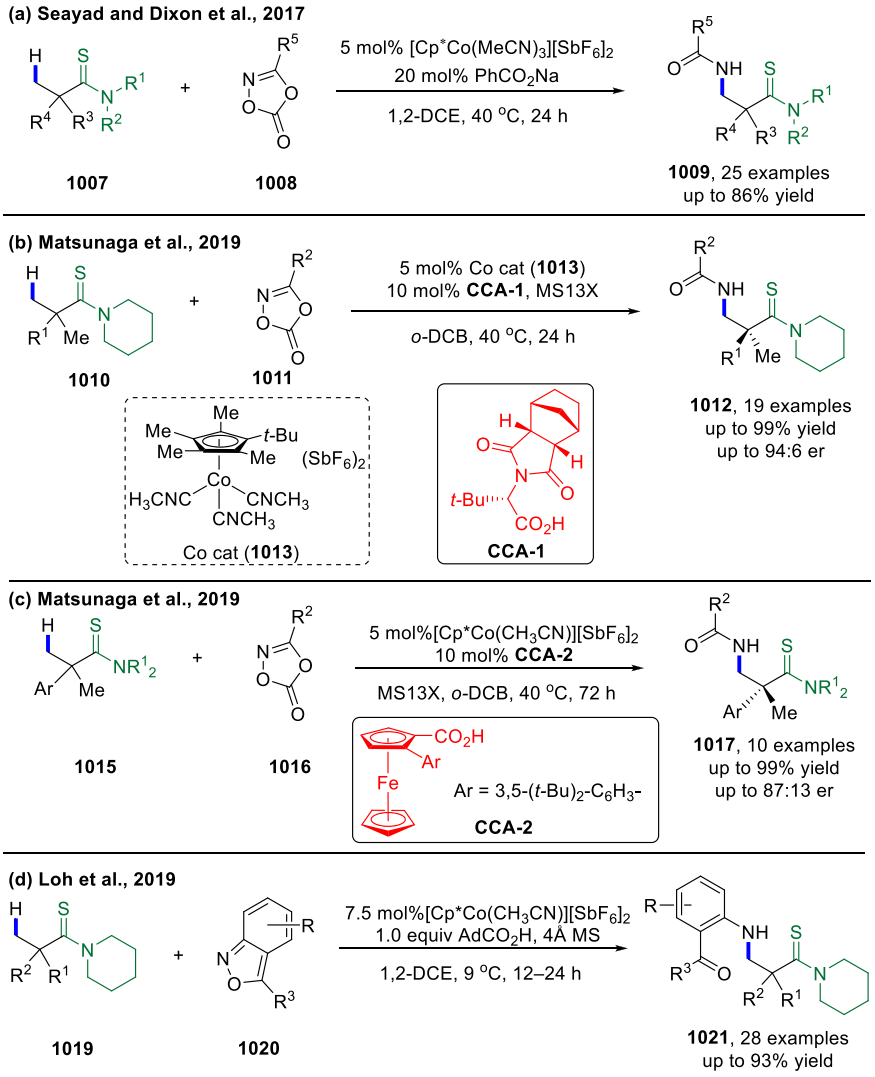
Scheme 157. (a) Thioamide-Directed, Cobalt(III)-Catalyzed C(sp^3)−H Amidation,[452] (b) Enantioselective C(sp^3)−H Amidation of Thioamides Catalyzed by a Cobalt(III)/Chiral Carboxylic Acid,[453] (c) Enantioselective C(sp^3)−H Amidation of Thioamides with Chiral 2-Aryl Ferrocene Carboxylic Acid Ligand,[454] and (d) Cobalt(III)-Catalyzed C(sp^3)−H Amination with Anthranils[455]



order to overcome the limited structural diversity of imide-protected amino acids, chiral 2-aryl ferrocene carboxylic acids (**CCA-2**) were developed by the Matsunaga group as a type of efficient chiral ligand that also displayed good reactivity and enantioselectivity.[454] Recently, Loh and co-workers demonstrated a Cp*Co^{III}-catalyzed, thioamide-directed amination of C(sp^3)−H bonds using anthranils as the amine electrophiles.[455]

Co(acac)$_2$-catalyzed C(sp^3)−H carbonylative cyclization of aliphatic amides was independently reported by the Lei,[456] Sundararaju,[457] and Gaunt[458] groups (Scheme 158). Ag_2CO_3 is found to be an excellent oxidant for this type of carbonylation reaction.

Zhang and co-workers demonstrated a cobalt-catalyzed C(sp^3)−H alkynylation/cyclization of aliphatic amides and terminal alkynes (Scheme 159).[459] Aromatic amides bearing either electron-withdrawing or electron-donating groups are also compatible under similar reaction conditions. Control experiments indicated that a catalytic amount of Ag_2CO_3 (10 mol %) and stoichiometric TBAI were required for this cyclization.

In 2017, the Shi group reported a Co(OAc)$_2$·4H$_2$O-catalyzed, 8-aminoquinoline-directed multiple C(sp^3)−H activation strategy for the synthesis of bicyclo[*n*.1.0]alkanes (Scheme 160).[460] This reaction was proposed to start with the coordination of the Co(II) species to 8-aminoquinoline and the alkene, which is in situ oxidized to the active Co(III) species **1033**, followed by methyl C(sp^3)−H activation and alkene insertion to form intermediate **1035**. The second methylene C(sp^3)−H activation of intermediate **1035** then occurs to give cobaltacycle intermediate **1036**. Subsequent reductive elimination and decomplexation leads to the formation of bicyclo[*n*.1.0]alkane product. Reoxidation of the Co(I) species with Ag(I) will regenerate the active Co(III) species to close the catalytic cycle.

6. RHODIUM-CATALYZED, COORDINATION-ASSISTED FUNCTIONALIZATION OF C(sp^3)−H BONDS

Compared to Rh-catalyzed C(sp^2)−H functionalization, Rh-catalyzed activation of C(sp^3)−H bonds has received much less attention.[6,9,461−463] The functionalization of electronically

