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Review

Transition-metal-catalyzed site-selective γ- and δ-C(sp^3)–H functionalization reactions

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SUMMARY

C(sp^3)–H bonds are ubiquitously present in natural raw materials. Direct functionalization of these bonds provides a highly valuable approach to increasing molecular complexity. However, the inertness of these bonds and their high bond-dissociation energies, low acidity, and unreactive molecular orbital profiles make them challenging reaction components. To overcome these hurdles, the site-selective C(sp^3)–H functionalization approach has been developed via various strategies that provide distinct, straightforward, and atom-efficient access to constructing C–C and C–X bonds. This review discusses transition-metal-catalyzed site-selective γ- and δ-C(sp^3)–H functionalization of simple aliphatic substrates. The purpose of this review is to characterize the current state of the art in transition-metal-catalyzed site-selective γ- and δ-C(sp^3)–H functionalization reactions, their mechanisms, and their application in the late-stage functionalization of medicinal compounds and the construction of medicinally important complex molecules.

INTRODUCTION

Transition-metal-catalyzed direct C(sp^3)–H bond functionalization has emerged as a powerful synthetic strategy in modern synthetic organic chemistry, and it has aroused great interest among organic, material, medicinal, and agricultural scientists owing to its significant advantages.[1–7] This approach provides a distinctive, straightforward, and atom-efficient access to common and/or complex molecular skeletons in biologically active natural products, pharmaceutics, and functional materials from cheap, easily accessible starting materials. Additionally, these processes offer a great opportunity for the late-stage functionalization of biologically active natural products and medicinal compounds, facilitating the drug discovery and development processes.[2–7]

Transition-metal-catalyzed direct α- and β-C(sp^3)–H functionalization reactions of various aliphatic substrates have been extensively studied in the past decades and have been well summarized and updated by many prestigious research groups.[2–4] In contrast, the development of transition-metal-catalyzed γ- and δ-C(sp^3)–H functionalization has been a much slower process. Examples of such functionalizations have been generally scarce due to the difficulties of forming the required high-energy six-membered or larger metallacycles intermediates, a kinetically unfavorable process.

Despite these challenges, significant progress on the selective and efficient functionalization of unactivated γ- and δ-C(sp^3)–H bonds of simple alkyl substrates has been made possible with efforts from many research groups in recent years

The bigger picture

Direct C(sp^3)–H bond functionalization has aroused great interest among organic, material, medicinal, and agricultural scientists because of its superior role in (1) providing practical approaches to preparing common and/or complex molecular skeletons in biologically active natural products, pharmaceutics, and materials that cannot be easily prepared by other approaches; (2) employing less toxic chemical reagents and enabling previously unachievable synthetic transformations; and (3) offering a great tool for the late-stage functionalization of biologically active natural products and medicinal compounds. Transition-metal-catalyzed site-selective γ- and δ-C(sp^3)–H functionalization has been developing rapidly in recent years through a variety of catalytic approaches. Meanwhile, a series of natural products and drug molecules have already been efficiently constructed via these protocols.

by using a variety of catalytic approaches. Currently, there is an urgent need to summarize this field, analyze the strategies used, and discuss the detailed mechanisms of these processes to further accelerate the development of this research. Although similar topics were published during the preparation of this review,[5–7] there is still plenty of space for discussion from different angles and focus points. The transition-metal-catalyzed site-selective γ- and δ-C(sp^3)–H functionalization reactions reported until March 2022 will be comprehensively detailed in this review. We will discuss various strategies pertaining to the insertion, oxidation, non-covalent interaction, and hydrogen-atom-transfer (HAT) processes directed by auxiliary groups, transient directing groups (TDGs), and native functional groups. The reaction mechanisms will also be discussed in detail. Furthermore, we will include a series of natural products and drug molecules that were constructed according to these protocols to showcase the potential applications of these strategies. We hope to offer readers a robust understanding of the state of development in transition-metal-catalyzed direct γ- and δ-C(sp^3)–H functionalization reactions. We will also present a brief perspective on the remaining challenges and future directions.

AUXILIARY-CONTROLLED γ- AND δ-C(sp^3)–H FUNCTIONALIZATION

The inertness of alkyl C(sp^3)–H bonds due to the high bond-dissociation energies and low polarity difference between the carbon and hydrogen atoms makes them challenging reaction partners.[2–4] Moreover, the desired site selectivity is often an issue in reactions with multiple analogous sp^3 C–H bonds. To overcome these problems, transition-metal-catalyzed site-selective C(sp^3)–H functionalization has been developed with the assistance of various well-designed directing groups (DGs) that can coordinate to a metal center and deliver it on a targeted C–H bond through an appropriate spatial arrangement, enabling C–H activation via the formation of a metallacyclic complexes bearing covalent M–C bonds. The M–C bonds enable a subsequent reaction with functionalization reagents, eventually releasing the desired products. The DGs are largely dominated by the nitrogen-, sulfur-, or phosphorus-based functional groups, including pyridines, oxazolines, amides, acetanilides, nitriles, sulfide, and phosphine, etc. When compared with conventional cross-coupling reactions, this strategy does not require pre-functionalized starting materials and can avoid the use of stoichiometric organometallic reagents, allowing it to be more environmentally and economically beneficial. As a result, auxiliary-assisted transition-metal-catalyzed site-selective C(sp^3)–H functionalization has been considered a very effective synthetic method in organic chemistry.

Auxiliary-controlled γ-C(sp^3)–H functionalization of amides

Amides are important structural motifs in a variety of biologically active natural products and pharmaceutical agents.[8–15] Thus, the transitions metal-catalyzed C(sp^3)–H functionalization of amides were of significant interest and have been extensively studied in the past decades. Especially, the β-C(sp^3)–H functionalization of amides by the predominant five-membered metal cycles has been extensively demonstrated.[2–4] In addition, the direct γ-C(sp^3)–H functionalization of amides was also developed with the less favored six-membered palladacycle with the use of a ligand or auxiliary group.

C–H amination

In 2013, the Chen group reported a Pd-catalyzed intramolecular amination reaction of unactivated γ-C(sp^3)–H bonds to provide pyrrolidones by using a readily removable auxiliary group. Either 8-aminoquinoline (AQ) or 2-pyridylmethyl amine (PM)

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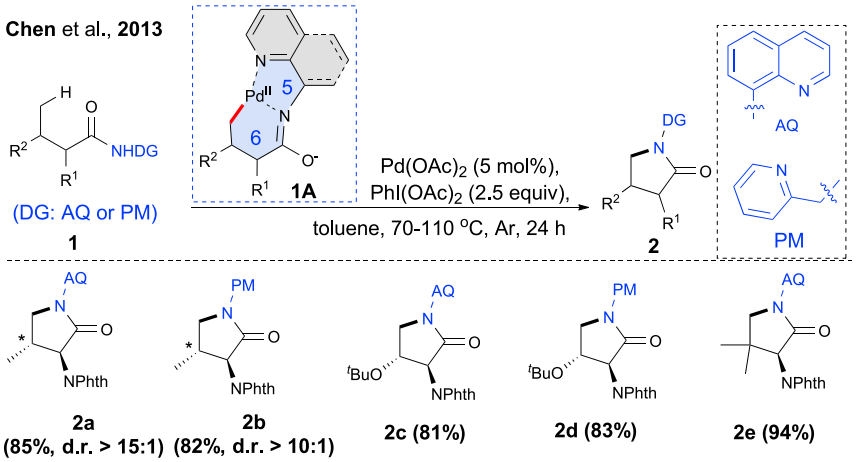
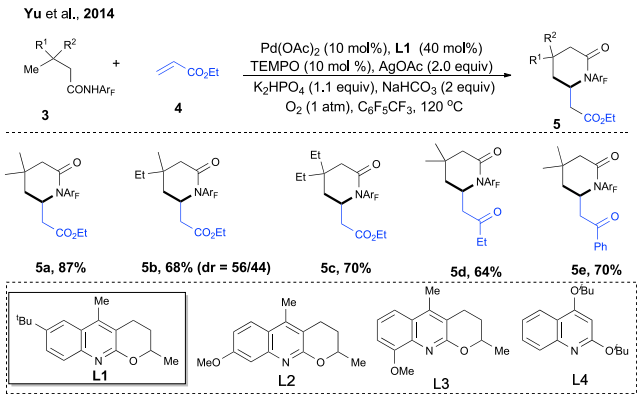


Scheme 1. The Pd-catalyzed intramolecular amination of unactivated γ-C(sp^3)–H bonds

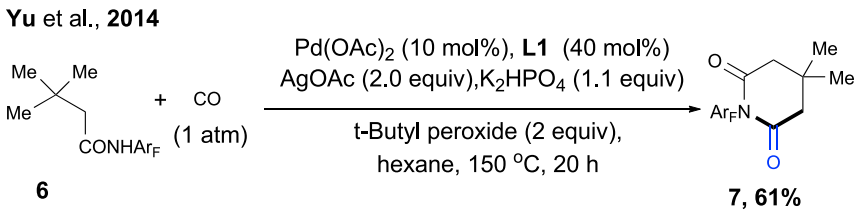
was used as an auxiliary group (Scheme 1).[8] The authors speculated that the reaction proceeds via a 6,5-bicyclic Pd intermediate **1A**. A series of pyrrolidones were obtained in good yields with excellent diastereoselectivity under standard conditions.

C–H olefination and carbonylation

In 2014, the Yu group reported Pd-catalyzed direct γ-C(sp^3)–H olefination and carbonylation of aliphatic amides by using a quinoline-based ligand in combination with a weakly coordinating amide DG ($CONHAr_F$, *N*-(2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenyl)amide) (Schemes 2 and 3).[9] Quinoline-based ligands were found to play a crucial role in both transformations; otherwise, only trace amounts of products were detected with pyridine-based ligands or without ligands altogether. Among quinoline-based ligands, **L1** provided the best results, whereas ligands such as **L2–L4** proved less effective. The use of 2,3,5,6-tetrafluoro-4-(trifluoromethyl)aniline amides proved optimal, whereas the use of other amide DGs led to a significant decrease in the yield. A broad scope of aliphatic acid amides and olefins underwent olefination to afford highly functionalized all-carbon quaternary centers. Additionally, carbonylation of amide **6** was successful, providing the corresponding cyclic imide product in 61% yield. Later, the Maiti group successfully extended the substrate scope to include acrylates and vinyl



Scheme 2. The Pd-catalyzed direct γ-C(sp^3)–H olefination of aliphatic acids



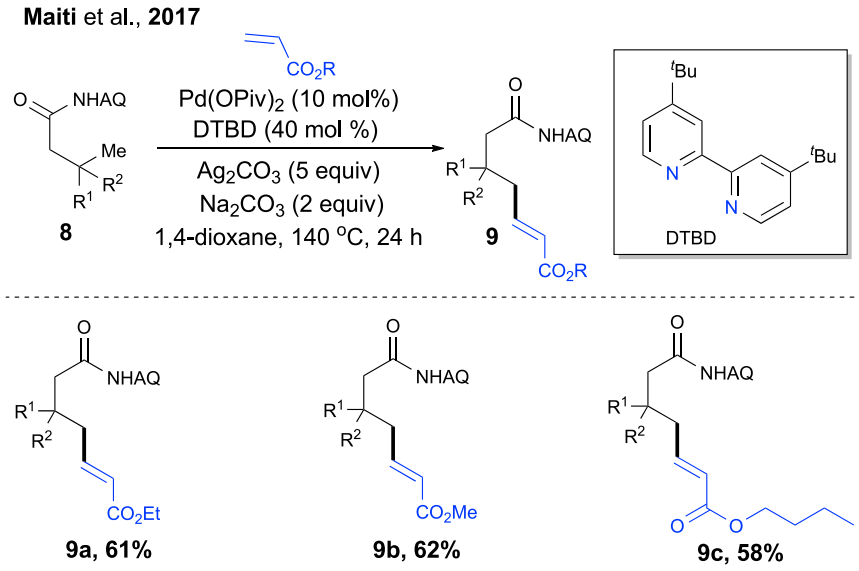
Scheme 3. The Pd-catalyzed direct γ-C(sp^3)–H carbonylation of aliphatic acids

iodides to achieve intermolecular γ-C(sp^3)–H olefination of aliphatic amides (Scheme 4).[10]

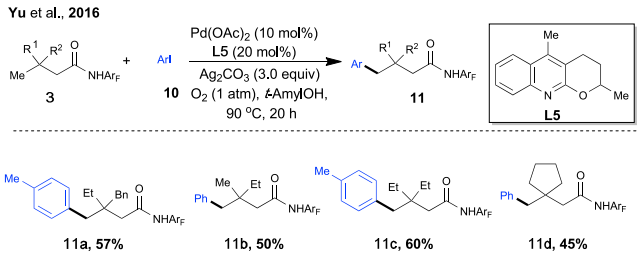
C–H arylation

This strategy was later utilized to perform direct γ-C(sp^3)–H arylation of aliphatic amides by the Yu group (Scheme 5).[11] It was found that the use of tricyclic quinolone ligands was crucial for the reactivity of the substrates, and among such ligands, **L5** was found to be the most effective. A series of simple aliphatic amides containing β-quaternary carbon centers successfully reacted with aryl iodides to afford the desired products in moderate to good yields. Unfortunately, under such conditions, the amide derived from 3-methylbutanoic acid was not tolerated due to the absence of the Thorpe-Ingold effect. To achieve γ-arylation of valine amides, more ligands were screened, and it was found that the bulky *tert*-butyl-substituted quinolone ligand (**L1**) enhances the reactivity (Scheme 6). Other amino acid amides such as isoleucine- and *tert*-leucine-based amides successfully underwent arylation with aryl iodides. Furthermore, amides **13b** can be hydrolyzed to form the corresponding γ-arylated aliphatic amino acids (Scheme 7).

In 2017, Babu and co-workers formed a new class of pyrrolidone-ring annulated thiophene/furan-based heterocyclic scaffolds via Pd(II)-catalyzed successive arylation/intramolecular amidation of γ-C(sp^3)–H bonds by using AQ as a bidentate DG (Scheme 8).[12] AgOAc was used as an oxidant along with Pd(OAc)$_2$ as a catalyst in toluene for 48–70 h to form the desired products. The major limitation of the work remains the usage of a large excess (20–30 mol %) of catalyst in most cases.



Scheme 4. The Pd(II)-catalyzed intermolecular γ-C(sp^3)–H olefination of aliphatic acids

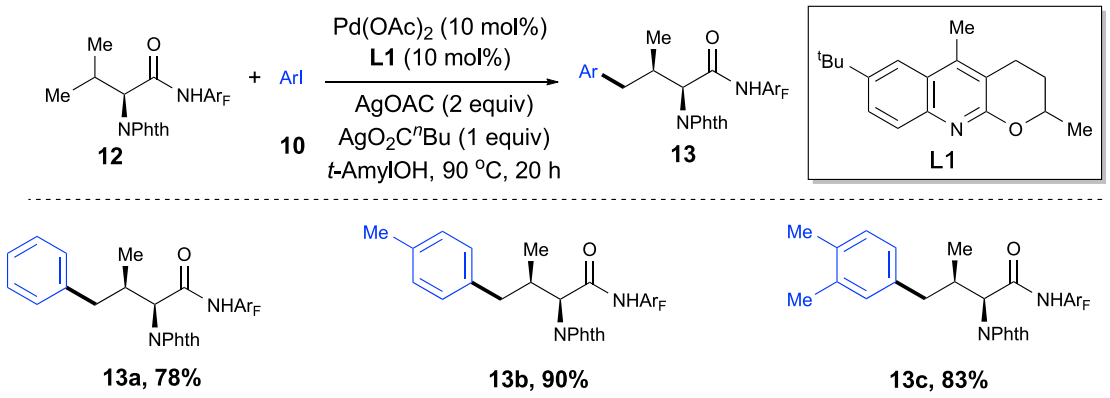


Scheme 5. The direct γ-C(sp^3)–H arylation of aliphatic amides

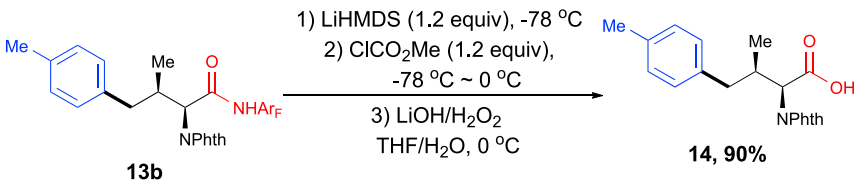
In addition, upon shortening the reaction period to 4–24 h and reducing the amount of catalyst, the γ-C(sp^3)–H arylation products could be obtained exclusively.

C–H silylation and germanylation

To further expand the substrate scope, the Maiti group modified the reaction conditions to develop distal Pd(II)-catalyzed γ-C(sp^3)–H silylation and germanylation of aliphatic amides (Schemes 9 and 10).[13] Bidentate 8-aminoquinoline was employed as a DG that can stabilize the six-membered palladacycle intermediate. 2-Chloroquinoline was found to be the optimal ligand. Various aliphatic amides and amino acids amides were silylated and germanylated at the γ-position with good yields and high diasteroselectivity. Although the authors achieved γ-C(sp^3)–H silylation and germanylation of aliphatic amides under the same conditions owing to the closely similar reactivity of silicon and germanium, the two reactions have shown some differences as their mechanisms were investigated. Intermolecular kinetic isotope effect (KIE) experiments were carried out, and low KIE values for silylation (1.07) and germanylation (1.27) were found (Scheme 11). The results of KIE experiments showed that the C–H cleavage in these reactions is not involved in the rate-determining step. The density functional theory computations further demonstrated that the highest energy point on the potential energy profiles of silylation (blue line) is oxidative addition. As for germanylation of aliphatic amides (green line), the highest energy point is reductive elimination (Figure 1). Hence, the calculated results are consistent with the KIE experiments. Together, these studies show that oxidative addition is the rate-determining step for silylation and that reductive elimination is the rate-determining step for germanylation instead of the C–H cleavage.



Scheme 6. Pd-catalyzed direct γ-C(sp^3)–H arylation of aliphatic amides

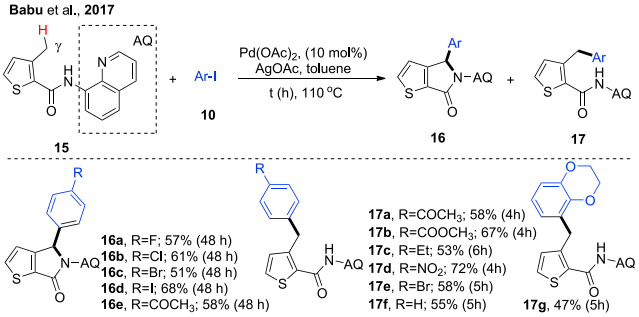


Scheme 7. The hydrolysis of amides 13b hydrolyzed to form γ-arylated aliphatic amino acids

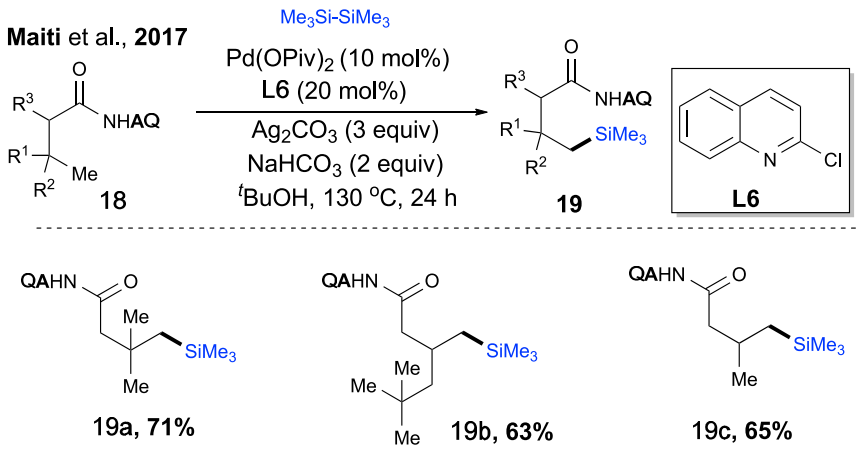
C–H alkylation

In 2019, Chatani reported an efficient method for the alkylation of benzylic γ-C(sp^3)–H bonds of 8-aminoquinoline-assisted (hetero)aryl amides with maleimide via palladium (Pd) catalysis (Scheme 12).[14] On the basis of their studies on the reaction mechanism, the authors suggested that both five-membered and six-membered palladacycles could be generated in the C–H bond activation process. However, the insertion of a maleimide into the six-membered palladacycle is more energetically favored than the five-membered palladacycle via *ortho*-C(sp^3)–H bond cleavage. As a result, the Pd-catalyzed C–H alkylation reaction occurs exclusively at the γ-benzylic C–H bond, such that no reaction occurs at the *ortho*-C(sp^2)–H bond.