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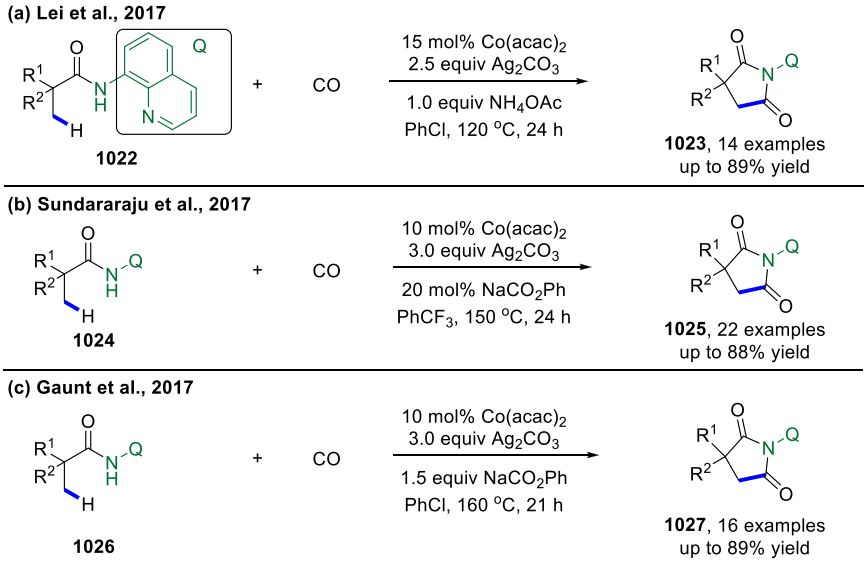
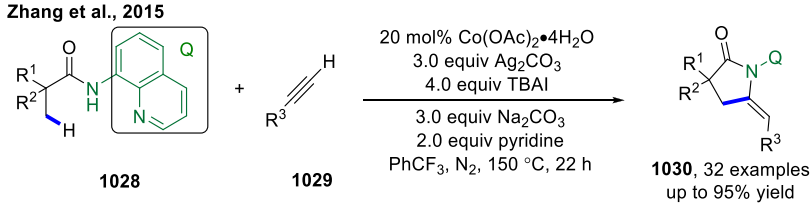
Scheme 158. 8-Aminoquinoline-Directed, Cobalt-Catalyzed Carbonylation of Unactivated C(sp^3)−H bonds of Aliphatic Amides: (a) Lei et al.;[456] (b) Sundararaju et al.;[457] (c) Gaunt et al.[458]



Scheme 159. Cobalt-Catalyzed β-C(sp^3)−H Alkynylation/Cyclization of Aliphatic Amides with Alkynyl Terminal Alkynes[459]



activated C(sp^3)−H bonds, such as allylic[464] or benzylic bonds[465−473] and those adjacent to heteroatoms,[474−478] have been investigated, but these systems are outside the scope of this review. Meanwhile, Rh-catalyzed activation of unactivated C(sp^3)−H bonds is more challenging and still relatively rare.

The Cp*Rh(III)-catalyzed β-arylation of unactivated C-(sp^3)−H bonds of 2-alkylpyridine derivatives was reported by the Glorius group in 2015 (Scheme 161a).[479] In this case, $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ (5.0 mol %) combined with Ag_2O (2.5 equiv) and triphenylboroxine (2.0 equiv) was effective for generating the desired product. Arylation of the C(sp^3)−H bond of 8-benzylquinoline was found to proceed at a lower temperature (80 °C) with a lower loading of the triarylboroxine and the oxidant. In this case, the products are attractive due to the biological properties of functionalized quinolines. In 2017, Zhao and co-workers achieved a Rh(III)-catalyzed, trimethyl-pyrazole-directed arylation of unactivated C(sp^3)−H bonds (Scheme 161b).[480] A wide range of functional groups were tolerated under the optimized conditions.

In 2015, the You group reported a Rh(III)-catalyzed, pyridine-directed amination of unactivated C(sp^3)−H bonds using sulfonamides as the nitrogen coupling partner at room temperature (Scheme 162a).[481] $[Cp^*Rh(CH_3CN)_3](SbF_6)_2$ and $PhI(OAc)_2$ were found to be the best catalyst/oxidant combination for this transformation. NaOAc (30 mol %) was required to improve the yield of the product. A variety of 2-ethylpyridine derivatives were suitable substrates for this transformation, and the method was compatible with different sulfonamides, such as aryl sulfonamides possessing an electron-withdrawing group on the aromatic ring and alkyl sulfonamides. Furthermore, cyclohexane ketoximes and (*E*)-2-methylcyclo-hexanone *O*-methyl oxime were viable substrate classes under the reaction conditions. Based on control experiments, the authors postulated that a nitrene intermediate is likely involved in the sulfonamidation process.

Rh(III)-catalyzed amidation of unactivated C(sp^3)−H bonds of ketoximes was reported by the Li group in 2015 with $[\{RhCp^*Cl_2\}_2]/AgSbF_6$ as the catalyst and AgOAc (8 mol %) as the additive (Scheme 162b).[482] 3-Substituted 1,4,2-dioxazol-5-one reagents were used as nitrogen electrophiles, and a variety of substituents at the 3-position were tolerated, including aryl groups bearing electron-donating or electron-withdrawing groups at different positions. Compatible substrates include 8-methylquinoline, the oxime ether of L-(−)-carvone, and even aliphatic cyclic and acyclic ketoximes. Deuterium-labeling experiments revealed that the C−H activation step is irreversible and thus the turnover-limiting step in the catalytic cycle. In 2018, the Xu group expanded the scope of Rh(III)-catalyzed amidation to 1-arylethan-1-ol oxime substrates (Scheme 162c).[483] Notably, C(sp^3)−H bonds were functionalized in preference to potentially more reactive C(sp^2)−H bonds. In 2019, the Wang group developed a Rh(III)-catalyzed bidentate group-directed amidation reaction with arylsulfonamides (Scheme 162d).[484]

Rh(I)-catalyzed alkenylation of primary C(sp^3)−H bonds of ketone derivatives with alkynes was documented by Dong and co-workers in 2017 (Scheme 163).[485] A hydrazone derived from 2-hydrazinyl-4-methylpyridine was used as the DG and was installed *in situ*. The alkenylation products were converted into corresponding alkylated ketones by reduction with H_2 over Pd/C. The hydrazone auxiliary could also be removed in one pot through the addition of aqueous HCl. A mechanism involving

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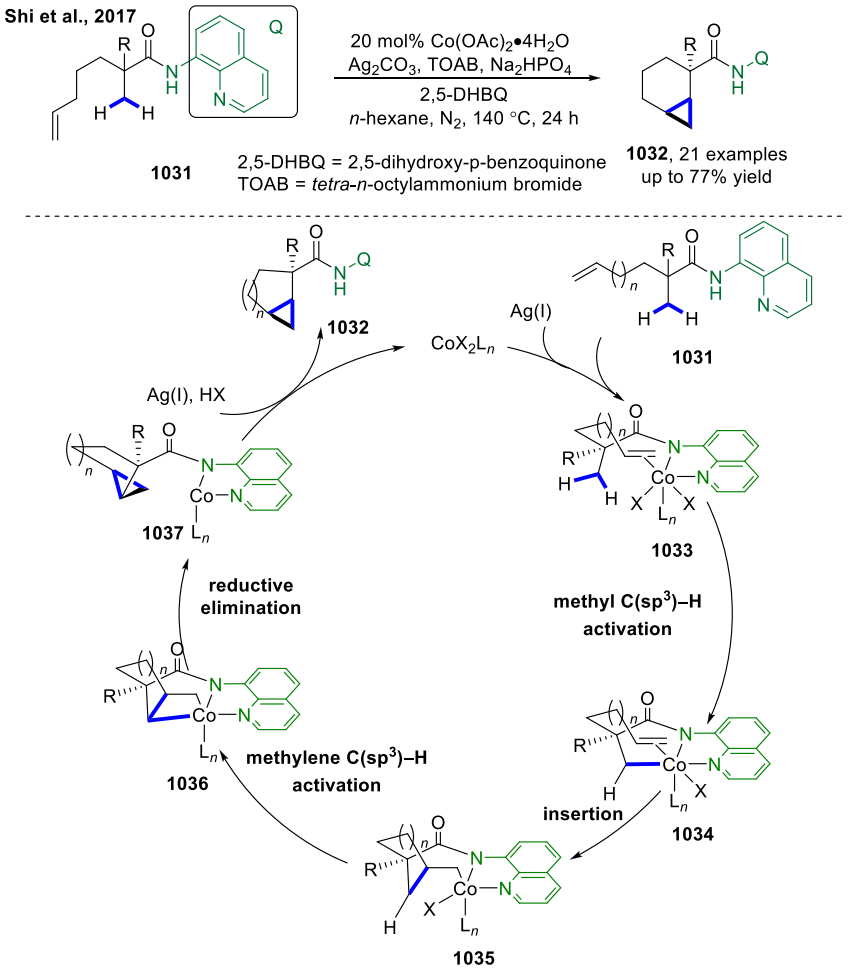
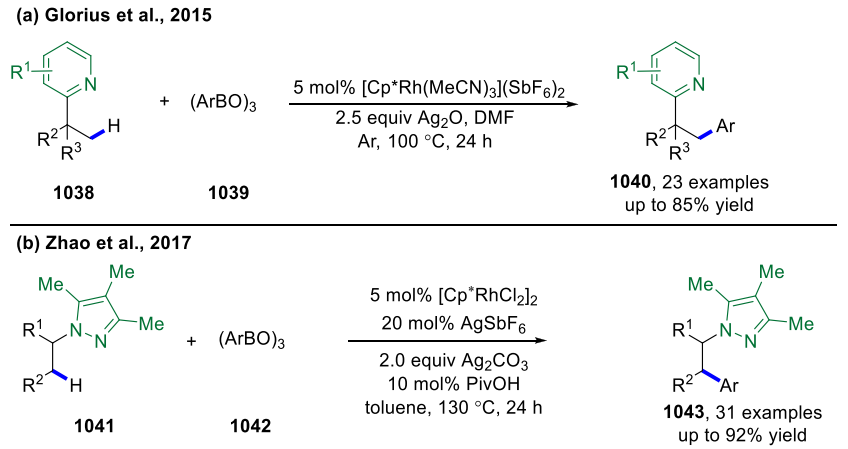
Scheme 160. Synthesis of Bicyclo[*n*.1.0]alkanes by a Cobalt-Catalyzed Twofold C(sp^3)−H Activation Cascade[460]



Scheme 161. (a) Rh(III)-Catalyzed *β*-C(sp^3)−H Arylation of 2-Alkylpyridine Derivatives[479] **and (b) Trimethylpyrazole-Directed Rh(III)-Catalyzed Arylation of Unactivated C(sp^3)−H Bonds**[480]



oxidative addition of Rh(I) to the C(sp^3)−H bond to form a Rh(III)(alkyl)(H) intermediate was proposed for this transformation based on the isolation of an analogous Ir(III)(alkyl)(H) complex.

7. IRIDIUM-CATALYZED, COORDINATION-ASSISTED FUNCTIONALIZATION OF C(sp^3)−H BONDS

It is well-known that iridium complexes react with a broad range of directing-group-containing compounds to form iridacycles via C−H bond activation.[486] However, early reports of iridium-catalyzed C(sp^3)−H activation were limited to C−H bonds adjacent to heteroatoms,[487−492] which is outside the scope of this review as this class of C−H bonds are uniquely activated.

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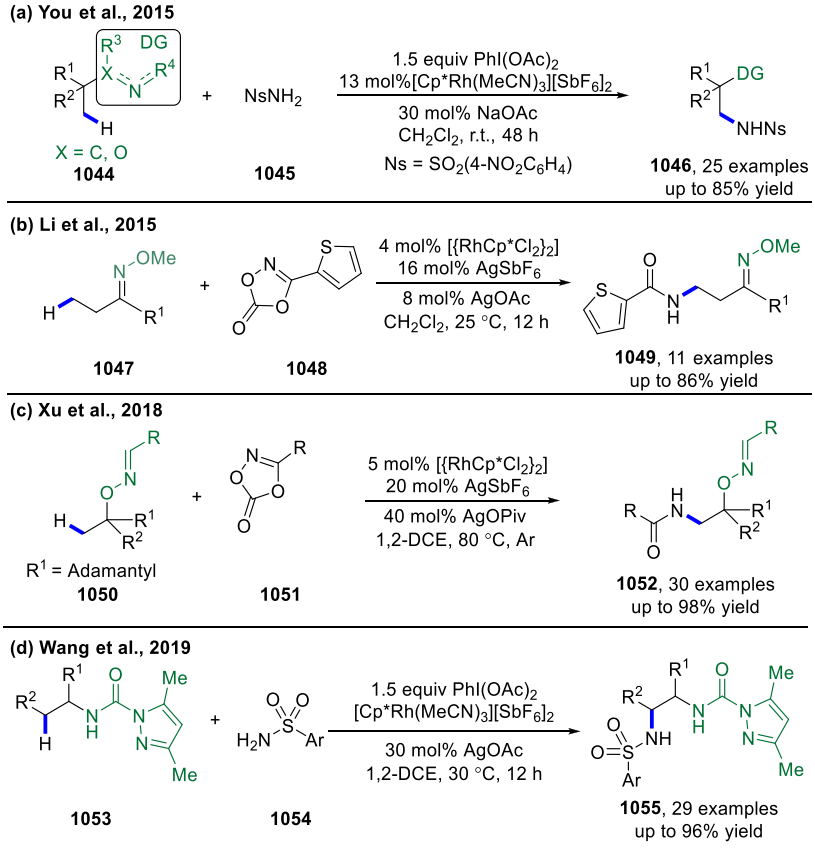
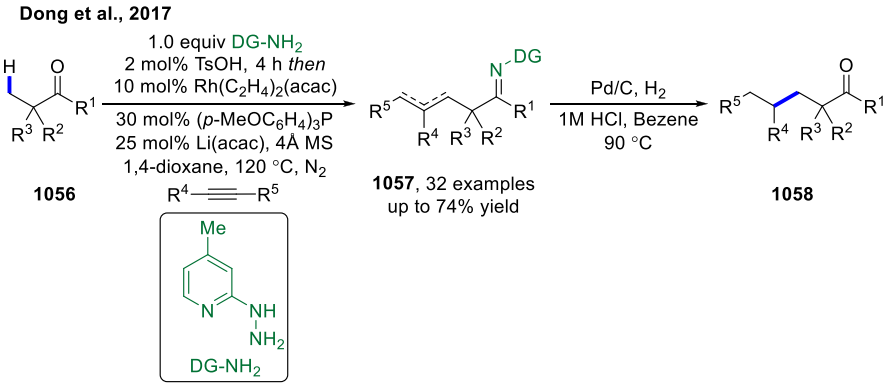
Scheme 162. Rh(III)-Catalyzed β-C(sp^3)−H Amidation Reactions: (a) with Sulfonamides Directed by Pyridine and Oxime;[481] (b) with 3-Substituted 1,4,2-Dioxazol-5-Ones Directed by Oxime;[482] (c) of 1-Arylethan-1-ol Oxime with 3-Substituted 1,4,2-Dioxazol-5-Ones Directed by Oxime;[483] (d) with Arylsulfonamides Directed by 3,5-Dimethylpyrazole Amides[484]