In 2020, Shi and Yu reported an elegant approach to ligand-enabled remote γ-alkylation of saturated aliphatic carboxamides with 8-aminoquinoline as the auxiliary (Scheme 13).[15] Despite C(sp^3)–H functionalizations of aliphatic carboxamides being reported by many groups previously, in the presence of accessible β-C(sp^3)–H bonds, remote γ-alkylation of such aliphatic carboxamides was challenging because the β-position functionalization would proceed via a kinetically favored five-membered palladacycle and since γ-alkylation would require the formation of the kinetically less favored six-membered palladacycle. In this reaction, γ-alkylation was achieved via changing the regioselectivity determining step from the C–H cleavage step to the unassuming Pd migration step. In addition, the use of 2-pyridone as an external ligand was crucial to the success of the reaction. Otherwise, only a trace amount of product was detected in its absence. Further studies showed that the external σ donor ligand 2-pyridone (**L7**) not only accelerates the *in situ* oxidation of Pd(0) to Pd(II) under air via the assistance of its pyridyl nitrogen but could also coordinate with and effectively stabilize the Pd(II) species as a strong X-type ligand, leading to promoting C–H activation. To gain some insights into the reaction mechanism, the authors conducted density functional theory (DFT) calculations and a series of experimental studies, including analyzing X-ray structures of some important palladacycle intermediates and implementing



Scheme 8. Pd-catalyzed successive arylation/intramolecular amidation of γ-C(sp^3)–H bonds

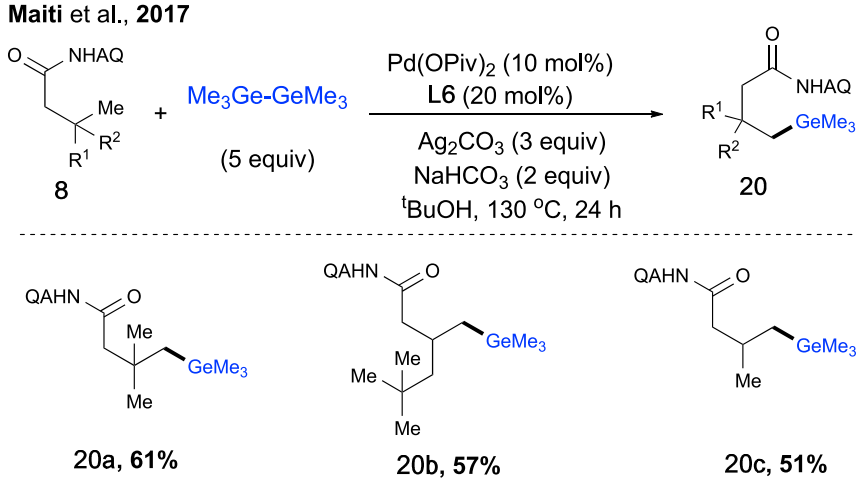


Scheme 9. Pd(II)-catalyzed distal γ-C(sp^3)–H silylation of aliphatic carboxylic acids

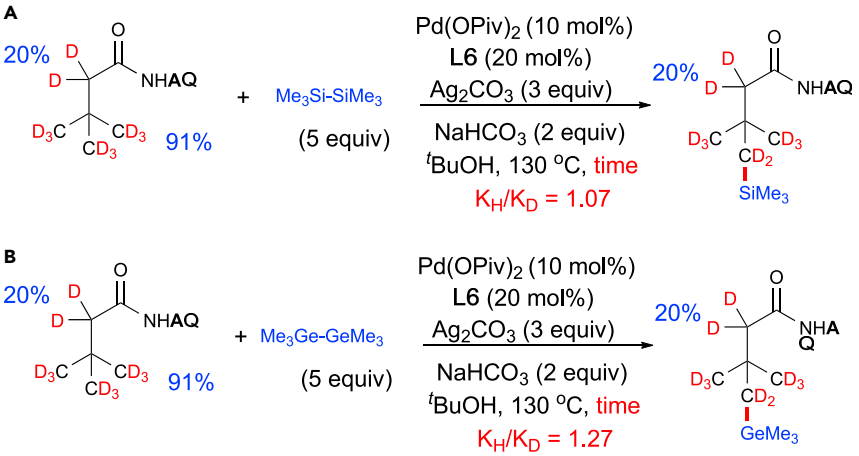
the deuterium-labeling experiment. Thus, a tentative mechanism was proposed by the authors (Scheme 14). First, the Pd(II) species forms through the oxidation of $Pd(dba)_2$ by air and then coordinates with two **L7** ligands to give rise to intermediate **24A**. The DG of substrate 18 coordinates with the Pd(II) from intermediate **24A** to form intermediate **18A**, liberating one **L7** ligand. Next, the external 2-pyridone ligand abstracts the γ-C–H bond to accelerate C–H activation forming the [6,5]-bicyclic Pd complex **18B**. Then, ligand exchanges between **23a** (alkene) and **L7** leads to the formation of intermediate **18C**, which undergoes alkene insertion to form intermediate **18D**. Subsequently, **18D** undergoes an unexpected 1,4-Pd migration process to afford **18E**. Finally, the protonation of **18E** generates the γ-alkylation product.

β-γ dehydrogenation

In 2008, Yu reported one example for Pd(II)-catalyzed β-γ dehydrogenation of propyl groups in cyclopentylcarboxamides by using oxazolylamide as a DG (Scheme 15).[16] In the study, $Pd(OAc)_2$ was used as the catalyst, and benzoquinone was employed as the stoichiometric oxidant. Despite the limited substrate scope and yield,



Scheme 10. Pd(II)-catalyzed distal γ-C(sp^3)–H germanylation of aliphatic carboxylic acids



Scheme 11. The intermolecular kinetic isotope effect study experiments of silylation and germanylation

(A) A small KIE value of 1.07 for silylation.

(B) A KIE value of 1.27 for germanylation.

the method has potential applications in organic synthesis. It is noted that this group further discovered the utility of quinoline-pyridone ligand in enabling divergent dehydrogenation via Pd-catalyzed β-methylene C–H activation of carboxylic acids to produce α,β-unsaturated carboxylic acids in moderate to good yields (Scheme 16).[17]

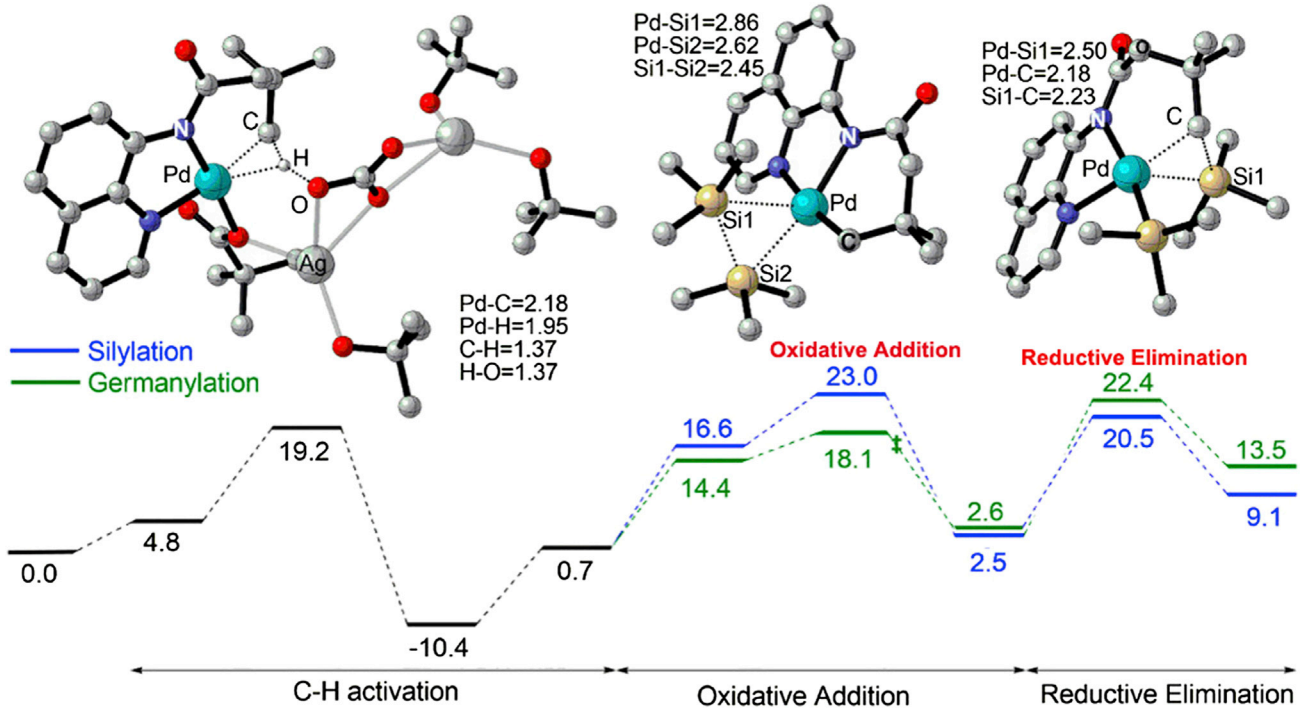


Figure 1. The Gibbs free energy profile (kcal/mol) of γ-C(sp^3)–H silylation and germanylation of aliphatic amides received at the SMD/M06/6-31G, SDD(Pd) level of theory**

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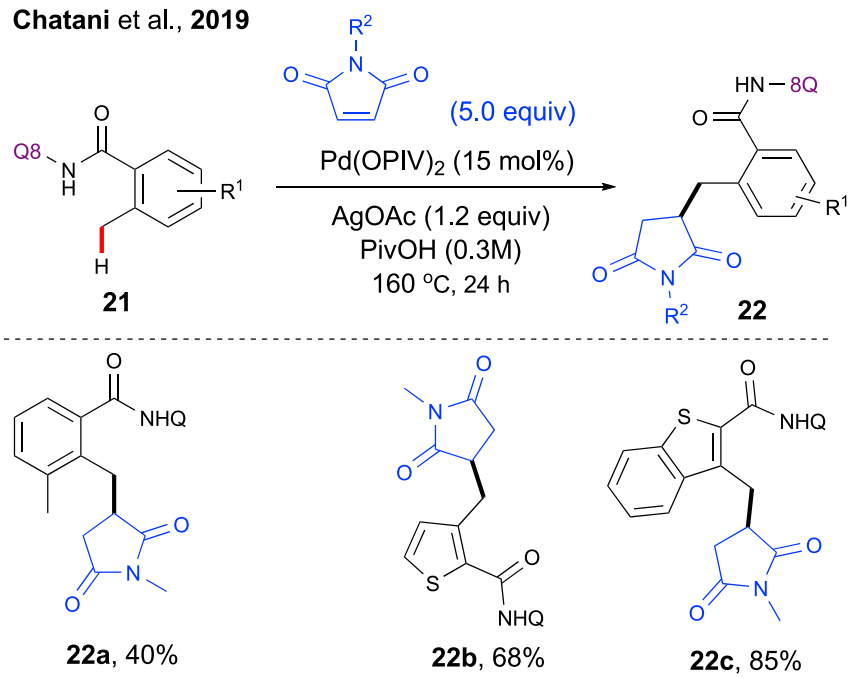


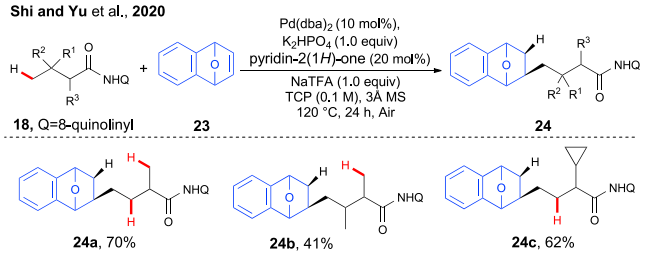
Scheme 12. Pd(II)-catalyzed alkylation of benzylic γ-C(sp^3)–H bonds

At present, the transition-metal-catalyzed site-selective γ-C(sp^3)–H functionalization of amides is still in its initial stages. The precious transition metal Pd is the only used catalyst thus far, and these reactions require catalyst loadings of 10∼15 mol % to be practical and effective at high reaction temperatures. There are only a few types of amide functionalization currently, and the scopes of amines are narrow. It is one of our future development directions to develop catalysis via inexpensive metals to achieve novel γ-C(sp^3)–H functionalizations of amides under mild conditions with a broad scope, good regioselectivity, and high functional-group compatibility. Reaching such target could accelerate the production of amides-based functional molecules.

Auxiliary-controlled γ-C(sp^3)–H functionalization of ketones

C–H arylation

The Yu group developed an electron-deficient 2-pyridione ligand that promotes γ-arylation of ketones by using an aminooxyacetic acid as a DG, a system that was found to be compatible with ketone substrates without a β-quaternary center (Scheme 17).[18] A variety of functional groups, including aryl, amino, hydroxyl, ether, or ester, were well tolerated. Utilizing this strategy, the authors successfully carried out the late-stage functionalization of biologically active natural products via a sequential C–H activation process (Scheme 18). It is worth mentioning that the DG, aminooxyacetic acid, could be readily removed by treatment with $Mn(OAc)_2$. It was found that the use of X-type 2-pyridone ligands was crucial in the transformation, among such ligands, 3-nitro-5-(CF_3)pyridine-2-ol was found to be the most effective. The 3-nitro-5-(CF_3)pyridine-2-ol helps the displacement of the OAc/OTFA on the Pd(II) catalyst to promote the formation of reactive Pd(II) precursor and accelerate C–H activation through abstraction of the γ-C–H bond. In another article, Ayan Datta's mechanistic studies again support this speculation.[19] The X-type 2-pyridone ligands have been found more energetically favorable to promote dissociations of $Pd_3(OAc)_6$ than the acetate. The activation energies of the

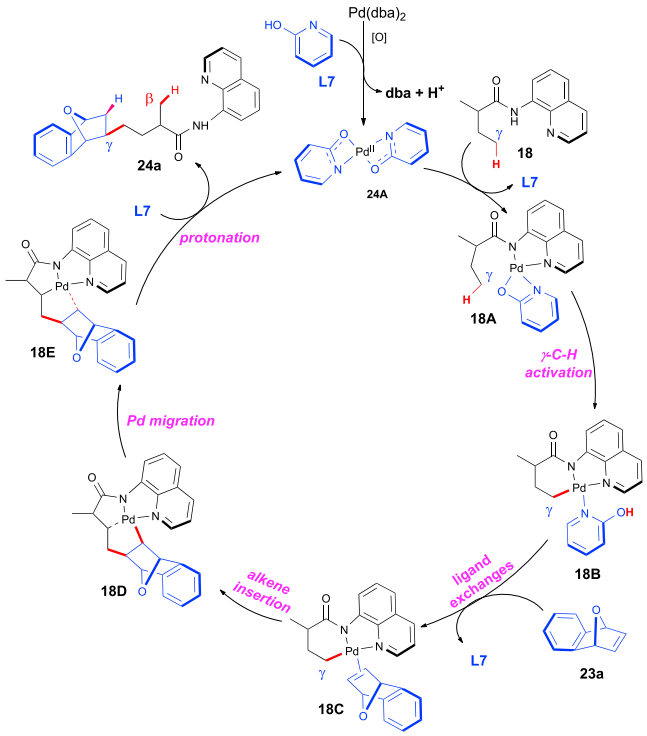


Scheme 13. Pd-catalyzed γ-alkylation of saturated aliphatic carboxamides

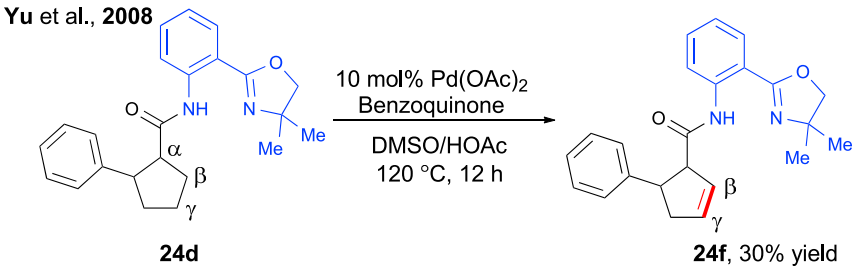
γ-C(sp^3)–H bond cleavage can be tuned by electron-deficient 2-pyridone ligands (3-nitro-5-(CF_3)pyridine-2-ol). In addition, Yu and co-workers performed a series of mechanism experiments and isolated and characterized the rare six-membered cyclopalladated intermediate by using PPh_3 as a stabilizing reagent (Schemes 19 and 27B). A possible mechanism was proposed (Scheme 19); first, the external ligand **L8** assists the coordination of substrate **27** to $Pd(OAc)_2$ to produce the reactive precursor **27A**. Subsequently, **L8**-accelerated γ-C–H bond cleavage gives rise to the [6,6]-bicyclic Pd intermediate **27C** via abstraction of the γ-C–H bond by the ligand oxygen. Then, oxidative addition of **27C** with an aryl iodide generates the Pd(IV) species **27D**, which undergoes reductive elimination and ligand exchange to yield the γ-arylated product **28**.

C–H alkenylation

Subsequently, Yu and co-workers successfully achieved Pd-catalyzed direct γ-C(sp^3)–H olefination of ketones (Scheme 20).[20] After screening various ligands,



Scheme 14. The plausible mechanism for the formation of the γ-alkylation product



Scheme 15. The Pd-catalyzed β-/γ-desaturation of cyclopentylcarboxamides by oxazolylamide as a DG

the combination of amino acid Ac–Ala–OH (**L9**) and 3-nitro-5-(trifluoromethyl) pyridin-2-ol was found optimal for this transformation. The downside of this protocol is that it requires additional steps to construct and remove the DG.

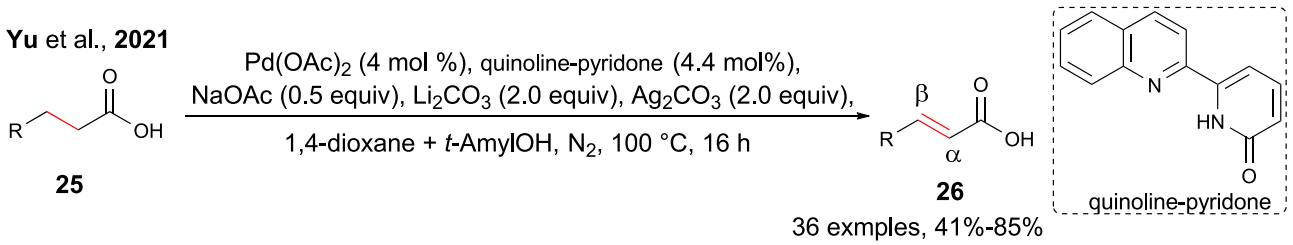
Currently, alkenylation and arylation stand as the only available examples of ketones γ-functionalization through Pd catalysis. Further advances in the γ-C(sp^3)–H functionalization reactions of ketones hinge on the development of more transformations and the synthesis of structurally complex and biologically relevant molecules.

Auxiliary-controlled γ- and δ-C(sp^3)–H functionalization of alcohols

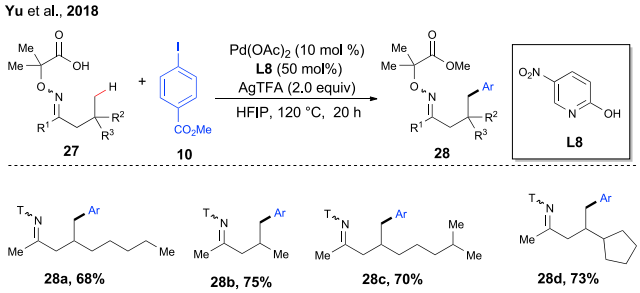
Alcohols are one of the most important classes of chemical synthetic intermediates that can be reversibly transformed into many other useful functional groups, such as esters, haloalkanes, alkenes, ketones, aldehydes, and carboxylic acids. Alcohols are also ubiquitous structural moieties in natural products, pharmaceuticals, and organic functional materials. Consequently, the development of transition-metal-catalyzed alcohol- or masked alcohol-directed site-selective C(sp^3)–H functionalization is of great importance. In the past decade, transition-metal-catalyzed direct β-C(sp^3)–H functionalization of alcohols or masked alcohols via a thermodynamically favored five-membered metallacycle intermediate has achieved a good progress.[21] However, examples of direct γ- and δ-C(sp^3)–H functionalization of these compounds are rare since these processes would require the formation of a less favorable six- and seven-membered metallacycle intermediate.