Scheme 163. Rh(I)-Catalyzed β-C(sp^3)−H Alkenylation of Ketones Using an *In Situ*-Installed DG[485]



Pyridine has been used as a DG to achieve Ir-catalyzed borylation of 2-alkylpyridines (Scheme 164a−c). In 2013, the Sato group discovered an Ir(I)-catalyzed, pyridine-directed triple C(sp^3)−H borylation in which pyridine DGs bearing electron-donating functional groups at the 4-position gave the desired products in high yield.[493] Ir-catalyzed primary and secondary C(sp^3)−H borylation of 2-alkylpyridines using silica-supported monophosphine−Ir catalysts was reported by the Sawamura group in 2013 (Scheme 163b).[494] The silica-supported monophosphine ligands show significant ligand-accelerating effect in this C(sp^3)−H borylation transformation and are crucial for the borylation of methylene C(sp^3)−H bonds. In the same year, Sawamura and co-workers also developed a novel type of polystyrene(PS)-phosphane covalently bound hybrid for Ir-catalyzed C(sp^3)−H borylation of 2-pentylpyridine.[495] Enantioselective borylation of secondary C(sp^3)−H bonds with an Ir(I) catalyst was reported by Sawamura and co-workers in 2019.[496] The extended aromatic environment on the BINOL-based monophosphite ligand (**L87**) increased the enantioselectivity significantly over atropisomeric BINOL-based monophosphite ligands. DFT calculations suggested that the monophosphite-Ir-tris(boryl) complex forms a narrow chiral reaction pocket.

In 2019, the group of Xu elegantly developed a new type of chiral bidentate boryl ligands (CBLs) containing a pyridyl group, a chiral boryl moiety, and a sterically bulky aryl, which successfully enabled the iridium-catalyzed asymmetric C(sp^2)−H borylation of diarylmethylamines.[497] Inspired by this

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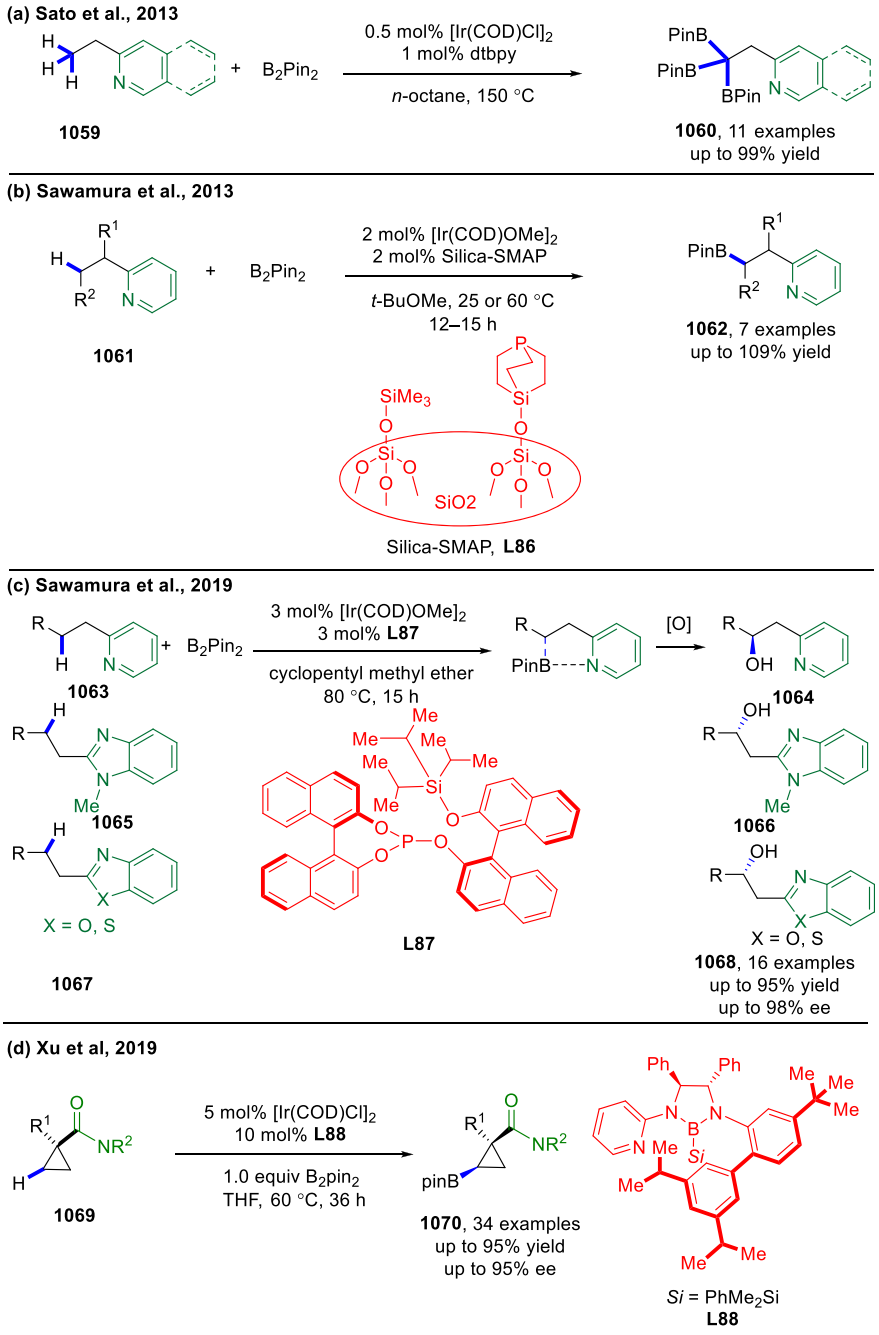
Scheme 164. Ir(I)-Catalyzed, Pyridine-Directed C(sp^3)−H Borylation: (a) Triple Methyl C(sp^3)−H Borylation;[493] (b) Using Silica-Supported Monophosphine−Ir Catalysts;[494] (c) Enantioselective Methylene C(sp^3)−H Borylation Using BINOL-Based Monophosphite Ligand.[496] (d) Ir(I)-Catalyzed, Amide-Directed Enantioselective C(sp^3)−H Borylation of Cyclopropanes with Chiral Bidentate Boryl Ligand[498]



promising result, they further extended this mode to Ir(I)-catalyzed, enantioselective C(sp^3)−H borylation of cyclopropanes using CBL **L88** as a chiral ligand (Scheme 164d).[498] A variety of cyclopropanecarboxamides with α-quaternary carbon centers are well tolerated, providing β-borylated products with high enantioselectivities (up to 96% ee). The resulting borylated products could be used as versatile precursors for subsequent stereospecific transformations and the synthesis of a bioactive compound, levomilnacipran, was achieved.