Auxiliary-controlled γ-C(sp^3)–H functionalization of alcohols

C–H arylation. In 2019, Yu and co-workers disclosed the Pd-catalyzed γ-C(sp^3)–H arylation of masked alcohols via six-membered cyclopalladation by using a designed pyruvic-acid-derived DG in combination with an external ligand, 3-nitro-5-chloro-2-pyridone (Scheme 21).[21] They discovered that the external ligand plays a critical role in the catalytic activity. Not only could the ligand coordinate with and effectively stabilize



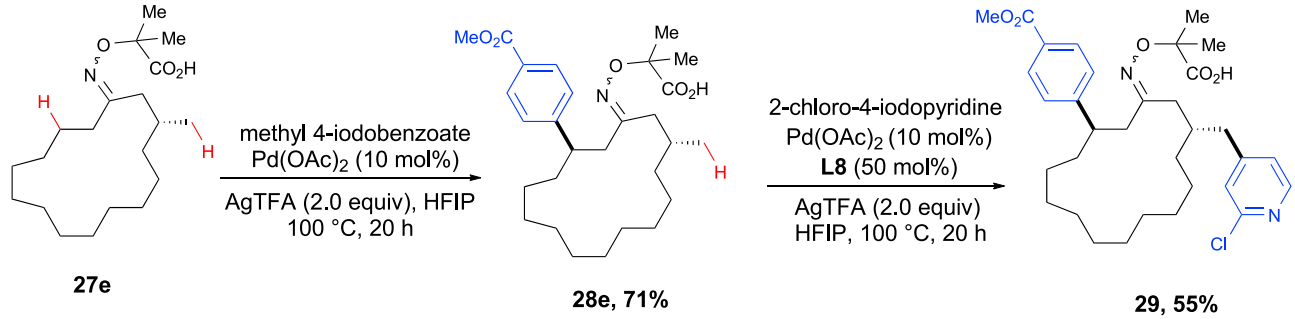
Scheme 16. The Pd-catalyzed α-/β-desaturation of carboxylic acids enables by a quinoline-pyridone ligand



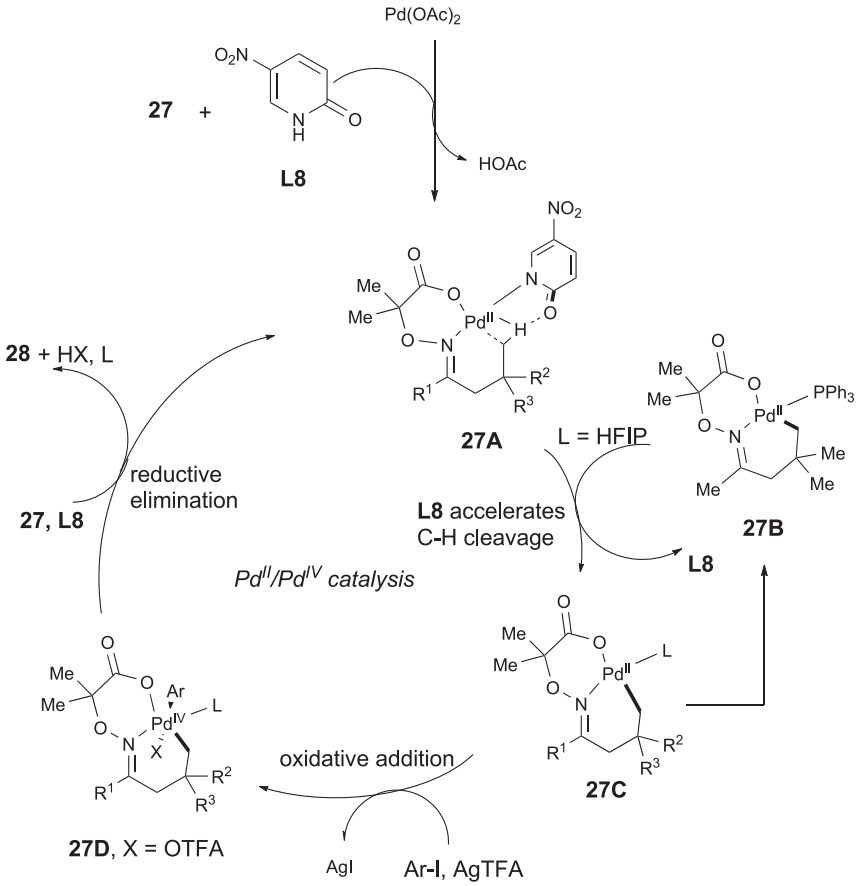
Scheme 17. Pd-catalyzed γ-C(sp^3)–H arylation of ketones directed by a 2,2-dimethyl aminooxyacetic acid auxiliary

the Pd catalyst, but it could also lower the transition-state energy of the C–H bond cleavage step, hence promoting and accelerating the process. In this study, the ligand 3-nitro-5-chloro-2-pyridone was found to be essential for the success of the reaction. Electron-rich pyridine-based ligands were not effective, whereas their electron-deficient counterparts were found to effectively improve yields. This protocol exhibits a broad substrate scope, and many functional groups, such as aldehydes, halogens, carboxylic esters, and benzyl groups, are well tolerated under standard reaction condition. It is worth mentioning that the DGs could be readily removed with copper powder or by esterification and subsequent hydrogenation. To gain some insights into the reaction mechanism, the authors successfully isolated and characterized the rare six-membered cyclopalladated intermediate (Scheme 22).

C–H silylation. In 2012, Hartwig and co-workers developed an Ir-catalyzed γ-C(sp^3)–H functionalization of alcohols with the assistance of a silicon DG via a six-membered iridacycle (Scheme 23).[22] In the protocol, the alcohol reacts with dihydridosilane to form (hydrido)silyl ether (intermediate **36**), which is then converted to oxasilolane (intermediate **37**) in the presence of [Ir(cod)OMe]$_2$, 3,4,7,8-tetramethyl-1,10-phenanthroline, and norbornene (Scheme 23). The norbornene was used as an H_2 acceptor to facilitate the C–H bond cleavage. It was also found that the more electron-rich 3,4,7,8-tetramethyl-1,10-phenanthroline (Me_4phen) provided better yields than 1,10-phenanthroline. This reaction displayed a broad substrate scope, and silyl ethers, carboxylic esters, acetals, benzyl groups, and halogens were among many functional groups tolerated under current reaction conditions. Notably, the observed preference for the five-membered oxasilolane formation over a four-membered oxasiloane is due to the excessive ring tension associated with the latter, favoring functionalization of the γ-position over the β-position. As expected, the diol (**38**) could be obtained by the oxidation of crude oxasilolane (**37**) with aqueous H_2O_2 under basic conditions. To facilitate the separation and purification, the crude diol

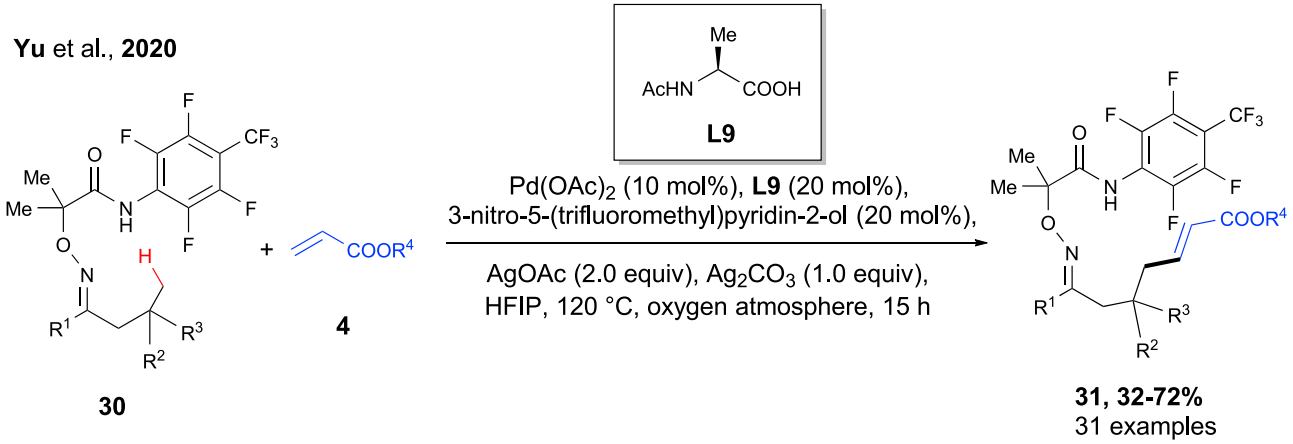


Scheme 18. Sequential Pd-catalyzed C(sp^3)–H arylation of muscone

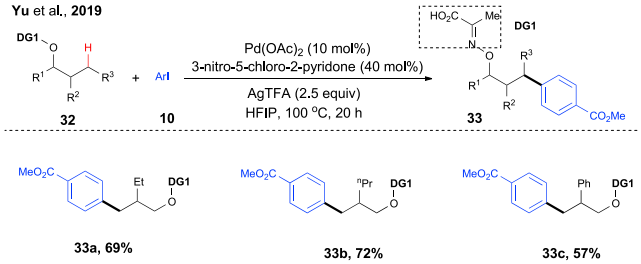


Scheme 19. A plausible mechanism of Pd-catalyzed γ-C(sp^3)–H arylation of ketones directed by a 2,2-dimethyl aminooxyacetic acid auxiliary

was acylated with Ac_2O (Scheme 23). In addition, a remarkably efficient late-stage functionalization of a complex natural product has been achieved by this methodology. The reaction of (+)-fenchol (**35f**), oleanolic acid (**39i**), and methyl oleanate (**35j**) under standard conditions led to the selective functionalization of the γ-position



Scheme 20. Pd-catalyzed γ-C(sp^3)–H arylation of olefination of ketone substrates

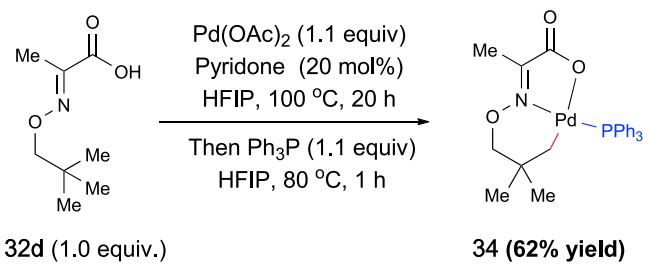


Scheme 21. Pd-catalyzed γ-C(sp^3)–H arylation of masked alcohols

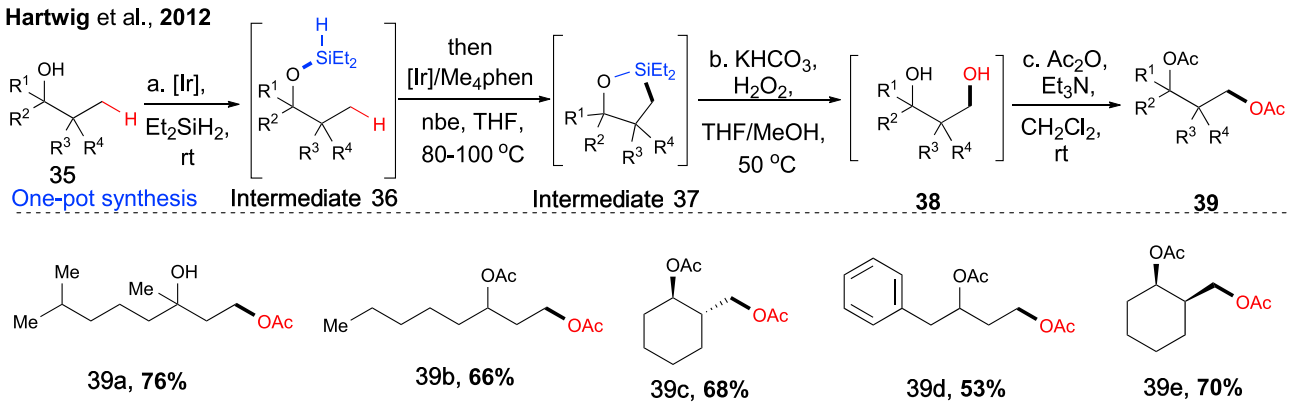
methyl group to generate corresponding products in good yields (Schemes 24 and 25).

In this study, transition-metal-catalyzed site-selective γ-functionalization was limited to only primary C–H bonds. At the time, similar silylation of secondary C–H bonds had not been achieved yet due to their low reactivity. In 2014, Hartwig successfully expanded the reaction scope to aliphatic secondary C–H bonds under slightly modified reaction conditions. In the presence of catalytic $[Ir(cod)OMe]_2$, Me_4Phen, and NBE (norbornylene), intramolecular cyclization yielded the corresponding five-membered oxasilolane products.[23] Through subsequent Tamao-Fleming oxidation reactions, various 1,3-diols were prepared from tertiary alcohols in good yields (Scheme 26). To gain an insight into the mechanism, KIE experiments were carried out and a significant KIE value (k_H/k_D = 2.0 ± 0.1) was observed (Scheme 27). This result indicates that γ-C(sp^3)–H cleavage is the rate-limiting step of the silylation of secondary C–H bonds.

C–H carbonylation. Transition-metal-catalyzed γ-C(sp^3)–H functionalization of alcohols can also be achieved without undergoing a six-membered metallacycle formation step. It should be noted however that such examples require a deliberate design of the DG or the use of a unique strategy. In 2019, the Yu group utilized a hemilabile benzyl ether DG to enable γ-C(sp^3)–H carbonylation of alcohols.[24] Benzyl ether was chosen as a readily removable DG to control regioselectivity. Treatment of protected alcohols under atmospheric CO in the presence of $Pd(OAc)_2$ (10 mol %), pentafluorobenzoic acid (50 mol %), and AgOAc (4.0 equiv) in hexafluoroisopropanol (HFIP) afforded the corresponding carbonylation products in moderate to good yields (Scheme 28). A plausible mechanism is depicted in Scheme 29; first, the DG coordinates to the Pd^{II} species, and subsequent γ-C–H bond activation forms the [6,5,5]-tricyclic Pd complex **42A**. Next, the weakly coordinating ether is exchanged by CO to produce **42B**, which then undergoes migratory insertion and ligand exchange with the solvent to afford **42C**. Finally, reductive elimination of Pd



Scheme 22. Synthesis and characterization of palladacycles



Scheme 23. Ir-catalyzed γ-C(sp^3)–H acylation of alcohols

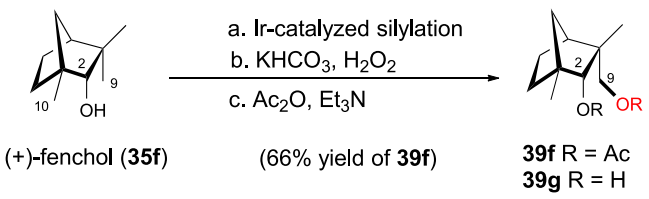
intermediate **42C** produces the carbonylation product **43** and Pd(0), which is then reoxidized by Ag(I) to regenerate the Pd(II) species.

C–H olefination. In 2019 Yu and co-workers accomplished the Pd(II)-catalyzed γ-C(sp^3)–H olefination of alcohols by using hemilabile benzyl ether as a DG (Scheme 30).[24] The authors showed only one example for Pd(II)-catalyzed γ-C(sp^3)–H olefination of masked alcohol to produce two mixed olefination products **44a** and **44b**. The mechanism of this process is similar to the carbonylation reaction (Scheme 29). To demonstrate the potential utility of the protocol, the authors applied the catalytic system to late-stage modification of β-estradiol. The ethylation of β-estradiol (**45**) has been accomplished in a 32% yield by Pd(II)-catalyzed γ-C(sp^3)–H olefination conditions and subsequent debenzylation (Scheme 31). In contrast, the corresponding compound required a 17-step synthesis previously.

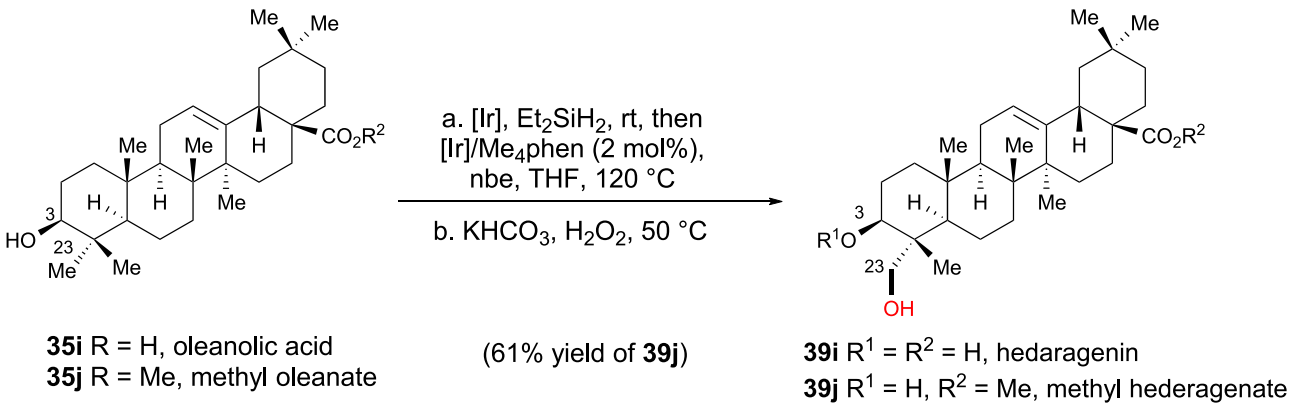
The installation of a removable external chelating group such as pyruvic acid or benzyl ether has been a widely used strategy for γ-C(sp^3)–H functionalization of alcohols. Another attractive strategy is Hartwig's intramolecular dehydrogenative γ-C(sp^3)–H silylation via six-membered iridacycles. Although many functionalization examples have been developed, including arylation, carbonylation, silylation, and olefination, the applications of these transofrmations are scarce. Further advances in the auxiliary-controlled γ-C(sp^3)–H functionalization of alcohols require introducing new removable DGs and improving the synthetic utility of the protocol by enabling application in the synthesis of complex pharmaceutically relevant compounds.

Auxiliary-controlled δ-C(sp^3)–H functionalization of alcohols

C–H silylation. In 2018, Hartwig group developed a one-pot (hydrido)silyl ether generation, rhodium-catalyzed intramolecular δ-C(sp^3)–H silylation, and oxidation sequence to net 1,4-diols (Scheme 32).[25] In this process, [Ir(OMe) (COD)]$_2$-catalyzed



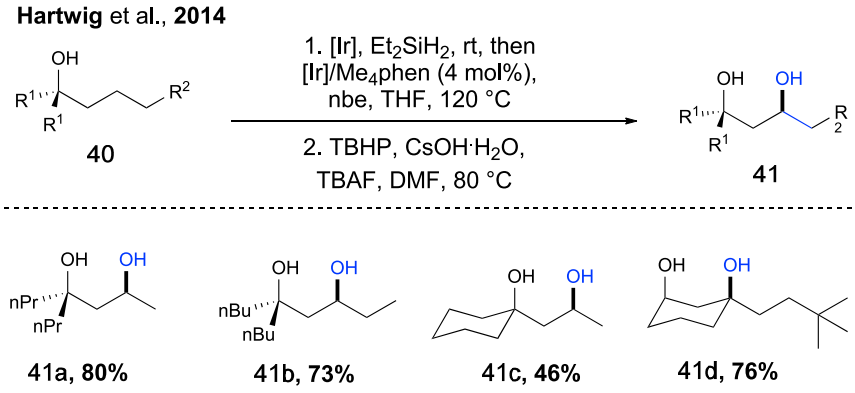
Scheme 24. Directed aliphatic C–H functionalization of the natural product (+)-fenchol (35f)



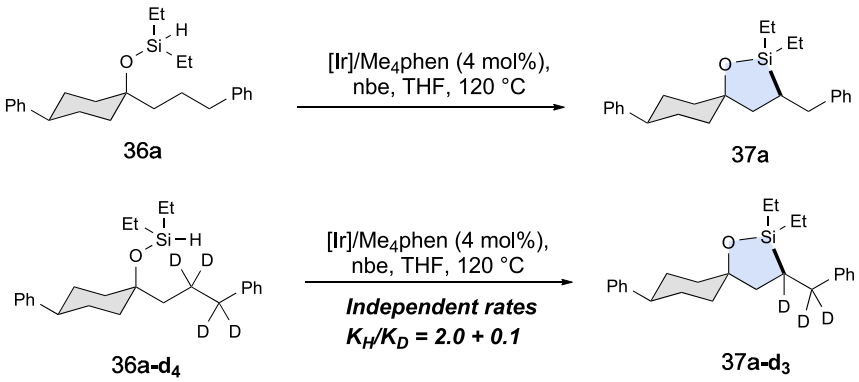
Scheme 25. Directed aliphatic C–H functionalization of oleanolic acid 35i and methyl oleanate 35j

tertiary alcohol dehydrogenative coupling with diethylsilane generates (hydrido)silyl ethers *in situ*, which then undergo intramolecular δ-C(sp^3)–H silylation to provide six-membered oxasilolanes with [(Xantphos)Rh(Cl)] as the catalyst. Subsequent 1,4-diols were obtained under the conditions of the Fleming-Tamao oxidation. The formation of six-membered oxasilolanes requires the intermediacy of a less favorable seven-membered rhodium metallacycle as well as a primary alkyl intermediate formed by cleavage of the δ-C(sp^3)–H bond, making it an extremely challenging process. The authors used Xantphos-ligated rhodium as the catalyst to make the silylation occur at the δ-C(sp^3)–H bond with high selectivity. The oxidative addition of the δ-C(sp^3)–H bond to rhodium was found to be the rate-limiting step. Mechanistic studies demonstrated that reductive elimination from the seven-membered metalacyclic has a lower energy barrier than reductive elimination from the six-membered metalacycle formed by the cleavage of the γ-C(sp^3)–H bond. This method is one of the blocking strategies. In addition, the authors successfully carried out the natural product oxysterol modification and sequential C–H silylation toward the synthesis of triol **48** (Scheme 33).

A plausible mechanism was proposed in Scheme 34. First, oxidative addition of a silyl hydride to the Rh(Cl)L_n produces the intermediate **49A**, followed by reductive elimination generates the active Rh(I) hydride catalyst. The migratory insertion of norbornene forms the Rh(I) norbornyl complex **50A**, which further reacts with the



Scheme 26. Examples of the silylation of secondary C–H bonds



Scheme 27. Kinetic isotope effect on the silylation reaction

(hydrido)silyl ether via oxidative addition of a silyl hydride and reductive elimination of norbornane to afford the intermediate **49B**. The intermediate **49B** could either bind to norbornene reversibly to produce the resting-state intermediate **49E** or undergo δ-C–H bond intramolecular oxidative addition to form the seven-membered rhodacycle intermediate **49C**. Finally, the six-membered oxasilolane (**49D**) and Rh(I) hydride catalyst were generated by C–Si bond reductive elimination.

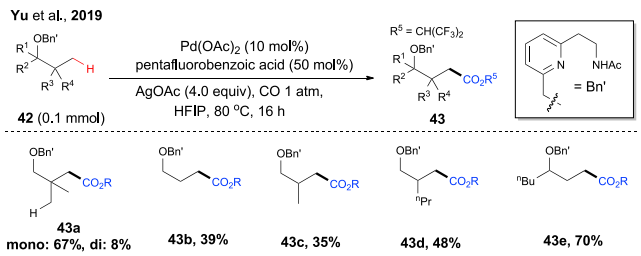
The design of new types of DGs continues to be an important topic for the development of new types of functionalization of remote C(sp^3)–H bonds. Only silylation of alcohols has been developed through rhodium-catalysis as of now. To solve this problem, encouraging new efforts to develop more δ-C(sp^3)–H functionalization examples of alcohols by designing new DGs is needed to expand the scope of substrates and transformations.