Ir(III)-catalyzed C−H amidation of methyl C(sp^3)−H bonds of ketoximes with sulfonyl or acyl azides under mild conditions was reported by the Chang group in 2014 (Scheme 165a).[499] A range of α-methyl cyclic ketoximes and acyclic ketoximes reacted with acyl or sulfonyl azides to afford the corresponding products in moderate to excellent yields. This amidation protocol occurred exclusively at the methyl C(sp^3)−H bond without functionalizing methylene C(sp^3)−H bonds. As is evident from the broad substrate scope and mild conditions of this procedure, it is effective for late-stage functionalization of natural products and complex synthetic compounds, such as a derivative of santonin.

The same group later extended this mode of reactivity to synthesize various 1,2-amino alcohols from alcohol-derived

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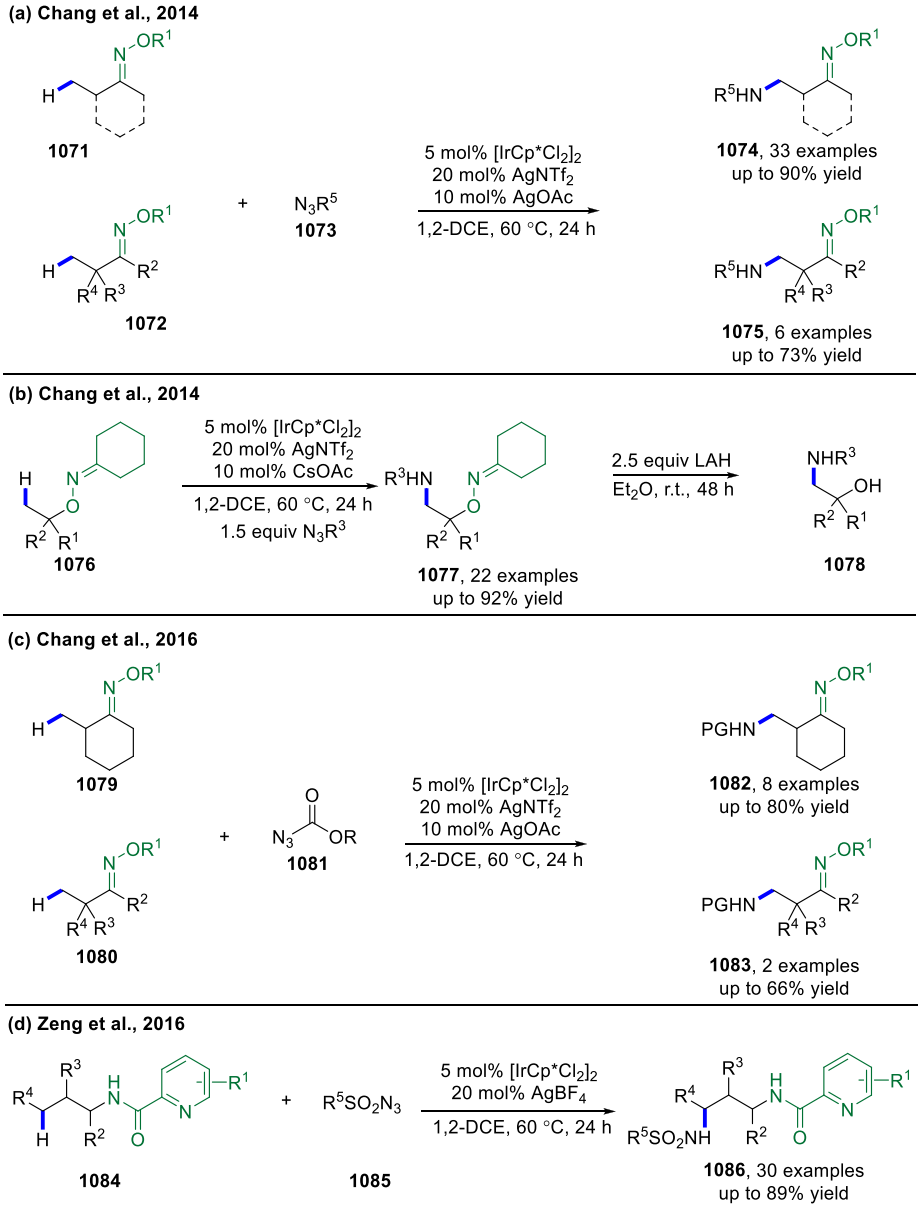
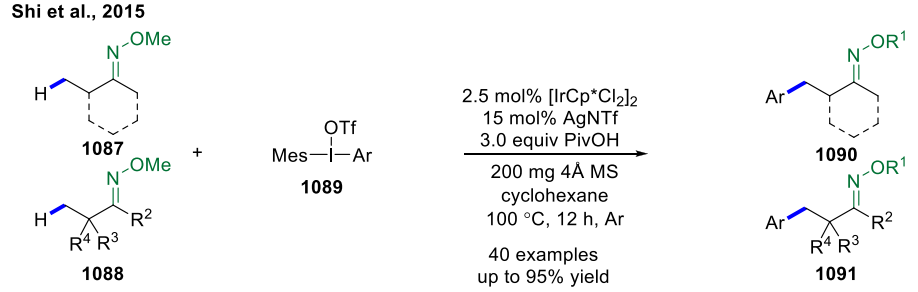
Scheme 165. Ir(III)-Catalyzed C(sp^3)−H Amidation: (a) Ketoximes with Sulfonyl or Acyl Azides;[499] (b) Alcohol-Derived Oximes;[500] (c) Ketoximes with Azidoformates;[501] (d) Picolinamide-Directed Methylene C(sp^3)−H Sulfonylamidation[502]



Scheme 166. Ir(III)-Catalyzed C(sp^3)−H Arylation of Ketoximes with Diaryliodonium Salts[503]



substrates (Scheme 165b).[500] Azidoformates have also been investigated by the Chang group as nitrogen coupling partners in the synthesis of primary alkylamines (Scheme 165c).[501] An Ir(III)-catalyzed, bidentate-auxiliary-directed intermolecular sulfonylamidation of methylene C(sp^3)−H bonds with azides was disclosed by the Zeng group in 2016 (Scheme 165d).[502]

In 2015, [(Cp*$IrCl_2$)$_2$]-catalyzed C(sp^3)−H arylation of ketoximes with diaryliodonium triflate salts was reported by the Shi group (Scheme 166).[503] Reaction optimization revealed that the addition of PivOH and 4 Å MS resulted in significantly improved yield. This protocol was demonstrated to serve as an

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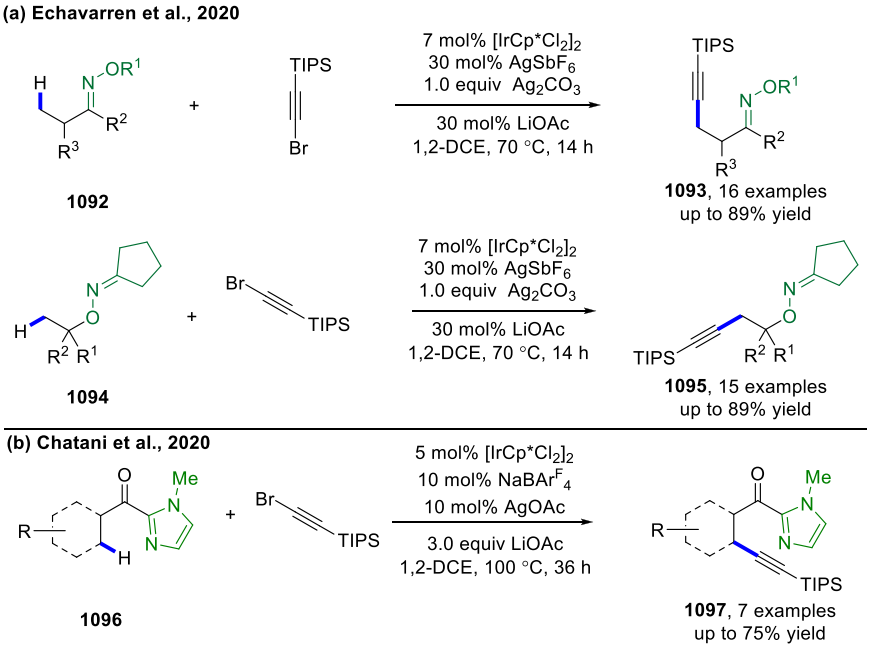
Scheme 167. (a) Ir(III)-Catalyzed β-C(sp^3)−H Alkynylation Directed by Oximes[504] and (b) Ir(III)-Catalyzed C(sp^3)−H Alkynylation of 2-Acylimidazoles[505]



efficient tool for the synthesis of C(β)-arylated lanostane and for the late-stage C(sp^3)−H arylation of oleanolic acid.

In 2020, the Echavarren group reported an Ir(III)-catalyzed primary C(sp^3)−H alkynylation of ketones and alcohols directed by oximes using a bromo-alkyne (1.2 equiv), catalyzed by $[Cp^*IrCl_2]_2$ (7 mol %), with substoichiometric amounts of $AgSbF_6$(30 mol %) and LiOAc (30 mol %), with Ag_2CO_3 (1 equiv) in 1,2-DCE. (Scheme 167a).[504] Under the same reaction conditions, pyridine, pyrazole, and pyrazine-directed primary C(sp^3)−H alkynylation was also achieved. 2-Acylimidazole-directed, Ir(III)-catalyzed primary C(sp^3)−H alkynylation using alkynyl bromides was reported by the Chatani group in 2020 (Scheme 167b).[505] During the course of mechanistic studies, a catalytically competent six-membered iridacycle was successfully isolated and characterized.

8. IRON-CATALYZED, COORDINATION-ASSISTED FUNCTIONALIZATION OF C(sp^3)−H BONDS

Iron is the second-most abundant metal in the earth's crust after aluminum and is inexpensive compared to the precious metals often used in catalysis.[506] Moreover, unlike palladium, iron can adopt oxidation states from −2 to +5 (and in rare cases +6). High-oxidation state iron catalysts (+3, +4, or even +5) are most commonly used in nonactivated C(sp^3)−H bond functionalization reactions. In terms of reactivity, iron-catalyzed C(sp^3)−H bonds functionalization is currently limited to C−C bond-forming reactions, such as arylation and alkylation.[507,508]

In 2013, Nakamura and co-workers reported the first 8-aminoquinoline-directed C(sp^3)−H arylation of aliphatic carboxamides catalyzed by $Fe(acac)_3$ (Scheme 168a).[509] Arylzinc reagents were employed as nucleophiles in combination with 1,2-bis(diphenylphosphino)benzene (dppbz) as ligand and 1,2-dichloro-2-methylpropane (DCIB) as the organic oxidant. This reaction is sensitive to the choice of ligand and shows a complete preference for C−H bond activation of the methyl group over a potentially competitive benzylic site. They also found that the arylation reaction was very sensitive to the structure of the substrate. All of the reactive substrates have an α-quaternary carbon center, while those containing either a wider or small CH_3−C−C(=O) bond angle (e.g., 1-methylcyclobutanecarboxamide and 1-methylcyclopropanecarboxamide) are unreactive. KIE studies and the observed selectivity and reactivity indicate that the reaction proceeds through the formation of a metallacycle intermediate via rate-determining C−H cleavage rather than a radical pathway. In 2015, the direct methylation of a C(sp^3)−H bond with an $AlMe_3$/Fe(III) system was also reported by the Nakamura group (Scheme 168b).[510] In 2017, the Nakamura group then expanded this methodology by using aryl-, heteroaryl-, and alkenylboron reagents as coupling partners (Scheme 168c).[511]

The triazolyldimethylmethyl (TAM) moiety was used as a directing group by the Ackermann group for the iron-catalyzed arylation and methylation of unactivated C(sp^3)−H bonds (Scheme 168d-e).[241,512] The high selectivity for functionalization of the methyl C(sp^3)−H bond over the weaker benzylic C(sp^3)−H bond is indicative of an organometallic C−H metalation mechanism.

9. RUTHENIUM-CATALYZED, COORDINATION-ASSISTED FUNCTIONALIZATION OF C(sp^3)−H BONDS

Ruthenium catalysts are among the earliest catalysts employed for C−H bond activation.[48,513−515] Ruthenium-catalyzed direct functionalization of electronically biased C(sp^3)−H bonds, such as those at benzylic positions or adjacent to heteroatoms, has been well studied and is outside of the scope of this review.[516−526] Beyond examples with activated C−H bonds, C(sp^3)−H activation reactions catalyzed by ruthenium are rare, and only two examples have been reported thus far. In 2011, the Chatani group developed the first Ru(0)-catalyzed carbonylation of unactivated β-C(sp^3)−H bonds of aliphatic amides to give the corresponding succinimides (Scheme 169).[527] The presence of the 2-pyridinylmethylamino moiety is required as an N,N-bidentate ligand, as evidenced by formation of a dinuclear