Auxiliary-controlled γ-C(sp^3)–H functionalization of thiols

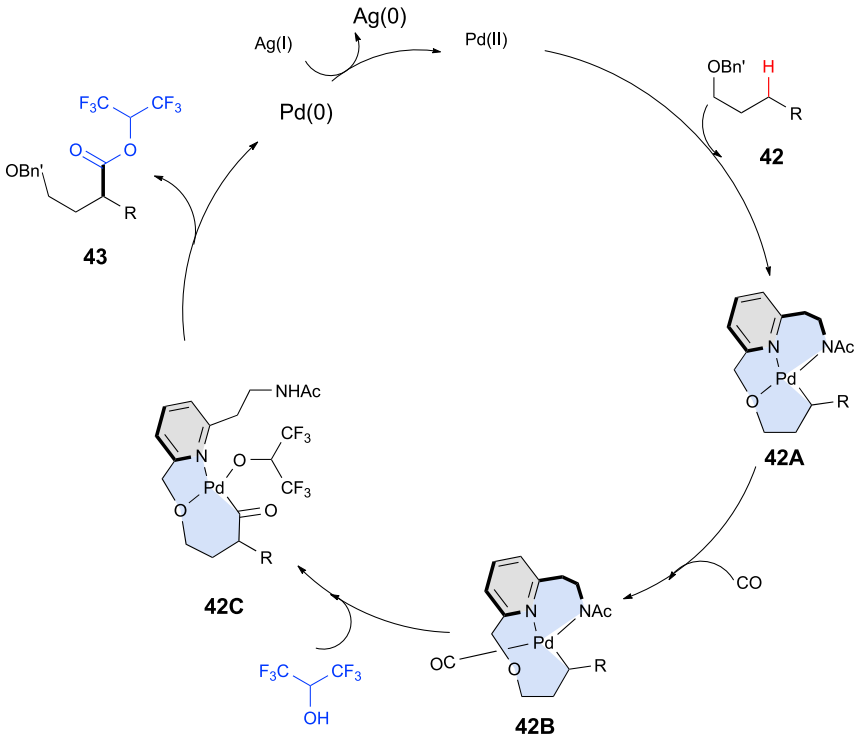
Thiol derivatives widely exist in natural products and medicinal compounds, and thus, a variety of synthetic methods have been developed targeting the construction and derivatization of thiols.[26] Transition-metal-catalyzed direct γ-C(sp^3)–H functionalization of thiols is an attractive method for the construction of sulfur-containing biologically active natural products and pharmaceuticals.

C–H arylation

In 2018, Dong and co-workers demonstrated Pd-catalyzed-directed γ-C(sp^3)–H arylation of protected thiols.[26] This protocol utilizes a novel, easily installable or removable ethyl-acrylate-derived protecting group or DG that enables selective activation at the γ-position (Scheme 35). Under optimal conditions comprising of catalytic $Pd(OAc)_2$, 5-(trifluoromethyl)-2-pyridinol, Ag_2O, and HFIP/AcOH (19/1),



Scheme 28. Pd-catalyzed γ-C(sp^3)–H carbonylation of masked alcohols



Scheme 29. A plausible mechanism for Pd-catalyzed γ-C(sp^3)–H carbonylation of alcohols

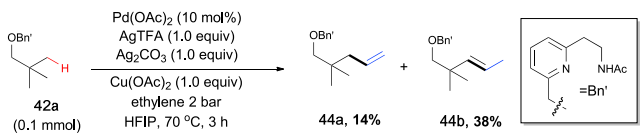
various protected aliphatic thiols reacted with both electron-rich and electron-deficient aryl iodides to provide the corresponding desired products in moderate to good yields. Thioether-directed benzylic C(sp^3)–H arylation can also be achieved under slightly modified reaction conditions (Scheme 36). A limitation of this method is that many substrates produced mixtures of mono- and di-arylated products.

The γ-C(sp^3)–H arylation of protected thiols has been developed through Pd catalysis. Although the mechanism of the transformation was proposed, detailed studies are yet to be conducted. The intermediates of these processes have still not been isolated and characterized; also, kinetic investigations and computational studies are still lacking. New efforts toward developing more γ-C(sp^3)–H functionalization examples of thiols through various strategies are still needed.

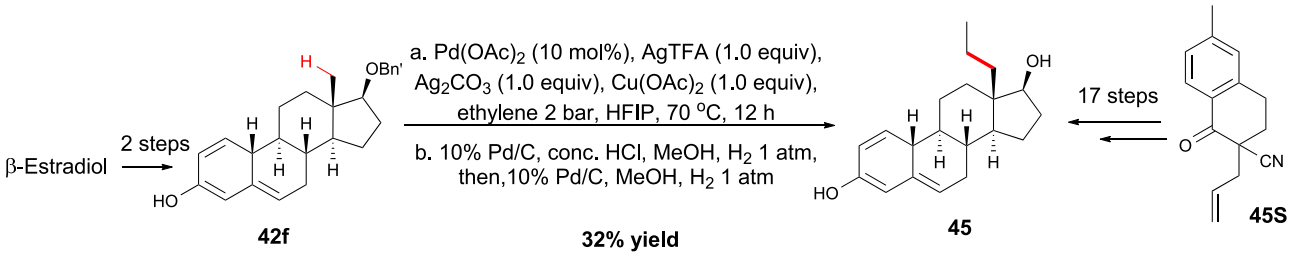
Auxiliary-controlled γ- and δ-C(sp^3)–H functionalization of amines

Auxiliary-controlled γ-C(sp^3)–H functionalization of amines

Aliphatic amines are key intermediates in organic synthesis as they widely exist in biologically active natural products, small-molecule biological probes, and pharmaceuticals. There are more than 100 "best-selling" medicines that contain aliphatic amine scaffolds.[4] Therefore, tremendous efforts have been devoted to developing



Scheme 30. Pd-catalyzed γ-C(sp^3)–H olefination of alcohols

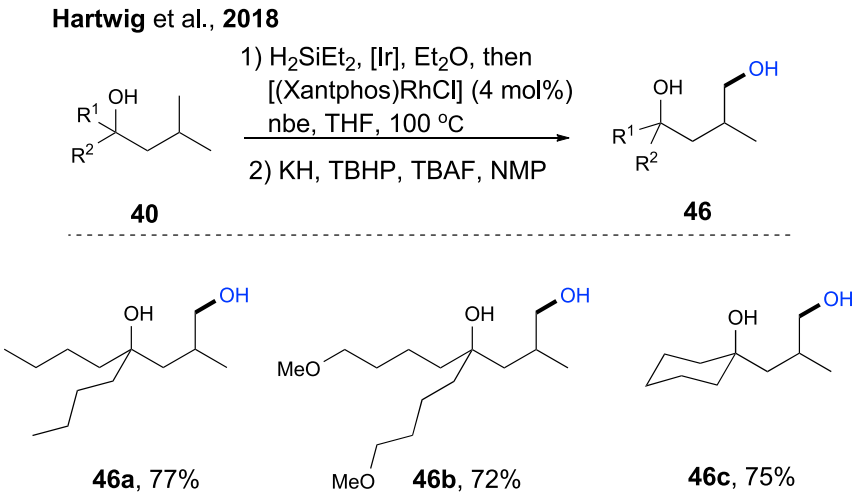


Scheme 31. Late-stage derivatization of β-estradiol by Pd(II)-catalyzed γ-C(sp^3)–H olefination and subsequent debenzylation

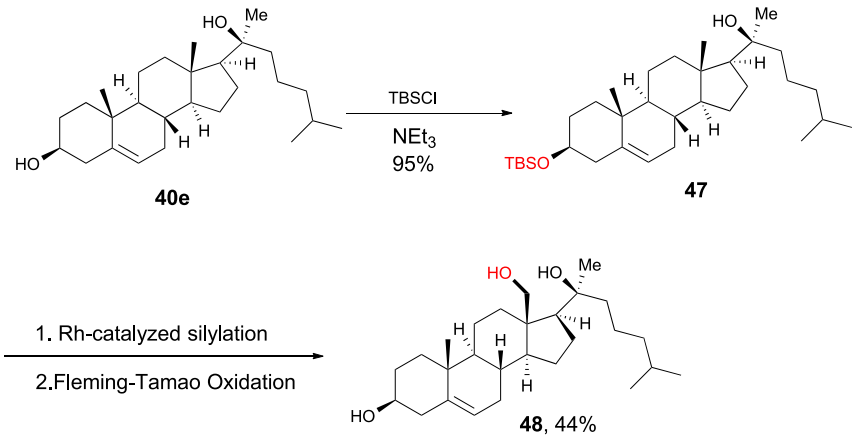
efficient and straightforward methods for the synthesis and derivatization of aliphatic amines.[4] One of the most successful strategies to achieve the site-selective C(sp^3)–H functionalization of aliphatic amines is the use of DGs. In general, transition-metal-catalyzed direct β or δ-C(sp^3)–H functionalization of aliphatic amines via a thermodynamically less favored four- or six-membered metallacycle intermediate is rare.[4] In comparison, site-selective γ-C(sp^3)–H functionalization of aliphatic amines has progressed significantly as a result of the formation of stable five-membered metallacyclic intermediates. Three strategies have been developed to realize site-selective γ-C(sp^3)–H functionalization of aliphatic amines including the DG, TDG, and free-amine-directed strategies.

Auxiliary-controlled γ-C(sp^3)–H functionalization of primary amines. Although DG strategies typically require additional steps for the installation and removal of the DG component, various selective γ-C(sp^3)–H functionalization of aliphatic amines can be achieved with high effectiveness by this approach.

In 2005, Daugulis and co-workers were first to disclose a Pd-catalyzed γ-C(sp^3)–H arylation of primary amines by using picolinamide (PA) as a DG (Scheme 37).[27] A plausible mechanism is depicted in Scheme 38; first, picolinamide coordinates to the Pd species, and subsequent γ-C–H bond activation forms a 5,5-fused palladacycle intermediate **55A**. Then, the oxidative addition of intermediate **55A** with an aryl iodide produces the Pd(IV) species **55B**. Finally, the reductive elimination of **55B** yields the γ-arylated product.



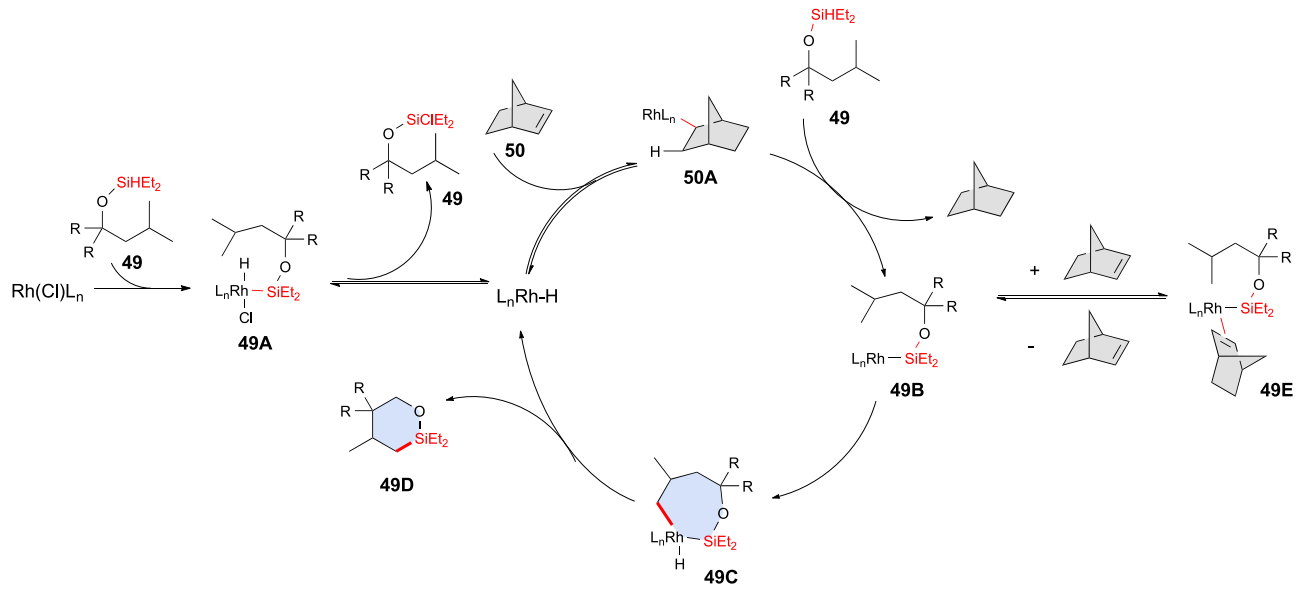
Scheme 32. Rhodium-catalyzed δ-C(sp^3)–H silylation and oxidation sequence to produce 1,4-diols



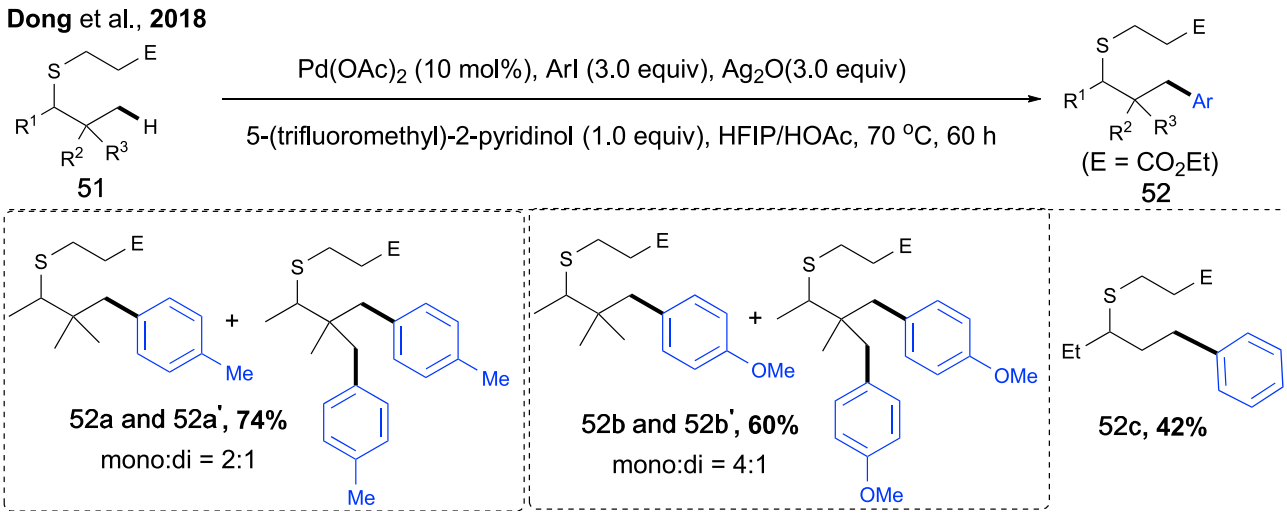
Scheme 33. The synthesis of triol 48 by rhodium-catalyzed δ-C(sp^3)–H silylation and oxidation sequence

Inspired by this work, Chen and co-workers used PA as a DG to realize a series of Pd-catalyzed γ-C(sp^3)–H functionalization reactions of aliphatic amines. In 2011, Pd-catalyzed γ-C–H arylation of cyclohexylamino acid were developed by Chen (Scheme 39).[28] In 2016, they demonstrated enantioselective benzylic C(sp^3)–H arylation of aliphatic amines by using 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) phosphoric acid as a ligand (Scheme 40).[29] This reaction demonstrated a broad substrate scope for various substituted aryl iodide with good yields and high enantioselectivity.

Cyclicpeptides have important applications in medicine as they have shown considerable potential in modulating complicated biological processes, such as protein-protein interactions.[30] In 2019, the Chen group developed Pd-catalyzed intramolecular γ-C(sp^3)–H arylation of various N-terminal aliphatic amino acid units with aryl



Scheme 34. The plausible mechanism for the δ-C(sp^3)–H silylation

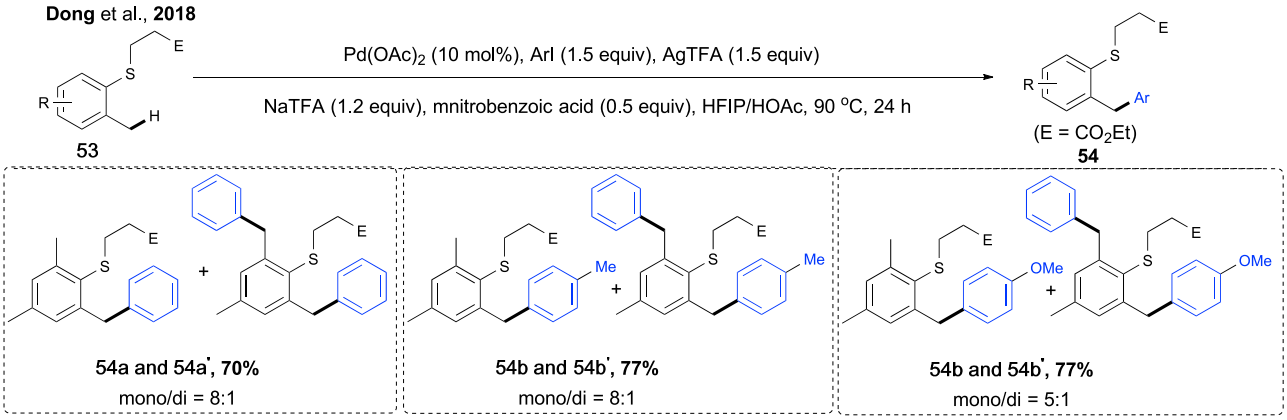


Scheme 35. Pd-catalyzed directed γ-C(sp^3)–H arylation of protected thiols

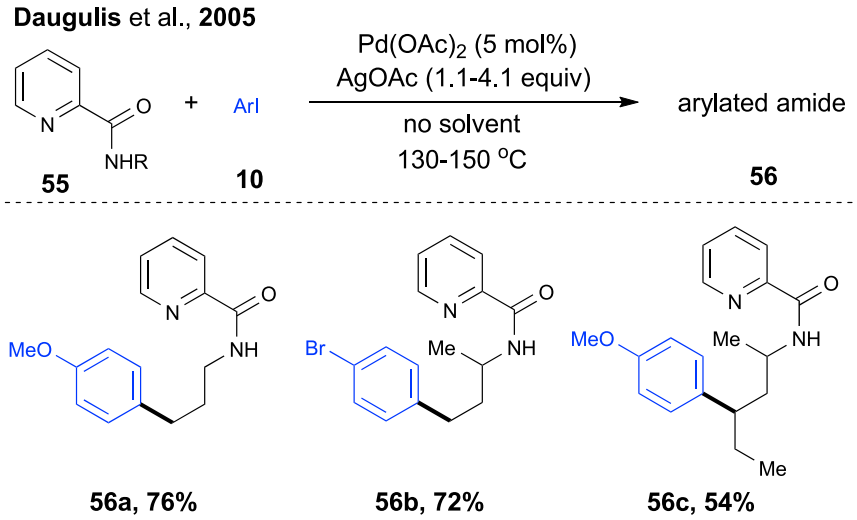
iodides to construct natural product-like cyclophane-braced peptide macrocycles (Scheme 41).[30] It is worth mentioning that the DG PA could be readily removed by treatment with Zn powder in aq. HCl at room temperature. Notably, the authors found that many of these synthesized cyclic peptides exhibit highly ordered structures by X-ray crystallography. This method provides a valuable prospect orthogonal reactivity trend for peptide chemistry.

In 2016, Zhang and co-workers developed an arylation reaction by using the antiviral drug rimantadines as a substrate and a mono-N-protected amino acid (MPAA) as a ligand (Scheme 42).[31] This reaction displayed a broad substrate scope for multi-substituted rimantadine substrates as well as aryl iodides with high functional-group compatibility. A series of optically pure rimantadine derivatives were obtained in high regio- and diastereoselectivities via this technique.

Aside from PA, other DGs have also been developed and utilized in the past several years. In 2013, the Carretero group described the use of an *N*-(2-pyridyl)sulfonyl (SO_2Py) as a DG for Pd-catalyzed γ-C(sp^3)–H arylation of amino



Scheme 36. Pd-catalyzed arylation of benzylic C(sp^3)–H bonds with protected thiols

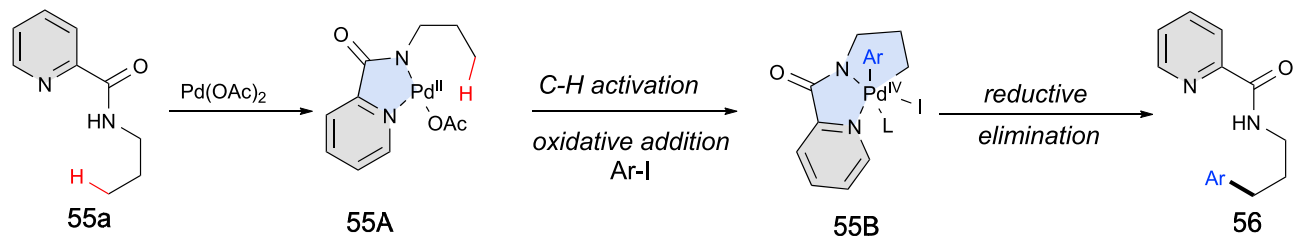


Scheme 37. Pd-catalyzed γ-C(sp^3)–H arylation of primary amines

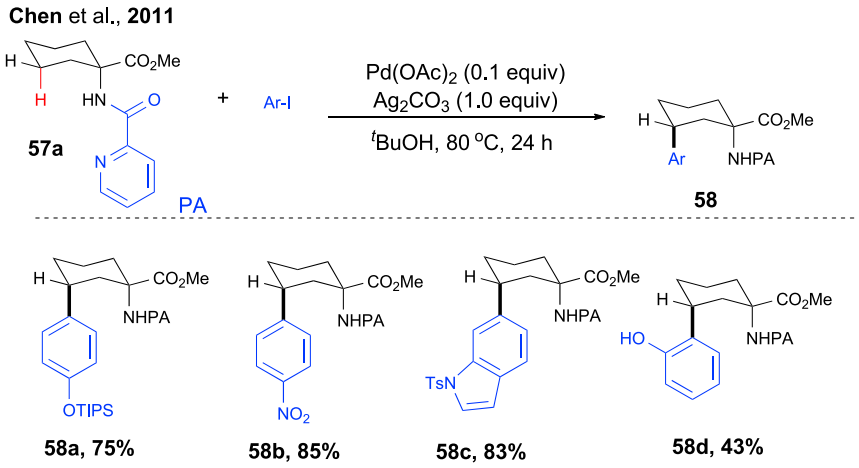
acid esters (Scheme 43).[32,33] A variety of substituted *N*-(2-pyridyl)sulfonamide amino acid derivatives, including α-quaternary amino acid, β-amino acid substrates, and dipeptide substrates, were successfully arylated at the γ-position in moderate to good yields via this protocol. The successful γ-arylation of non-natural amino acids using this strategy depends on the introduction of the key 2-pyridylsulfonyl DG.