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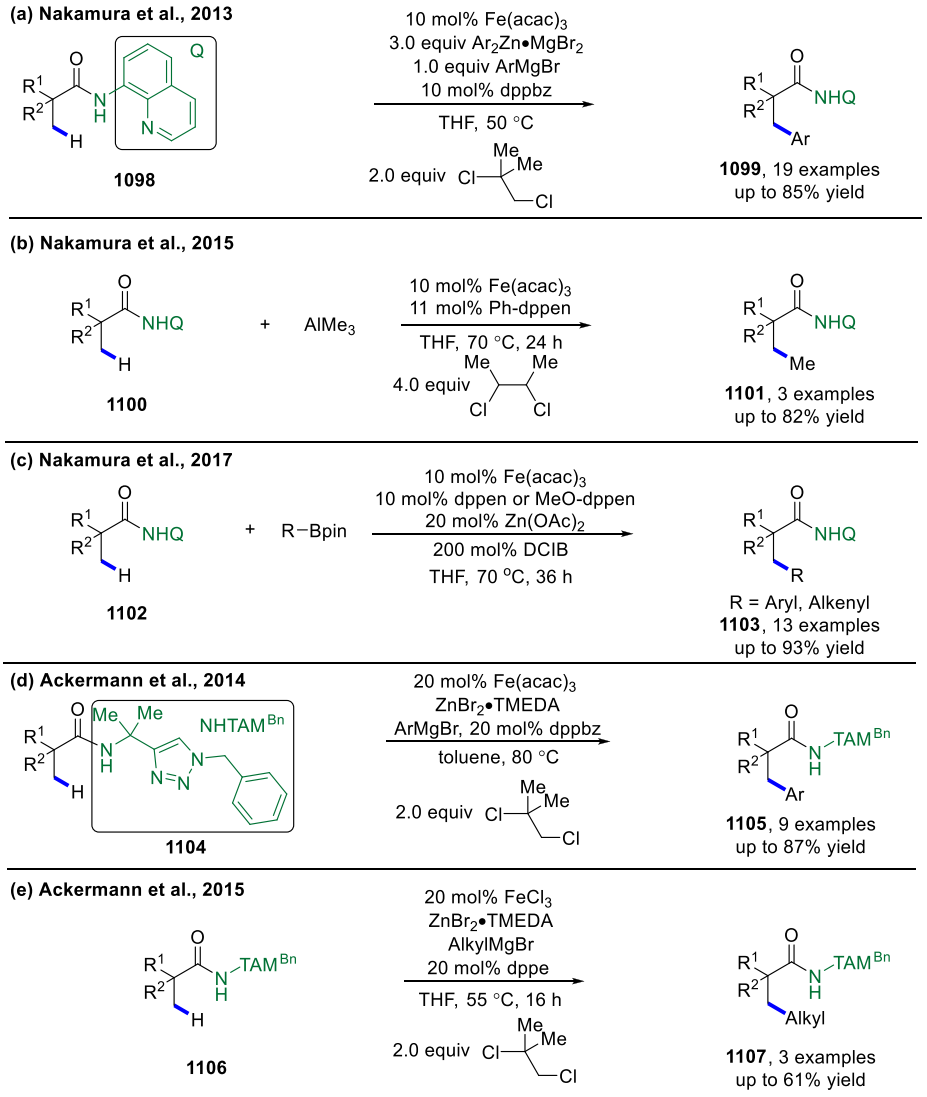
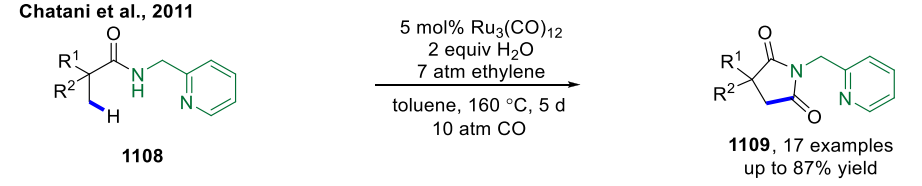
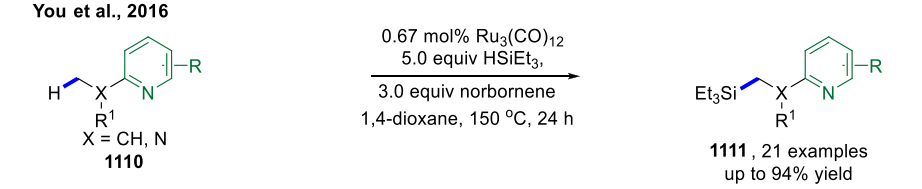
Scheme 168. Iron-Catalyzed, 8-Aminoquinoline-Directed β-C(sp^3)−H Functionalization of Aliphatic Amides: (a) Arylation with Arylmagnesium Bromides;[509] (b) Methylation with Trimethylaluminum;[510] (c) Arylation and Alkenylation of C(sp^3)−H Bonds with Organoborates.[511] Iron-Catalyzed, Triazole-Directed β-C(sp^3)−H Functionalization of Aliphatic Amides: (d) Arylation with Arylmagnesium Bromides;[241] (e) Alkylation with Alkylmagnesium Bromides[512]



Scheme 169. Ru(0)-Catalyzed β-C(sp^3)−H Carbonylation of Aliphatic Amides[527]



Scheme 170. Ru(0)-Catalyzed Intermolecular Direct Silylation of Unreactive C(sp^3)−H Bonds[528]



ruthenium complex when the substrate is combined with $Ru_3(CO)_{12}$. Although the reaction still proceeds when water is removed, the efficiency of the reaction decreases significantly. Interestingly, in the absence of ethylene, no carbonylation

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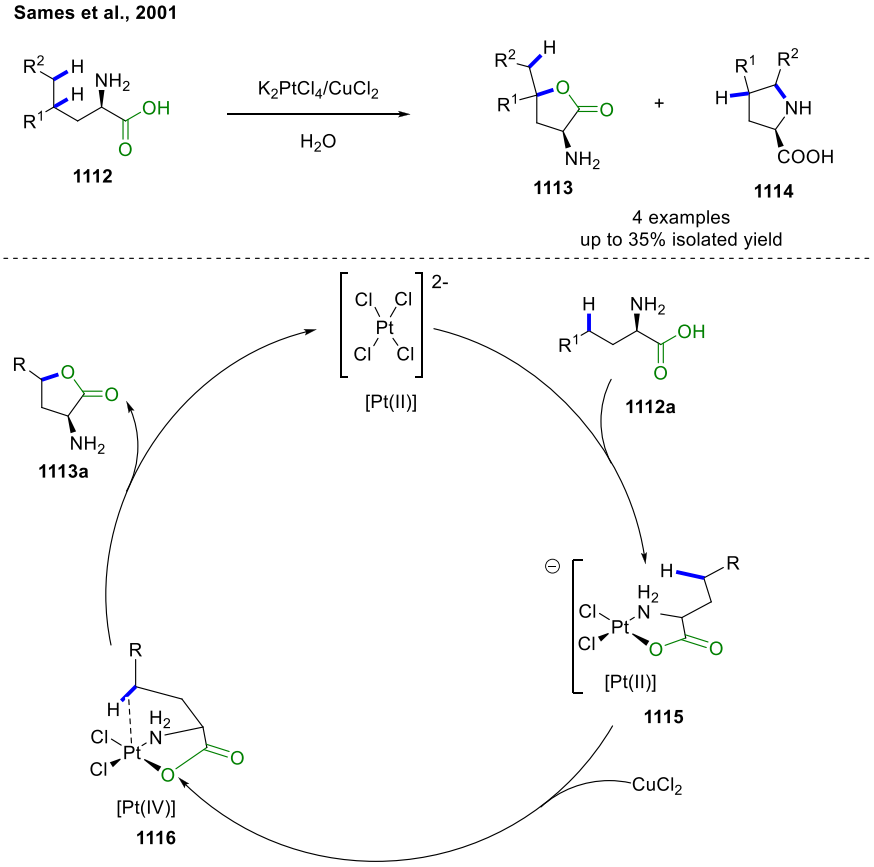
Scheme 171. Pt(II)-Catalyzed Intramolecular Hydroxylation of Unreactive C(sp^3)−H Bonds[532]



product could be detected. The authors postulated that ethylene functions as a hydrogen acceptor. Moreover, long reaction time (5 days) is needed.