To better understand the importance of the DG, we compare 2-pyridylsulfonyl with PA DG. This SO_2Py DG can be readily introduced or removed to the amino acid backbone under mild conditions in good yield, without racemization at the Cα center (Table 1). The synthetically versatile PA DG also could be installed easily to the parent amines and removed under mildly acidic conditions in good yield. In PA-directed Pd-catalyzed γ-C(sp^3)–H arylation reactions, the reaction undergoes a 5,5-fused palladacycle intermediate (**56A** and **58A**) through PA's nitrogen coordination. Although with SO_2Py as the auxiliary, the reaction undergoes the bimetallic five-membered ring palladacycle complex (**66A**) displaying the key role exerted by the SO_2Py.

In recent work, Carretero and co-workers used SO_2Py and PA as contrastive DGs for Pd-catalyzed C–H arylation of α-amino acids under identical reaction conditions (Scheme 44).[34] The δ-arylation product was only obtained when SO_2Py was used as the DG, although just replacing the carbonyl connector of PA led to a mixture of γ-arylation and γ,δ-diarylation products. The authors further used the experimental and DFT studies to provide insights into the controlling factors of site



Scheme 38. Plausible mechanism for Pd-catalyzed γ-C(sp^3)–H arylation of primary amines

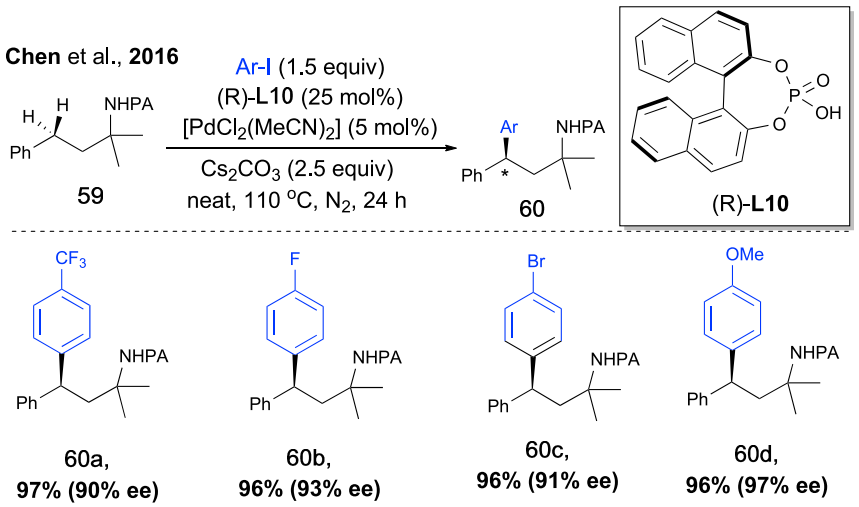


Scheme 39. Pd-catalyzed γ-C–H arylation of the cyclohexylamino acid

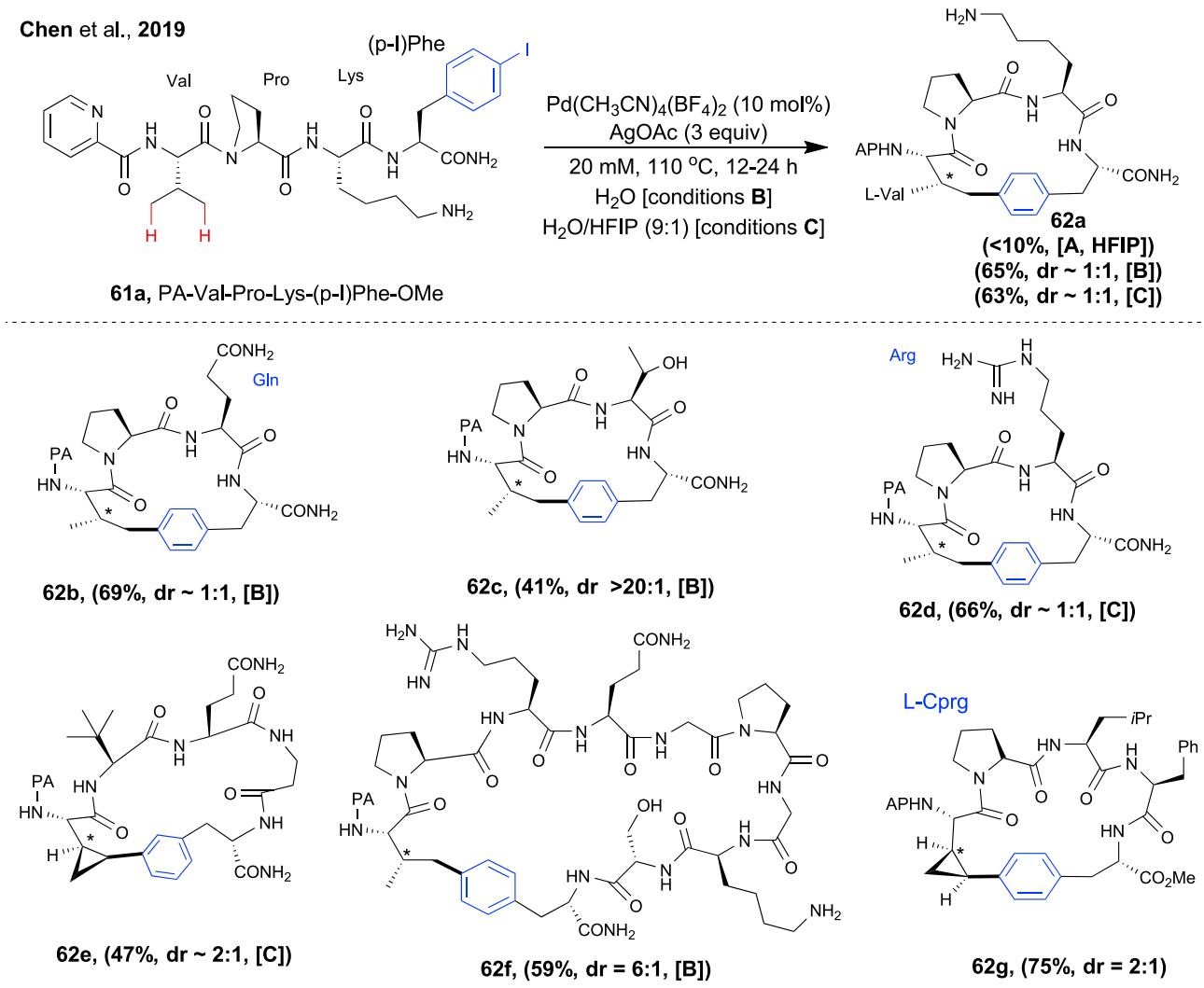
selectivity. In comparison with the PA, distinct elements of SO_2Py are the sp^3 hybridization of the sulfonyl moiety and its lack of conjugation with nitrogen. These elements significantly influenced the reactivity of five- and six-membered palladacyclic intermediates, which led δ-C–H cleavage to be kinetically favored over γ-C–H cleavage in the SO_2Py auxiliary α-amino acids.

Furthermore, the PA has been used by many research groups in Pd-catalyzed γ/δ-C(sp^3)–H functionalizations, and SO_2Py is currently mainly used by Carretero's group.[5–7] These two strategies exhibit complementarity in the Pd-catalyzed γ/δ-C(sp^3)–H functionalization of amines. Overall, auxiliaries PA and SO_2Py can be readily introduced or removed, usually showing impressive substrates scopes and precise site selectivity. They have become one of the important assets of the amines γ/δ-C(sp^3)–H functionalization toolkit.

Furthermore, a weakly coordinating monodentate auxiliary strategy was developed for Pd-catalyzed γ-C(sp^3)–H functionalization reactions of aliphatic amines.

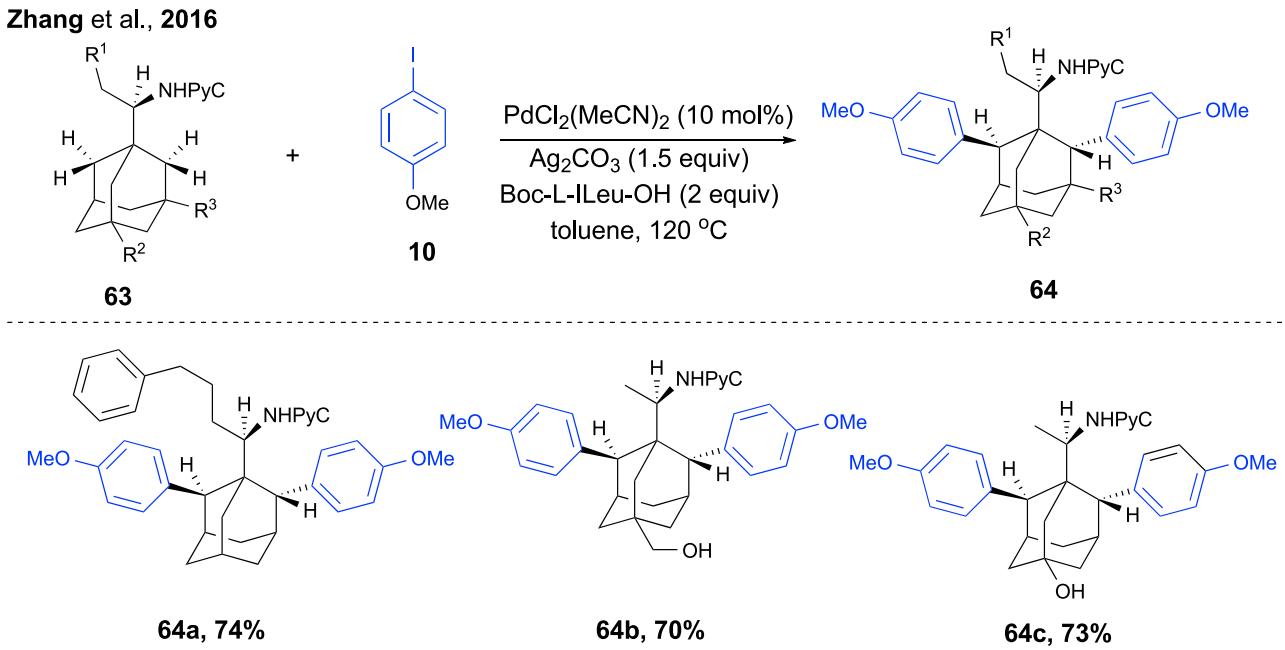


Scheme 40. Enantioselective benzylic C(sp^3)–H arylation of aliphatic amines



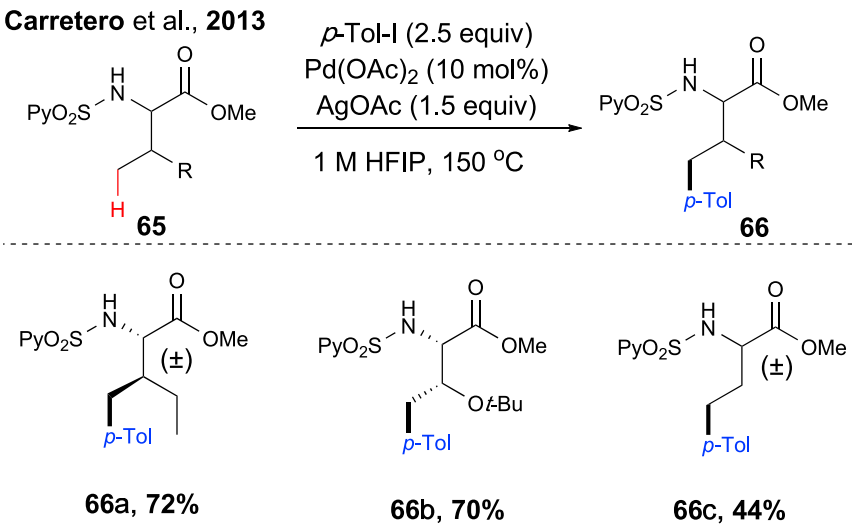
Scheme 41. Build-up natural-product-like cyclophane-braced peptide macrocycles

In 2013, the Ma group utilized methoxyimino acetamide as an auxiliary for direct γ-C(sp^3)–H arylation of 2-aminobutanates (Scheme 45).[35] A variety of substituted homophenylalanines and peptides were successfully arylated at the γ-position via this method. In 2015, the Shi group demonstrated the use of acetamido oxazoline as a DG to develop Pd-catalyzed arylation of unactivated γ-methylene C(sp^3)–H bonds (Scheme 46).[36] In 2014, the Yu group reported cross-coupling of triflyl-protected amines with arylboron reagents by using a MPAA as a ligand (Scheme 47).[37] The authors found that the amino acid ligand plays a critical role in promoting the catalytic activity by altering the steric and electronic properties of the active Pd catalyst, hence facilitating C(sp^3)–H activation. A wide variety of arylboronic acid pinacol esters (ArBPins) were well tolerated under the standard reaction conditions. The same strategy was further utilized to achieve highly enantioselective (up to 99.5% ee) arylation of cyclopropylmethylamines with aryl iodides (Scheme 48).[38] This protocol was the first successful example of enantioselective C–H arylation through a Pd(II)/Pd(IV) catalytic manifold. In 2017, they realized a cross-coupling reaction of 4-nitrobenzenesulfonyl (Ns)-protected amines by using



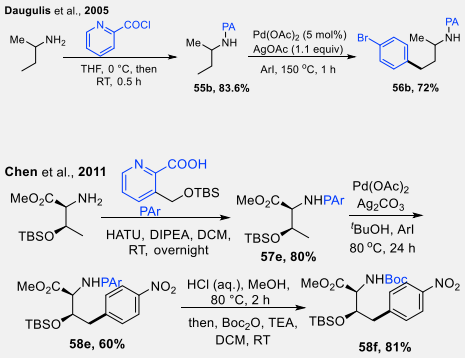
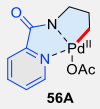
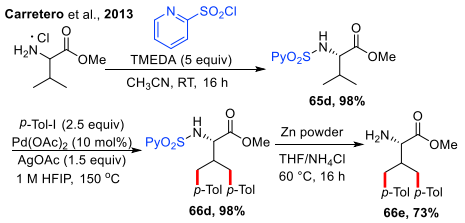
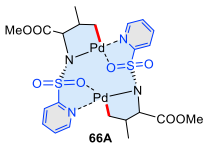
Scheme 42. Arylation of the antivirus drug rimantadines

arylboron and alkylboron reagents with acetyl-protected aminomethyl oxazoline as a ligand (Scheme 49).[39] Notably, the nosyl protecting group could be readily removed upon functionalization. Finally, the same group later demonstrated successful enantioselective cross-coupling between alkyl amines and aryl-/vinyl-boron reagents (Scheme 50).[40] The chiral acetyl-protected aminomethyl oxazoline ligands (APAO) were found to be crucial in controlling the enantioselectivity of these processes. A wide range of aryl- and vinyl-boron reagents were readily coupled with triflyl (Tf) protected alkyl amines, yielding the chiral γ-arylated alkylamine products in good yields and excellent enantioselectivity. As expected, the Tf group could be readily removed via a two-step procedure to afford free amines



Scheme 43. Pd-catalyzed γ-C(sp^3)–H arylation of amino acid esters

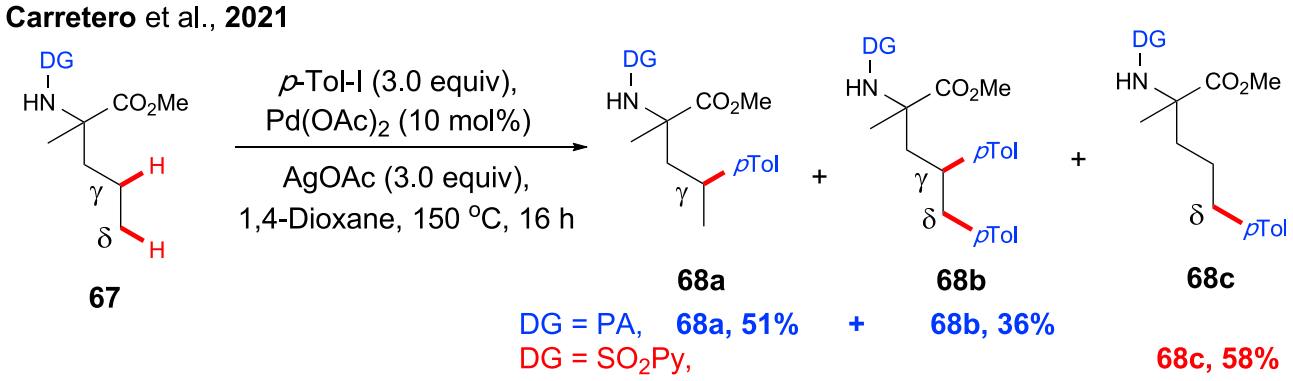
Table 1. The Pd-catalyzed γ-C(sp^3)–H arylation reaction used the PA or SO_2Py as a DG

Directing group	Introduction or removal of the directing group	Pd intermediate
PA		 Zaitsev et al.[27]
SO_2Py (Carretero auxiliary)		 Fan et al.[31] and Rodríguez et al.[32]

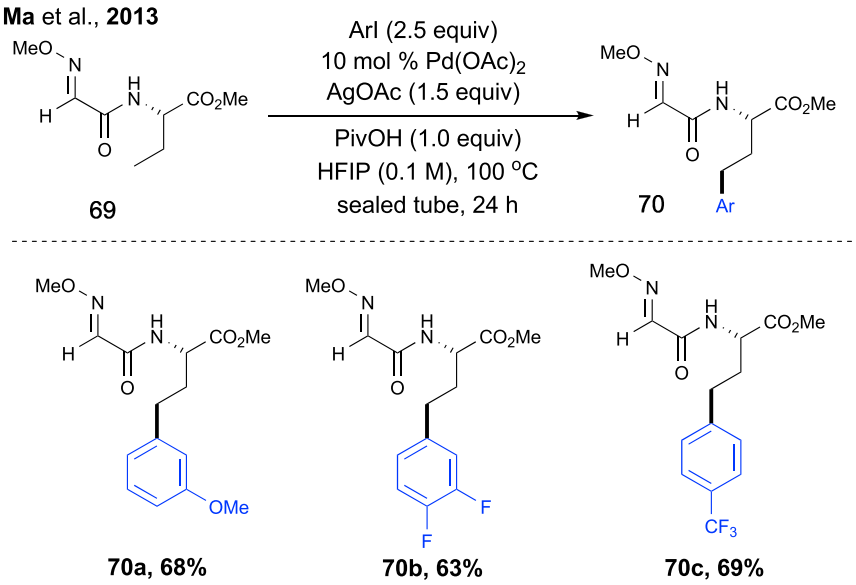
without loss of optical activity. In addition, Zhao reported the use of oxalylamide as a DG for Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic amines/amino acids in 2016 (Schemes 51 and 52).[41,42]

In 2011, Pd-catalyzed γ-C–H alkenylation of cyclohexylamino acids were reported by Chen (Scheme 53).[27] The Yu group later reported a Pd(II)-catalyzed olefination reaction of γ-C(sp^3)–H bonds of triflyl (Tf) protected amines with electron-deficient alkenes and styrenes by using 3-phenylquinoline as a ligand (Scheme 54).[43] Subsequently, aza-Wacker oxidative cyclization affords a variety of C-2 alkenyl pyrrolidines.

In 2012, Chen disclosed a novel Pd-catalyzed intramolecular amination of γ-C(sp^3)–H bonds of picolinamide with PA as a DG (Scheme 55).[44] The addition



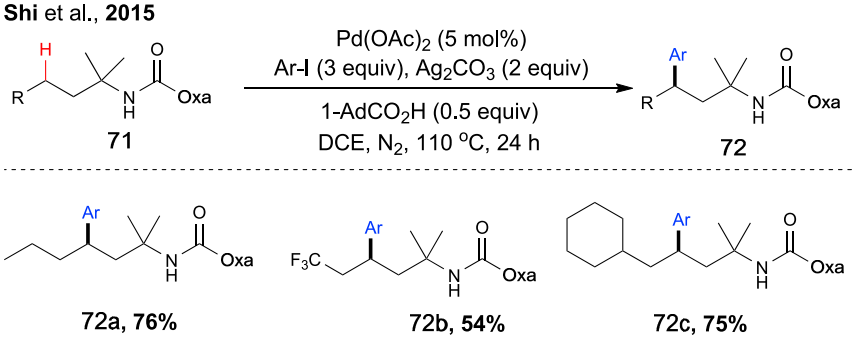
Scheme 44. Pd-catalyzed γ-C(sp^3)–H and δ-C(sp^3)–H arylation of amino acid esters using PA/SO_2Py as a DG



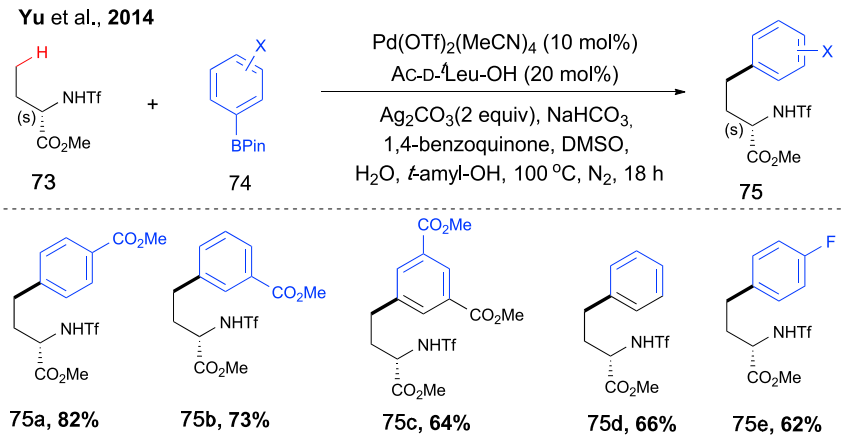
Scheme 45. Direct γ-C(sp^3)–H arylation of substituted 2-aminobutanates

of 2 equiv of AcOH could promote the formation of the cyclization product. The CN bond formation does not occur in the absence of $PhI(OAc)_2$. Mechanistic studies show that $PhI(OAc)_2$ was used as an oxidant, which can oxidize the 5,5-fused palladacycle(II) intermediate **90A** to form Pd(IV) intermediate. A series of azetidines can be obtained by this efficient, economical, and practical method with good to excellent yields.

Afterward, Chen and co-workers also reported intermolecular alkoxylation of unactivated γ-C(sp^3)–H bonds of picolinamides by using a wide range of alcohols (Scheme 56).[45] $PhI(OAc)_2$ was found to be the only effective oxidant for this transformation, whereas other commonly used oxidants such as Ag(I) salts, $K_2S_2O_8$, and oxone did not prove effective. The authors' investigations found that Xylene/EtOH mixtures provided markedly higher yields than other solvents because the noncoordinating solvent Xylene promotes the alkoxylation reaction pathway. Although strongly coordinating solvents such as DMF (*N*,*N*-dimethylformamide), dioxane, and CH_3CN (acetonitril) did not promote the alkoxylation reaction. A 4:1 Xylene to EtOH (ethanol) ratio stood out as best-performing, resulting in yields of up to 92% (Scheme 56). In the proposed mechanism



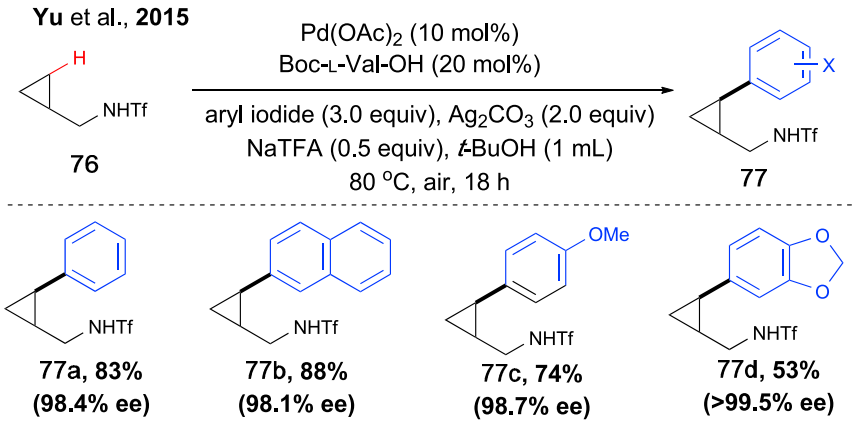
Scheme 46. Pd-catalyzed arylation of unactivated γ-methylene C(sp^3)–H bonds



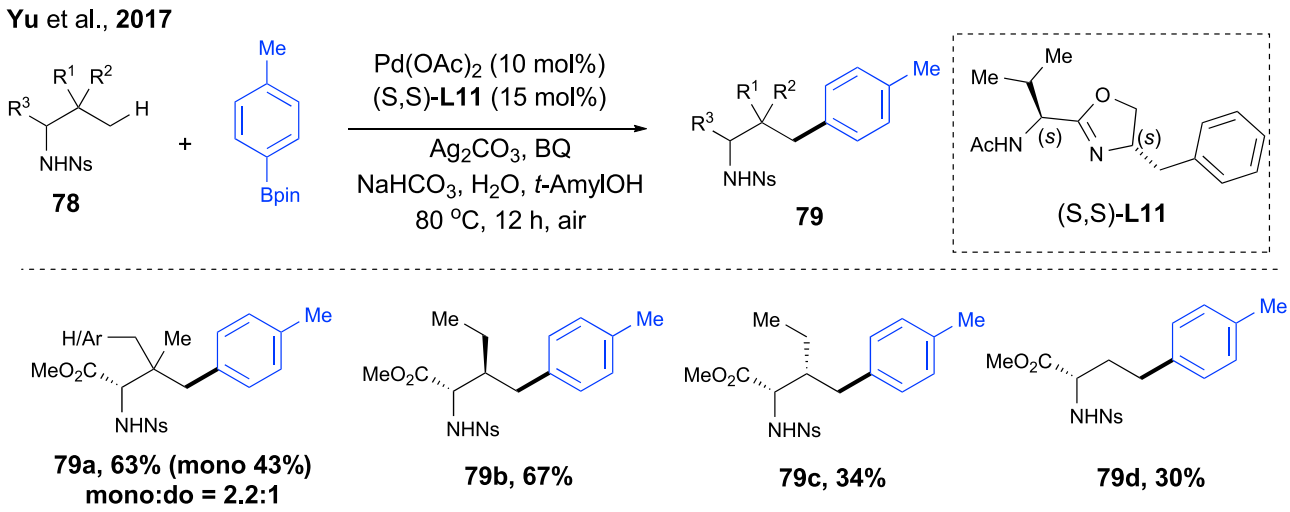
Scheme 47. Pd-catalyzed γ-C(sp^3)–H cross-coupling of triflyl-protected amines with arylboron reagents

(Scheme 57), $PhI(OAc)_2$ oxidates the 5,5-fused palladacycle(II) intermediate **92A** to give Pd(IV) intermediate **92B**, which undergoes a ligands exchange to form Pd(IV) intermediate **92C** under alcohol as cosolvent. The sequential Pd(IV) intermediate **92C** undergoes reductive elimination to provide the alkoxylated products.

In 2013, the same group developed an alkylation reaction of γ-C(sp^3)–H bonds of aliphatic amines with primary alkyl iodides via Pd catalysis (Scheme 58).[46] In this work, Ag_2CO_3 was used as an oxidant, dibenzyl phosphate was employed as a ligand, and $(BnO)_2PO_2H$ was utilized as an additive. All three components proved to be critical promoters of this reaction, mainly for the following reasons: first, the Ag_2CO_3 can offer Ag^+ ions to scavenge I^- to improve the catalytic turnover and thus increase the product's conversion. It can also promote the oxidative addition of alkyl iodides if an SN_2-type oxidative addition mechanism is operative. The commercially available dibenzyl phosphate $(BnO)_2PO_2H$ was employed as solid-to-solution phase-transfer catalyst for Ag_2CO_3 to promote the C–H alkylation reaction because high concentrations of free Ag^+ ion could suppress alkylation through decomposition of the electrophile, probably via an E_2 elimination pathway. However, $(BnO)_2PO_2H$ can slowly bring Ag^+ ions into the solution phase, and hence it can



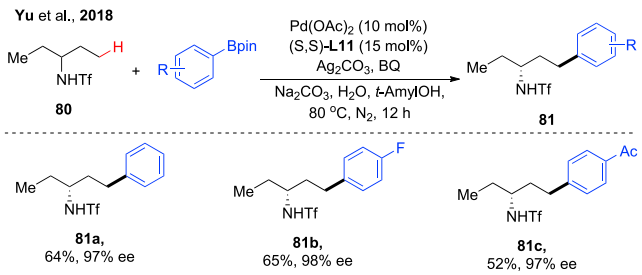
Scheme 48. Enantioselective arylation of cyclopropylmethylamines with aryl iodides



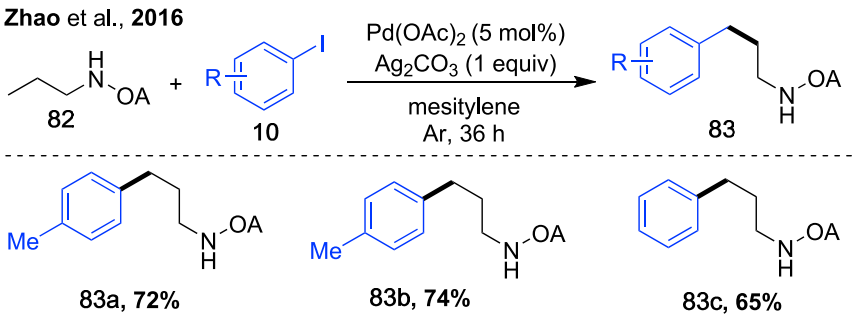
Scheme 49. γ-C(sp^3)–H cross-coupling of 4-nitrobenzenesulfonyl (Ns)-protected amines with arylboron reagents

effectively avoid the high concentration of Ag^+ ions. This mode of interaction between silver salts and organic phosphate promoters may provide a new guidance for our future development of remote C(sp^3)–H bonds alkylation reaction with alkyl iodides. The reaction was proposed to proceed via a C–H palladation/coupling sequence and a Pd(II)/Pd(IV) catalytic cycle (Scheme 59). First, the PA coordinates with $Pd(OAc)_2$ to form complex **94A**, which undergoes γ-C(sp^3)–H cleavage to yield five-membered palladacycles **94B**. Next, intermediate **94B** undergo oxidative addition with the alkyl iodide by an SN_2 mechanism to form Pd(IV) intermediate **94C**. Finally, reductive elimination of **94C** generates the γ-alkylated product.

Organoborane compounds are some of the most commonly used intermediates in organic synthesis, and they often were served as crucial precursors to alcohols, amines, and various functionalized molecules.[47] Therefore, the synthesis of organoboron compounds has generated great interest among scientists in chemistry research. In 2014, the Shi group reported the Pd-catalyzed borylation of γ-C(sp^3)–H bonds of aliphatic amines by using B_2pin_2 as a borylation reagent with PA as a DG (Scheme 60).[47] The reaction avoided the use of expensive silver oxidants with oxygen (O_2) as the terminal oxidant and is hence environmentally benign. Amino acids, amino alcohols, alkyl amines, and a series of bioactive molecules were successfully borylated by this method. To further demonstrate the utility of the protocol, a natural product was borylated with this method, and a derivative of the steroid estrone was obtained (Scheme 61).

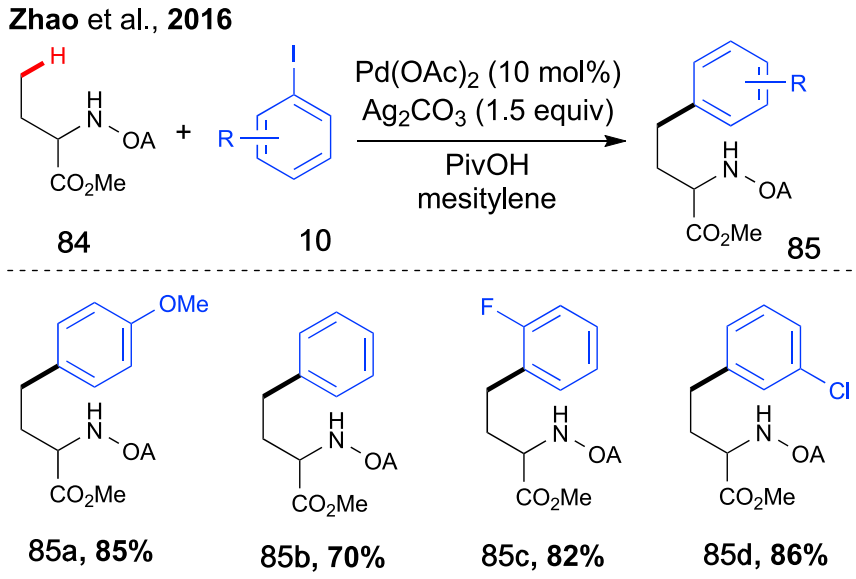


Scheme 50. Pd-catalyzed enantioselective γ-C(sp^3)–H cross-coupling of alkyl amines with arylboron reagents

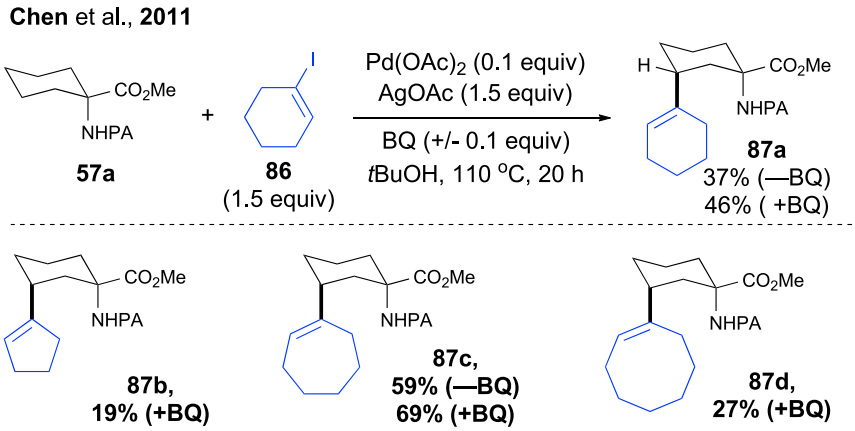


Scheme 51. Pd-catalyzed γ-C(sp^3)–H arylation and of aliphatic amines

In 2016, Carretero used *N*-(2-pyridyl)sulfonyl group as a DG to achieve site-selective γ-C(sp^3)–H carbonylation/cyclization of aliphatic amine derivatives. Solid $Mo(CO)_6$ was employed as a carbonyl source, avoiding the use of toxic CO gas (Scheme 62).[48] Both amino acids and cyclopropanes were effective for this transformation, but more complex multifunctional molecules such as di- and tripeptides and estrone derivatives can successfully be derivatized into richly functionalized γ-lactams in moderate to good yields. In further studies, a bimetallic Pd^{II}-complex **97A** was synthesized and then was reacted with $Mo(CO)_6$ to obtain the expected γ-lactam(+)-**98e** in 69% yield (Scheme 63). These results showed that the NH–SO_2Py bidentate DG is crucial for this transformation. The Carretero auxiliary(SO_2Py) can strengthen the interaction of the substrate to the metal leading to stable complexes and has a strong capability to control the site selectivity of the reaction. Interestingly, this protocol is effective for the carbonylation of less reactive cyclopropyl C(sp^3)–H methylene groups. A bicyclic lactam with good diastereoselectivity (**98d**, 98% yield, *cis*/*trans* = 9:1) could be obtained when cyclopropane derivative **97d** is used as a substrate. This result is important for medicinal chemists because the cyclopropane structural backbones are widely found in natural products and pharmaceuticals, and their derivatization is challenging with other methods. Furthermore, the



Scheme 52. Pd-catalyzed γ-C(sp^3)–H arylation and of amino acids

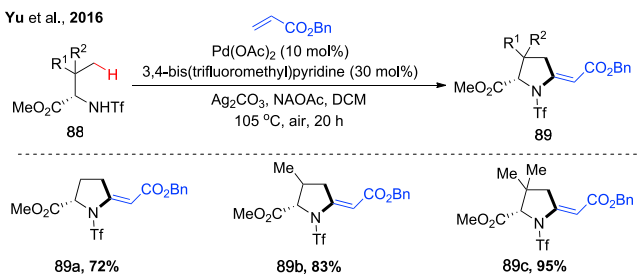


Scheme 53. Pd-catalyzed γ-C–H alkenylation of the cyclohexylamino acids

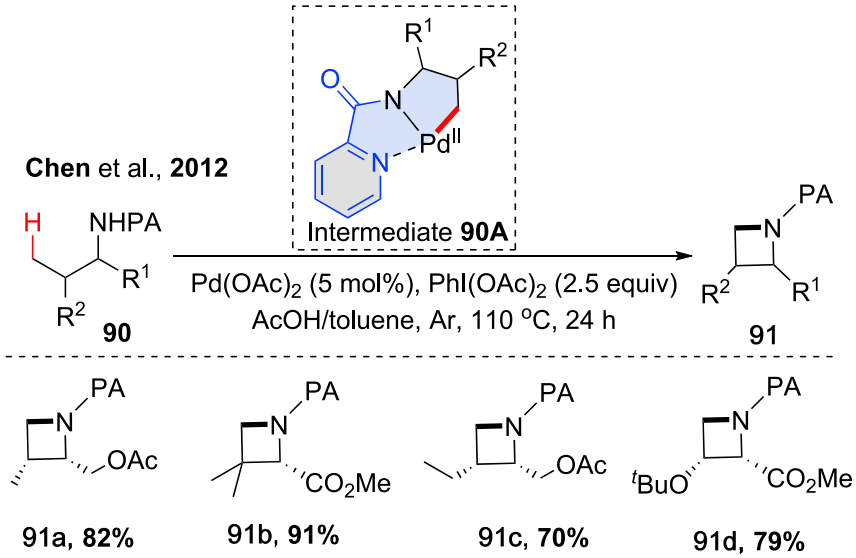
application of this transformation toward the late-stage carbonylation of the estrone derivative has proved particularly fruitful (Scheme 64).

The chemoselectivity between cyclization and substitution reactions in the field of directed C–H bond activation in amines remains a persistent challenge. Although the judicious choice of ligands and/or catalysts is a priority to control chemoselectivity in the Pd-catalyzed C–H activation reaction,[4–7] sometimes it is the directing or protecting group that plays the more important role. In 2013, the Shi group developed a directing- or protecting-group-controlled selective γ-C(sp^3)–H substitution or cyclization of amines (Schemes 65 and 66).[49] The Pd-catalyzed γ-C(sp^3)–H cyclization of amines was achieved with a removable TAA (N_1-aryl-1,2,3-triazole-4-carboxylic acids) group as a directing auxiliary. Conversely, using TA-Py (N_2-pyridine-1,2,3-triazole-4-carboxylic acids) as a removable DG resulted in acetylation instead (Schemes 65 and 66). Unfortunately, the substrate scope of acetylation is limited, and the reaction outcome is a mixture of monofunctionalized and difunctionalized products. The author provided a reasonable mechanism that indicated that the key Pd(IV) intermediate favored in-plane reductive elimination to give cyclization products by using TAA(N_1-aryl-1,2,3-triazole-4-carboxylic acids) as the DG (Scheme 67A), although the same intermediate prefers the out-of-plane C–O bond-forming reductive elimination pathway to yield acetylation products when using TA-Py as the DG (Scheme 67B).

In 2014, the Chen group reported a new protocol for the acetylation of aliphatic amines using $PhI(OAc)_2$ as an oxidant (Scheme 68).[50] Li_2CO_3 was used as an additive to offer the Li^+ cation and carbonate anion species because their incorporation had a



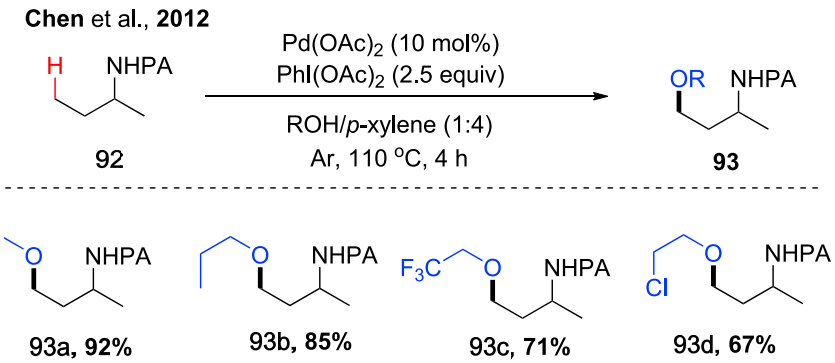
Scheme 54. Olefination of γ-C(sp^3)–H bonds of triflyl (Tf)-protected amines



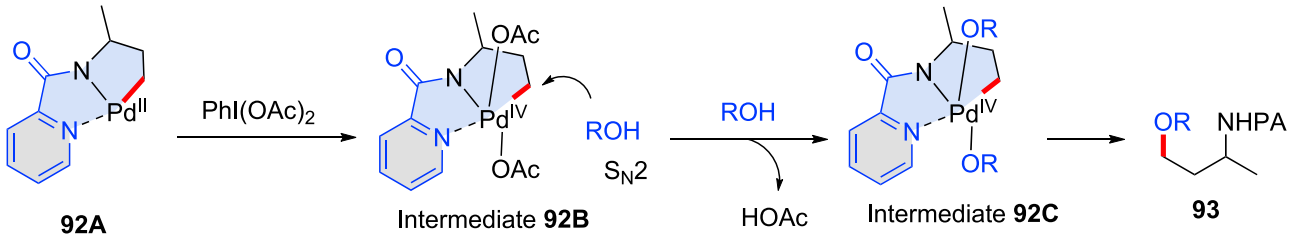
Scheme 55. The syntheses of azetidines via Pd-catalyzed intramolecular amination

notable impact on the reactivity and selectivity of the reaction. As shown in Scheme 69, the use of Li_2CO_3 effectively suppressed the amination product **103f** and afforded **103e** in 91% isolated yield. In contrast, a mixture of acetoxylated product **103e** (77%) and cyclized product **103f** (16%) were given when additive Li_2CO_3 was replaced by CsF. Hence, Li_2CO_3 effectively inhibited the competing intramolecular C–H amination processes. The authors further speculate that the L-type coordination mode **103B** could promote C–O reductive elimination to give acetoxylated products. Otherwise, the X-type coordination mode **103A** could assist with C–N reductive elimination to form the cyclized product (Scheme 70). Therefore, the Li^+ cation interacts with O-imidate to help form L-type coordination mode to favor C–H acetoxylation.