A second example of Ru(0)-catalyzed functionalization of unactivated β-C(sp^3)−H bonds was reported by You and co-workers in 2016.[528] They described a $Ru_3(CO)_{12}$-catalyzed, pyridine-directed silylation of unactivated C(sp^3)−H bonds (Scheme 170). A wide range of 2-alkylpyridines were converted to the corresponding silylated products in modest to excellent yields.

10. PLATINUM-CATALYZED, COORDINATION-ASSISTED FUNCTIONALIZATION OF C(sp^3)−H BONDS

Pt catalysts have a rich history in activation of C(sp^3)−H bonds via an electrophilic mechanism, dating back to pioneering work by Shilov.[529,530] Pt salts had also been shown to coordinate with amino acids.[531] In 2001, Sames and co-workers reported hydroxylation of α-amino acids using K_2PtCl_4 as a catalyst and $CuCl_2$ as a stoichiometric oxidant (Scheme 171).[532] Hydroxylation of various aliphatic substrates, including *n*-butylamine and *n*-pentanoic acid, has also been observed. A coordination directed mechanism was proposed based on the regioselectivity of reactions with α-amino acids.

11. CONCLUSIONS AND FUTURE OUTLOOK

Transition-metal-catalyzed, coordination-assisted C(sp^3)−H functionalization has grown rapidly as a research area over the last few decades. Continued developments in this field hold great potential to revolutionize synthetic planning and execution. As illustrated, the proliferation of different metal catalysts, the implementation of new strategies, and the expansion of directing groups (including native functional groups, auxiliaries, and transient groups), has opened the door to functionalization of more strategic C−H bonds in organic molecules. This flexibility allows chemists to envision a greater number of C(sp^3)−H functionalization disconnections in synthetic planning, in both target- and diversity-oriented pursuits.

This progress notwithstanding, numerous challenges remain toward the long-term vision of being able to functionalize any desired C(sp^3)−H bond within a molecule of interest. This includes the direct use of chemical feedstocks without introduction of stoichiometric auxiliaries, the ability to control site- and stereoselectivity through catalyst and ligand design, and the improvement of catalyst turnover. We anticipate that efforts devoted toward these ends will stimulate more exciting advances at the nexus of organic synthesis, organometallic chemistry, and homogeneous catalysis in the coming era.

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Author Contributions

[▽]B.L. and A.M.R. contributed equally to this work.

Notes

The authors declare no competing financial interest.

Biographies

Bin Liu was born in Shangrao, China. He received his B.Sc. from Nanchang University in Nanchang, Jiangxi, in 2009. He earned his Ph.D. in 2014 under the supervision of Prof. Bing-Feng Shi at Zhejiang University, where his research focused on nitrogen containing functional group-directed C−H functionalization. In 2016, he joined the laboratory of Prof. Garret. M. Miyake at University of Colorado, Boulder, as a postdoctoral researcher, focusing on visible light promoted reactions based on electron donor−acceptor complexes and synthesis of brush copolymers. In 2017, he moved to Colorado State University with the Miyake group. In 2021, he joined the College of Chemistry at Nanchang University as a Professor.

Andrew M. Romine was born in the Philadelphia area. He received his B.S. in chemistry and business, economics, and management from the California Institute of Technology in 2016 performing research in the laboratories of Prof. G. Jeffrey Snyder (2013) and Prof. Robert H. Grubbs (2015−2016). During his undergraduate studies, he also attended a summer research program at Institut Català d'Investigació Química in 2014 performing research in the laboratory of Prof. Vladimir V. Grushin. Andrew completed his graduate studies as an NSF fellow at the Scripps Research Institute with Prof. Keary M. Engle (Ph.D., 2021), and, in 2021, he joined the Boston Consulting Group in the Philadelphia office as an Advanced Degree Consultant.

Camille Z. Rubel received a B.S. degree in chemistry and a minor in gender and women's studies from UC Berkeley where she carried out undergraduate research under the supervision of Prof. John Hartwig. She is currently a graduate student in the group of Prof. Keary Engle at Scripps Research, and her research is supported by the Schimmel Family Endowed Fellowship.

Keary M. Engle grew up in West Michigan and received his undergraduate education at University of Michigan (B.S., 2007) during which time he carried out research in the laboratory of Prof. Adam J. Matzger. Following a one-year stint as a Fulbright Scholar at the Max-Plank-Institute für Kohlenforschung with Prof. Manfred T. Reetz, he completed graduate studies at the Scripps Research Institute with Prof. Jin-Quan Yu (Ph.D., 2013) and the University of Oxford with Profs. Véronique Gouverneur and John M. Brown (D. Phil., 2013). After two years as an NIH Postdoctoral Fellow at California Institute of Technology with Prof. Robert H Grubbs, he began his independent career as an Assistant Professor at the Scripps Research Institute in 2015 and was promoted to Professor in 2020.

Bing-Feng Shi grew up in Shandong, China, and received his B.S. degree from Nankai University in 2001 and a Ph.D. degree from the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, under the guidance of Professor Biao Yu in 2006. Following time as a postdoctoral fellow at the University of California, San Diego (2006−2007), he moved to The Scripps Research Institute working with Professor Jin-Quan Yu as a research associate. In 2010, he joined the Department of Chemistry at Zhejiang University as a professor. His research focus is transition metal-catalyzed C−H functionalization and its synthetic applications.

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ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
APAQ	*N*-acetyl-protected aminoethyl quinoline
AQ	8-aminoquinoline
Ar	aryl
atm	atmosphere
BDE	bond dissociation energy
BINOL	1,1′-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BQ	1, 4-benzoquinone
Bu	butyl
CAN	ceric ammonium nitrate
Cbz	carboxylbenzyl
cod	1,5-cyclooctadiene
CPA	chiral phosphoric acid
Cp*	pentamethyl cyclopentadienyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone
DFT	density functional theory
DG	directing group
2,5-DHBQ	2,5-dihydroxy-*p*-benzoquinone
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
de	diastereomeric excess
DMPU	*N*,*N*′-dimethylpropyleneurea
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
ee	enantiomeric excess
er	enantiomeric ratio

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Et	ethyl
FG	functional group
HFIP	hexafluoroisopropanol
KTFA	potassium trifluoroacetate
L	neutral ligand
MIA	2-methoxyiminoacetyl
MPAA	mono-*N*-protected amino acid
MPAO	mono-*N*-protected aminomethyl oxazoline
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
Ns	nosyl
PA	picolinamide
Ph	phenyl
phen	phenanthroline
Phth	phthalimido
Pin	pinacolato
PIP	2-pyridylisopropylamine
Piv	pivaloyl
TBAB	tetrabutylammonium bromide
TBAI	tetra-*n*-butylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TDG	transient directing group
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethylsulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
Tle	*tert*-leucine
TM	transition metal
TOAB	*tetra-n*-octylammonium bromide
Tol	*p*-tolyl, 4-methylphenyl
X	halogen or anionic ligand

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