Using a $Pd(OAc)_2$ catalyst and $PhI(OAc)_2$ oxidant, acetylation of amines has been developed rapidly by manly research groups. In 2015, the Zhao group disclosed a practical Pd-catalyzed γ-C(sp^3)–H oxygenation of alkylamine in good to excellent yields by using oxalyl amide(OA) as a DG (Scheme 71).[51] This DG was made from diisopropylamine and oxalyl chloride through S_N type reaction, and it is readily removed from the product under base conditions. The $PhI(OAc)_2$ was used as an



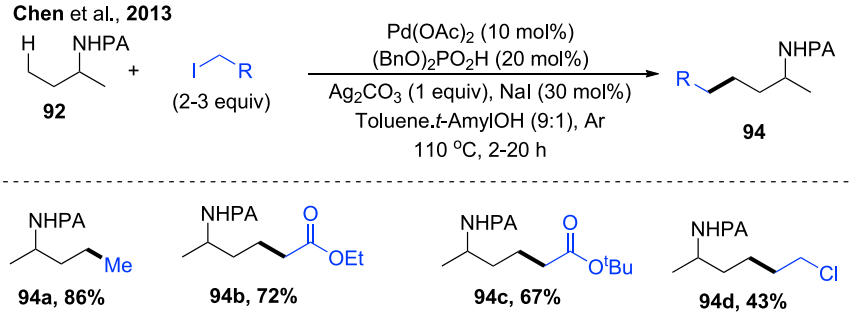
Scheme 56. Pd-catalyzed intermolecular alkoxylation of unactivated γ-C(sp^3)–H bonds



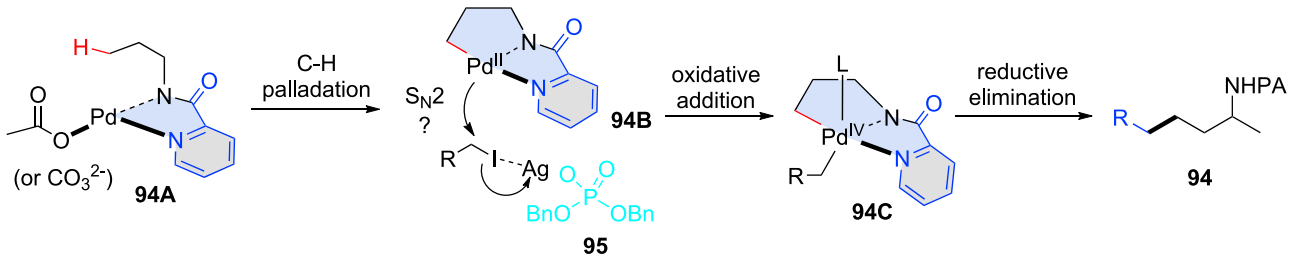
Scheme 57. A plausible mechanism of Pd-catalyzed intermolecular alkoxylation of unactivated γ-C(sp^3)–H bonds

oxidant, which could oxidize the Pd(II) intermediate to the Pd(IV) intermediate in the reaction. In 2016, Liu and co-workers used 5-methyl isoxazole-3-carboxamide(MICA) as a DG for the Pd-catalyzed γ-C(sp^3)–H acetoxylation of amino acids (Val, Thr, and Ile) (Scheme 72).[52] Interestingly, the γ-acetoxylated α-amino acid derivatives could be further utilized for synthesizing many biologically important compounds, such as γ-mercapto amino acids for native chemical ligation. In the study, the $PhI(OAc)_2$ was employed as an oxidant, and AcOH (1 equiv) was used as an additive. The MICA is a versatile bidentate DG, which can be readily removed under K_2CO_3 (Scheme 73). In 2018, Xuan and co-workers used benzothiazole-2-sulfonyl (Bts) as a DG for developing Pd-catalyzed γ-C(sp^3)–H acetoxylation of amines with inexpensive $PhI(OAc)_2$ as oxidant (Scheme 74).[53] The Bts is considered a useful protecting group or DG for amines and amino acids. It showed the stability of sulfonamide and was easily introduced and removed under mild conditions without racemization (Scheme 75). A series of acetoxylation of amines and amino acids were obtained in moderate and good yields using the protocol. In addition, γ-hydroxyl amine derivatives can also be obtained in the study.

In 2017, Jia and Fernández-Ibáñez used triflyl(Tf) as a protecting group of amines, Pd-catalyzed γ-C(sp^3)–H acetylation (Scheme 76).[54] A series of γ-hydroxy-α-amino acids and β,γ-dihydroxy amines were obtained in moderate to good yields using the protocol. Unlike the other DGs (OA, MICA, and Bts), the Tf group does not participate in the coordination of Pd, and it only acts as a protecting group. In the transformations, the selectivity is controlled by the amine's nitrogen and the external ligand 2,6-lutidine. A possible mechanism was proposed (Scheme 77); first, the amine's nitrogen coordinates with the Pd(II) to form the Pd intermediate **111A**. Subsequently, ligand-accelerated γ-C–H bond cleavage gives the cyclic Pd intermediate **111B**, which undergoes oxidative addition by $PhI(OAc)_2$ to form a Pd(IV) complex **111C**. Finally, **111C** reductive elimination yields the acetoxylated product.



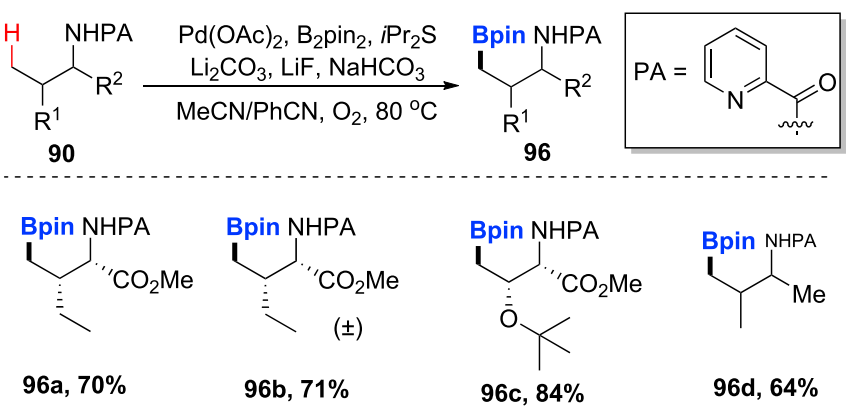
Scheme 58. Alkylation of γ-C(sp^3)–H bonds of aliphatic amines



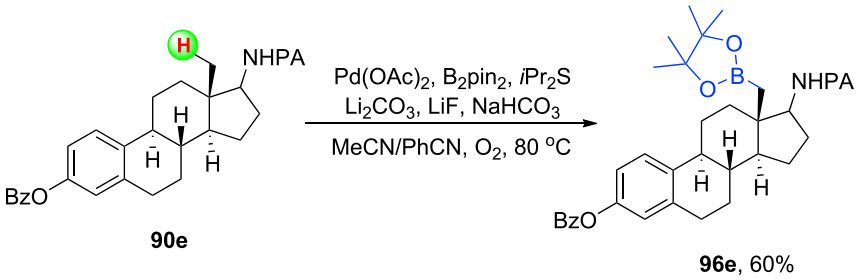
Scheme 59. A plausible reaction mechanism for alkylation of γ-C(sp^3)–H bonds of aliphatic amines

Various γ-C(sp^3)–H functionalizations of primary amines have been developed with well-designed weak and strong coordination DGs. However, the additional steps to install and remove the DGs after the desired operation reduce the overall efficiency and compatibility of the chemical processes. In addition, these reactions use the noble transition metal Pd as the only catalyst under a high reaction temperature. Encouragement of new efforts to resolve these long-standing problems, via developing inexpensive metal catalysis to achieve γ-C(sp^3)–H functionalizations of primary amines without DGs under mild conditions, would significantly strengthen the applications of these reactions.

Auxiliary-controlled γ-C(sp^3)–H functionalization of secondary amines. The DG strategy was also used in the γ-C(sp^3)–H functionalization of secondary amines. In 2016, the Sanford group described a Pd(II)-catalyzed γ-C(sp^3)–H arylation reaction of alicyclic amines by using fluoroamide as a DG (Scheme 78).[55] A variety of alicyclic amines were found to effectively couple with aryl iodides bearing an electron-donating, electron-neutral, or electron-withdrawing substituents to deliver the corresponding products via bridged palladacycle intermediates. This method exhibits a broad substrate scope and high functional-group compatibility; aryl bromides, unprotected phenols, and aromatic aldehydes were all tolerated under standard reaction conditions. The reaction proved effective for the late-stage C–H arylation of varenicline (**115**, a drug used to treat nicotine addiction; Scheme 79) and the natural product cytosine. It is worth mentioning that the DG could be readily removed via reductive cleavage with samarium diiodide (SmI_2). Although yields were originally moderate, the authors successfully developed a second-generation catalytic system to improve the transannular C–H arylation of alicyclic amines with 2-picolinic acid as a ligand (Scheme 80).[56]



Scheme 60. Pd-catalyzed borylation of γ-C(sp^3)–H bonds of aliphatic amines



Scheme 61. Pd-catalyzed γ-C(sp^3)–H borylation of natural product (the steroid estrone)

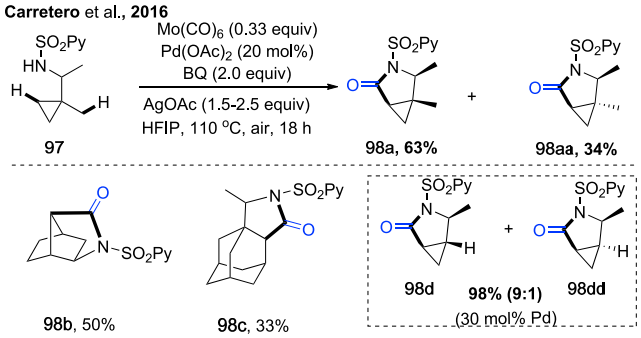
Only the Pd(II)-catalyzed γ-C(sp^3)–H arylation of secondary amines has been achieved with fluoroamide as the DG to date. Future development hinges on exploring more γ-C(sp^3)–H functionalization examples of secondary amines by designed new DGs.

Auxiliary-controlled δ-C(sp^3)–H functionalization of amines

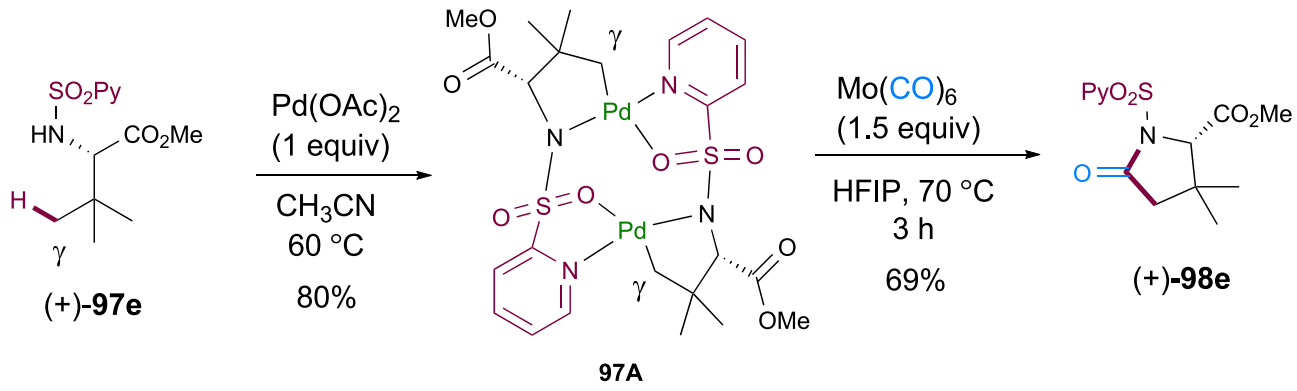
Auxiliary-controlled δ-C(sp^3)–H functionalization of primary amines. In 2012, Chen and colleagues developed Pd-catalyzed intramolecular amination of δ-C(sp^3)–H bonds to synthesize pyrrolidines using PA as the auxiliary group. The reaction involves the use of PhI(OAc)$_2$ as an oxidant and AcOH (10 equiv) as an additive that can effectively suppress the competitive acetylation reaction while slightly decreasing the cyclization rate (Scheme 81).[44] This protocol is efficient, economical, and practical. In particular, leucines bearing both primary δ-C(sp^3)–H bonds and a sterically less accessible γ-C(sp^3)–H bond can transform into the pyrrolidine product **121d** in good yield under mild reaction conditions, although a mixture of two diastereomers was observed (diastereomeric ratio ~ 7: 1).

In the same year, the Daugulis group independently reported Pd-catalyzed δ-C(sp^3)–H/N–H cyclization reaction to construct pyrrolidines and indolines by employing a picolinic acid DG (Scheme 82).[57] The method employs Pd(OAc)$_2$ as a catalyst, PhI(OAc)$_2$ as an oxidant, and toluene as a solvent at 80°C–120°C. This cyclization is effective for aliphatic δ-C(sp^3)–H as well as benzylic δ-C(sp^3)–H bonds.

Later in 2014, Yao and Zhao described the use of the oxalyl amide as the DG in the Pd-catalyzed intramolecular δ-C(sp^3)–H/N–H cyclizations to synthesize pyrrolidines in good yields under mild conditions (Scheme 83).[58] The cyclization of the substrates



Scheme 62. Site-selective γ-C(sp^3)–H carbonylation and cyclization of aliphatic amine derivatives



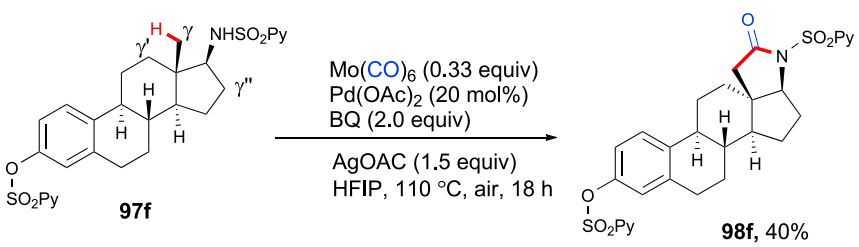
Scheme 63. The bimetallic Pd^{II}-complex 97A was synthesized and then was reacted with $Mo(CO)_6$ to obtain the expected γ-lactam(+)-98e

bearing aliphatic δ-C(sp^3)–H as well as benzylic δ-C(sp^3)–H bonds proceeded smoothly to obtain the corresponding pyrrolidine products. The method employs $PhI(OAc)_2$ as oxidant and mesitylene as a solvent under Ar. Linear primary amines were transformed to the corresponding pyrrolidines in low yields, and γ-secondary, tertiary, and quaternary amines could be cyclized in synthetically useful yields. To showcase the synthetic applicability of this reaction, a gram-scale reaction was executed, and the corresponding cyclized product was successfully obtained in 86% yield with a slightly longer reaction time.

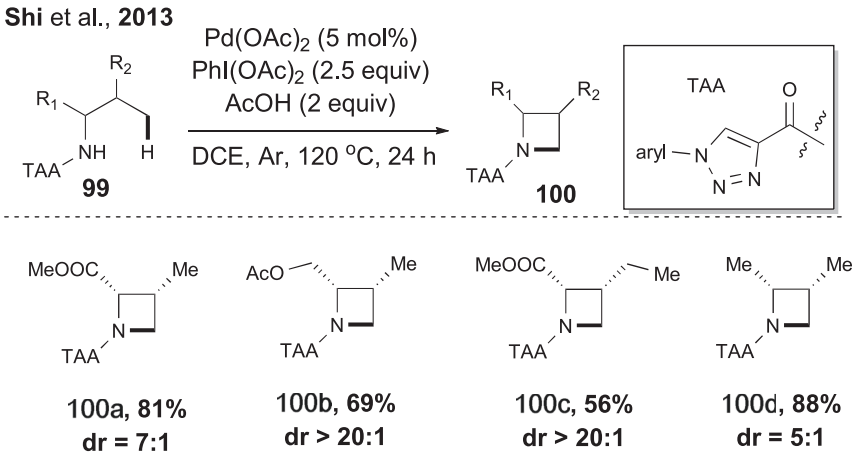
In 2014, Wang and Hu reported the first direct arylation of 3-pinanamine with aryl halides by using PA as a DG (Scheme 84).[59] The site selectivity toward the δ-methylene position can be explained by the rigidity in this substrate conformation. A variety of aromatic iodides and bromides bearing different functionalities were tolerated in moderate to good yields.

Shi reported a Pd-catalyzed arylation of unactivated remote δ-(sp^3)–H bonds by using a removable oxazoline-carboxylate auxiliary in 2015 (Scheme 85).[36] However, only one substrate was demonstrated and reflected a relatively low yield.

In 2019, Maiti and Paton reported a Pd-catalyzed remote δ-C(sp^3)–H arylation of amino acids and analogous aliphatic amines by using PA as a DG via a six-membered palladacycle intermediate (Schemes 86 and 87).[60] The ligands played a crucial role to tune the reactivity according to the nature of substrates. In this protocol, 4-benzoyloxy-2(1H)-pyridone turned out to be the better choice for the functionalization of amine substrates possessing a tertiary γ-center. Pyridine and 1-hydroxy isoquinoline were proven to be the best for the δ-C(sp^3)–H bond (hetero)arylation of substrates bearing a quaternary γ-position. The six-membered organopalladium δ-C(sp^3)–H activation intermediate was isolated and characterized, which is essential for the understanding of these catalytic



Scheme 64. Late-stage carbonylation of the estrone derivative using SO_2Py as a DG

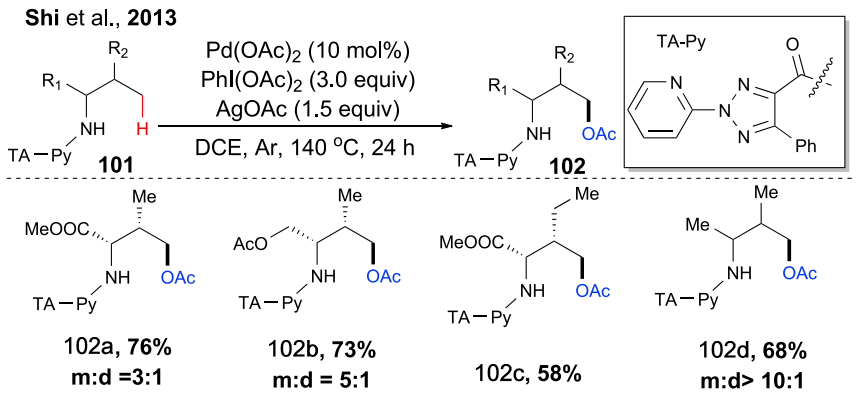


Scheme 65. Pd-catalyzed γ-C(sp^3)–H cyclization of amines

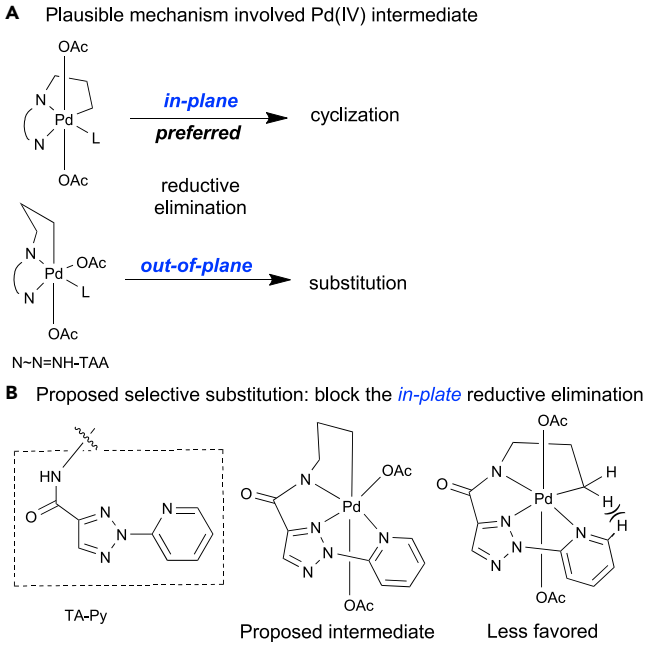
transformations. It is noted that this reaction is quite practical and could be performed by introducing diverse natural products and drugs in amines, labeling bioactive amines with the BODIPY (dipyrromethene boron difluoride) motif (Scheme 88).

They proposed a plausible mechanism for γ-*tert*-butyl substrates (Scheme 89). First, the PA-linked amine coordinates with the trimeric complex $Pd_3(OTFA)_6$ to generate the trinuclear complex **129A**, which then undergoes dissociation by the coordination to a pyridine-type ligand to form the mononuclear Pd complex **129B**. Subsequently, reversible C–H activation leads to the generation of a [5,6]-fused palladacycle intermediate **129C**. Next, pyridine-type ligand dissociation and oxidative addition with an aryl iodide afford the Pd(IV) species **129D**. Then, intermediate **129D** undergoes reductive elimination, and the pyridine-type ligand coordinates back to produce the Pd intermediate **129E**. Finally, protonation of **129E** to yield the δ-arylation product.

In 2016, the Shi group reported the first Pd-catalyzed site-selective δ-C(sp^3)–H alkenylation of aliphatic amines with internal alkyne by using PA as a DG (Scheme 90).[61] The reaction involves the use of 2,6-dimethylbenzoquinone, $NaHCO_3$, and LiF as additives and 1,1,2,2-tetrachloroethane (TCE) and HFIP (hexafluoroisopropanol) as co-solvents. A wide range of functional groups are tolerated and various δ-selective



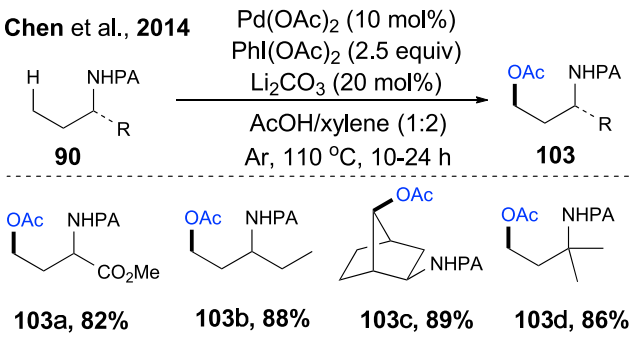
Scheme 66. Pd-catalyzed γ-C(sp^3)–H acetylation of amines using TA-Py as a DG



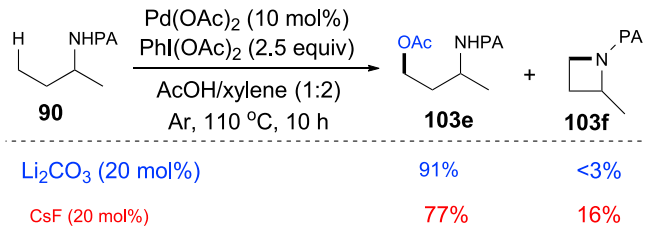
Scheme 67. Proposed TA-Py/TAA DG for selective substitution or cyclization

alkenylation products can be obtained in moderate to good yields. The δ-selective alkenylation reaction occurs via a kinetically less favored six-membered palladacycle. The method was applied to the synthesis of chiral piperidines, which are widely existing in bioactive natural products.

Using the same strategy, the Shi group further expanded the scope of substrates. In 2018, they first disclosed a Pd-catalyzed site-selective δ-C(sp^3)–H alkylation of amino acids and peptides with maleimides by using PA as a DG through a kinetically less favored six-membered palladacycle intermediate even in the presence of more accessible γ-C(sp^3)–H bonds (Scheme 91).[62] Mechanism studies demonstrated that C(sp^3)–H bond cleavage occurs reversibly and preferentially at the γ-methyl over the δ-methyl position. However, the subsequent alkylation process is exclusively selective toward the six-membered palladacycle generated via δ-C(sp^3)–H activation. To further explore the high δ-selectivity motives, a series of H/D exchange experiments were performed by the authors (Scheme 92). The γ- and δ-C–H bonds of **134** were deuterated under standard reaction conditions



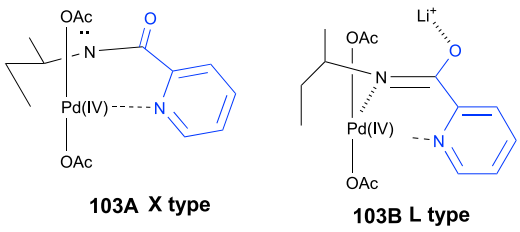
Scheme 68. Acetylation of the γ-C(sp^3)–H bonds of aliphatic amines



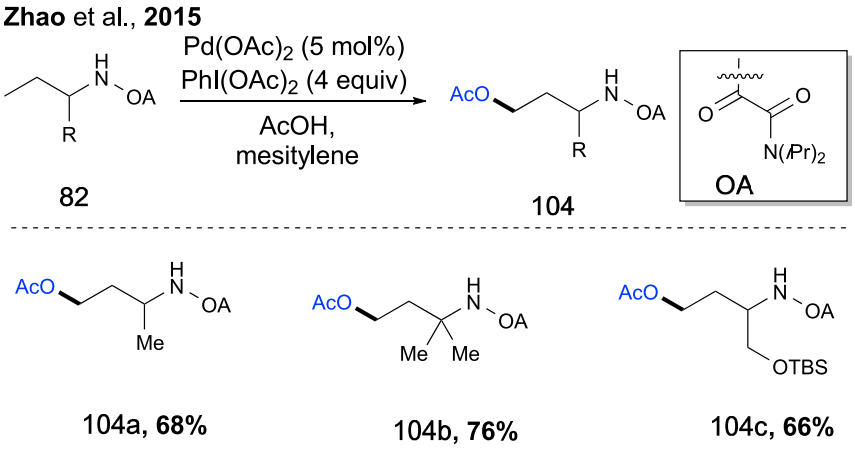
Scheme 69. Comparative experiments for acetylation of the γ-C(sp^3)–H bonds of aliphatic amines using additive Li_2CO_3 or CsF

in the absence of **135**, with low incorporation at the δ-position (Scheme 92A; γ: 57%, δ: 29% D). In contrast, only traces of H–/D exchange were observed on the δ-methyl group, and **136a** was obtained in 50% yield in the presence of **135** (Scheme 92B; γ: 50% D, δ: <5% D). Additionally, the γ-alkylation product did not appear, and only deuteration of the γ-C–H bonds was obtained under **137** and **138** as substrates (Schemes 92C and 92D). These experimental results demonstrated that (1) γ- and δ-C–H activation is reversible and γ-C–H activation is favored under the reaction conditions, (2) the subsequent migratory insertion of δ-palladacycle **134B** is significantly faster than the δ-C–H activation of **134A**, and (3) although γ-C–H activation to form palladacycle **134B1** is kinetically favored, the subsequent γ-alkylation of **134B1** cannot occur (Scheme 93). Importantly, the selectivity-determining migratory insertion of the maleimide led to the δ-selectivity results because only the γ-arylated product **139** was detected when methyl 4-iodobenzoate was instead of maleimide **135** (Scheme 92E). The high site selectivity toward the δ-methyl position can be explained by the Curtin–Hammett principle. In the catalytic system, the pair of intermediates **134B** and **134B1** that irreversibly led to γ- or δ-alkylation product undergo rapid interconversion at equilibrium in the reaction. The distribution of the γ- or δ-alkylation product is determined by the free energy of the transition state instead of the position of the equilibrium of the reaction. In Schemes 92C and 92D, the γ-alkylation product was not observed and hence demonstrated that the alkylation of **134B1** has a relatively high energy barrier. In sharp contrast (Scheme 92B), the alkylation of **134B** has a relatively low energy barrier.

Due to peptides ubiquity and importance, the late-stage derivatization of various oligo-peptides has widespread utility in organic chemistry and medicinal chemistry. This protocol allows the rapid and direct late-stage modification of oligo-peptides, and the facile removal of the PA group renders this method highly valuable. In addition, a plausible mechanism was proposed (Scheme 93); first, the substrate **134** coordinates to $Pd(OAc)_2$ forming complex **134A**, which undergoes reversible δ-C(sp^3)–H cleavage to yield the kinetically less favored



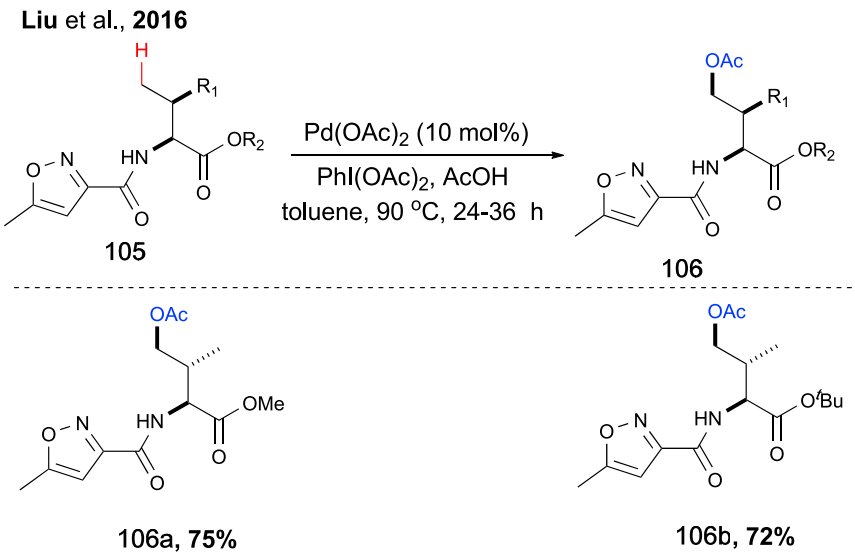
Scheme 70. X-type coordination mode 103A and L-type coordination mode 103B



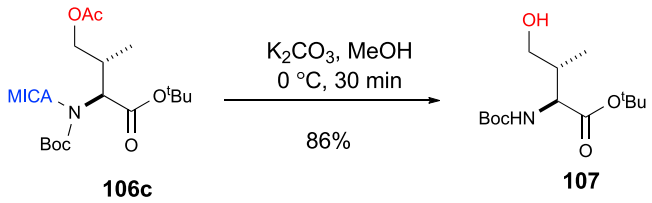
Scheme 71. Pd-catalyzed γ-C(sp^3)–H acetylation of amines using OA as a protecting group

six-membered palladacycle intermediate **134B** and γ-C(sp^3)–H cleavage to give the kinetically favored five-membered palladacycles **134B1** and **134B2**. Next, as a result of steric repulsion, it is less favored for palladacycles **134B1** and **134B2** to undergo migratory insertion of maleimide **135** to form the seven-membered intermediates **134C1** and **134C2**, whereas the palladacycle **134B** undergoing migratory insertion with maleimide **135** to generate the eight-membered intermediate **134C** is a fast and favored process. Finally, intermediate **134C** undergoes protodemetalation to obtain δ-alkylation product 136a and regenerate $Pd(OAc)_2$.

Very recently, Ge and Maiti further extended the scope of the reaction. They reported the borylation at the distal delta position of aliphatic amines using a combination of $Pd(OAc)_2/O_2$/6-methylpyridin-2-ol as an efficient catalyst system, without the need for a co-oxidant (Scheme 94).[63] Various borylating agents



Scheme 72. Pd-catalyzed γ-C(sp^3)–H acetylation of amines using 5-methylisoxazole-3-carboxamide as a DG



Scheme 73. Removal of the MICA group through K_2CO_3 in methanol, giving 107 in 86% yield

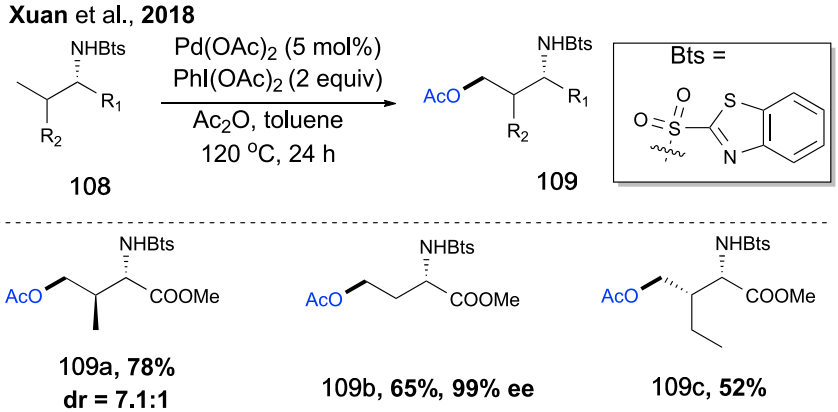
including bis(2,4-dimethylpentane, 2,4-glycolato)diboron, bis(hexylene glycolato) diboron, bis(pinanediolato)diboron, and the chiral borylting agent bis [pinanediolato]diborane reacted with aliphatic amines smoothly. Arene-substituted aliphatic amines and natural products containing substrates were compatible under this mild reaction condition resulting in good to excellent yields of the δ-borylated products (Scheme 95). The resulting δ-borylated amines can be subjected to various subsequent transformations (Scheme 96), which renders the protocol valuable for organic synthesis. To obtain some mechanistic insights, the acetonitrile coordinated [5,6]-fused cyclopalladated intermediate was successfully prepared. Moreover, the catalytic mechanism was studied via deuterium-labeling experiments that indicated that the C(sp^3)–H bond cleavage is not the rate-limiting step of the reaction. The authors proposed a plausible mechanism for the δ-C(sp^3)–H borylation reaction based on their mechanism experiments (Scheme 97). First, the pre-catalyst (**140A**) is formed via a $Pd(OAc)_2$ complex with 6-methylpyridin-2-ol. Coordination of **140a** with the pre-catalyst (**140A**) species produces the cyclic Pd complex **140B**, which then undergoes a C–H activation step to produce the six-membered palladacycle intermediate **140C**. Finally, borylation takes place to yield the desired product.

Several classes of δ-C(sp^3)–H functionalization, including amination, cyclization, arylation, alkylation, alkylation, and borylation have already been achieved via Pd catalysis. The downside of these transformations, however, is the extra steps needed to install and remove the DGs.

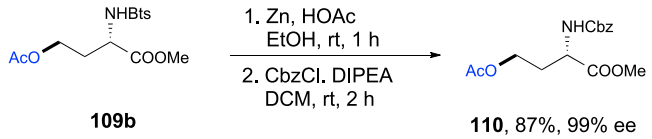
Auxiliary-controlled δ-C(sp^3)–H functionalization of alkyl silanes

C–H silylation

In 2014, the Gevorgyan group reported the first Ir-catalyzed C–H silylation of an unactivated δ-C(sp^3)–H bond to obtain a silolane intermediate using a Si,N-type



Scheme 74. Pd-catalyzed γ-C(sp^3)–H acetylation of amines using benzothiazole-2-sulfonyl as a DG



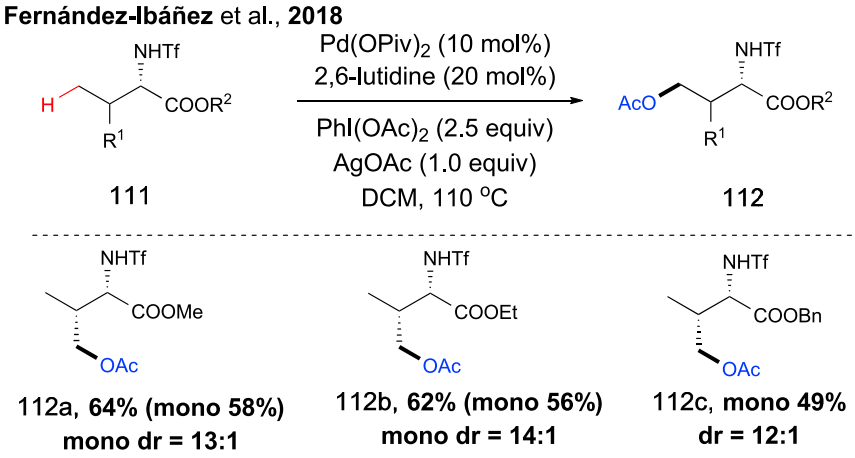
Scheme 75. Removal of the Bts group under mild conditions in good yield using zinc powder

chelating auxiliary group on the alkene (Scheme 98).[64] The key was to use *t*-butylpicolylsilicon hydride (TBPicSi) as the DG. The tert-butyl group could effectively stabilize the substrates, and the picolyl group was proven to play a key role in the reactivity of the δ-C–H silylation because the benzyl analog of TBPicSi was not effective in the same transformation. This reaction showed a broad substrate scope, good functional-group compatibility, high yields, and excellent site selectivity, thus providing an opportunity to assemble a series of cyclic silane products rapidly and efficiently. Subsequently, 1,4-diols can be obtained by the oxidation of the C–Si bonds of the silolane intermediate (Scheme 99). Furthermore, the late-stage C(sp^3)–H functionalization of natural products and drugs was successfully achieved using this protocol (Scheme 100).

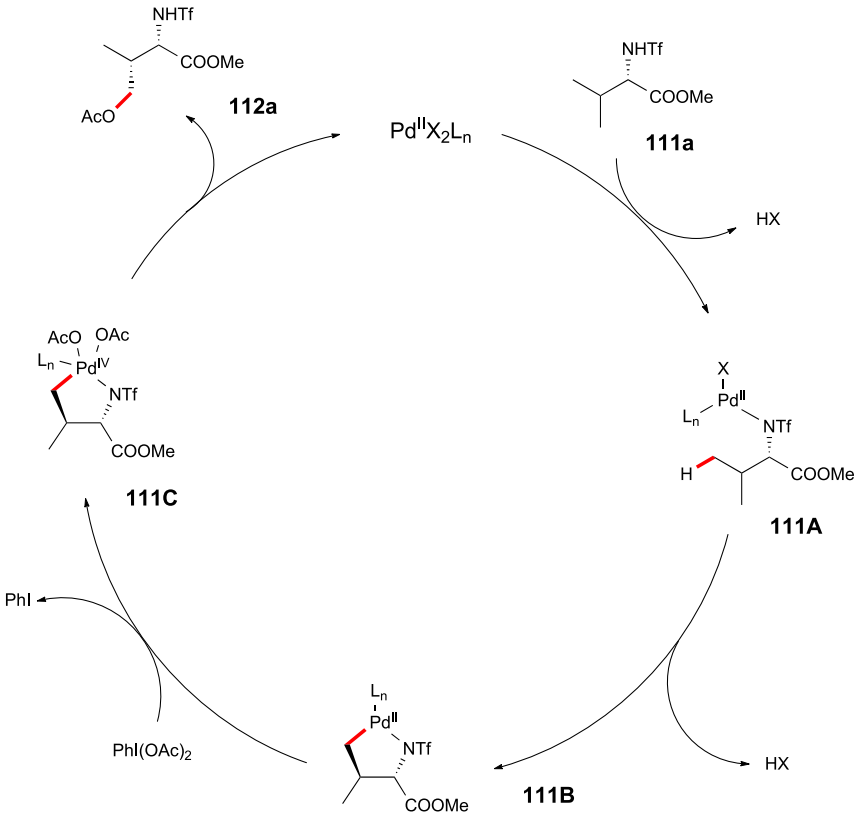
The δ-C(sp^3)–H functionalization of alkyl silanes is challenging, and only one example has been reported as of yet. Further advances in the auxiliary-controlled δ-C(sp^3)–H functionalization require the design of new catalytic systems and the further extension of the reactions scopes.

TDG-ASSISTED γ- AND δ-C(sp^3)–H FUNCTIONALIZATION

The TDG-enabled C–H functionalization process has emerged as a practical synthetic strategy and has aroused great interest among chemical scientists and engineers. The TDG functions by reversibly binding to the substrate, which upon coordination to a metal center, helps deliver it onto a targeted C–H bond through an appropriate spatial arrangement, enabling selective C–H activation via the formation of a cyclometalated species. This strategy has numerous advantages; it does not require the use of pre-functionalized starting materials, it helps avoid the use of stoichiometric organometallic reagents, and it does not demand additional steps to construct and remove DGs. This strategy represents a unique opportunity to



Scheme 76. Pd-catalyzed γ-C(sp^3)–H acetylation of amines using triflyl as a protecting group

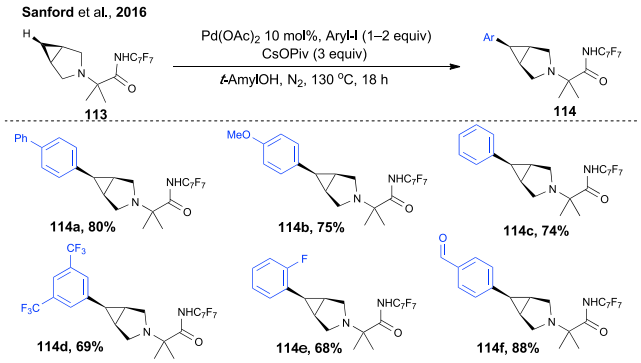


Scheme 77. Proposed catalytic cycle of Pd-catalyzed γ-C(sp^3)–H acetylation of amines using Tf as a protecting group

access novel building blocks and organic functional molecular structures via atom economical use of catalytic auxiliaries in a cooperative manner. As a result, various organic functional materials, bioactive compounds, and pharmaceuticals have been constructed efficiently by the TDG-assisted γ- and δ-C(sp^3)–H functionalization.

TDG-assisted γ-C(sp^3)–H functionalization of aldehydes

Aldehydes are one of the most important classes of organic synthetic compounds and are privileged structural motifs in biologically active natural products, pharmaceuticals, and organic functional materials.[65] Tremendous efforts have been devoted to developing efficient and straightforward methods for the construction and derivatization of aldehydes. α-C(sp^3)–H functionalization of aldehydes has been extensively studied, and substantial progress has also been made in the field of β-C(sp^3)–H functionalization of aldehydes, via radical, oxidative conjugated addition, and TDG-enabled C–H activation pathways.[65] In contrast, site-selective γ-C(sp^3)–H functionalization reactions of aldehydes are rare. In the case of transition-metal-catalyzed γ-functionalization, for example, the scarcity is mainly caused by the preference of aldehyde substrates to form five-membered metallacycle intermediates during the C–H activation step, which geometrically leads to β-functionalization, rather than γ-functionalization. On the other hand, γ-functionalization would require the formation of a less favorable six-membered intermediate (Scheme 101, a6). It has been well documented that a five-membered palladacyclic intermediate is more favorable to its six-membered or larger-sized counterpart due

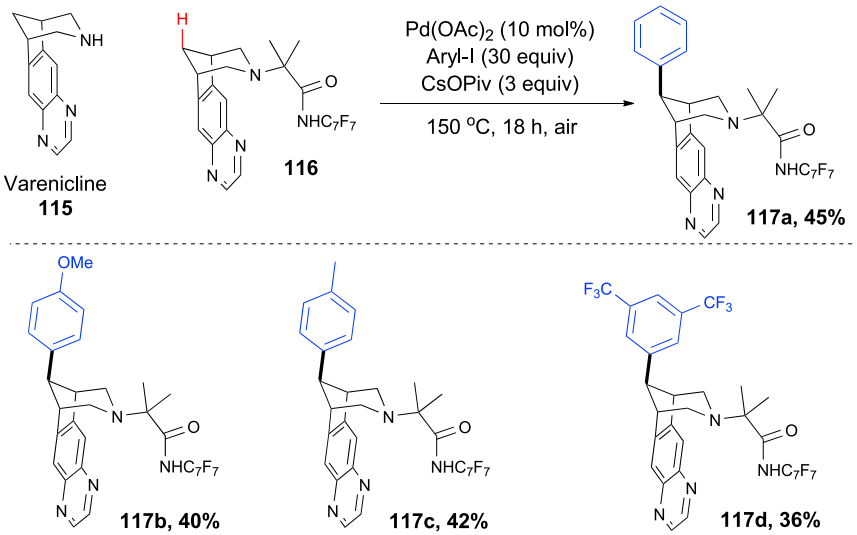


Scheme 78. Pd-catalyzed γ-C(sp^3)–H arylation of alicyclic amines using the fluoroamide group as a DG

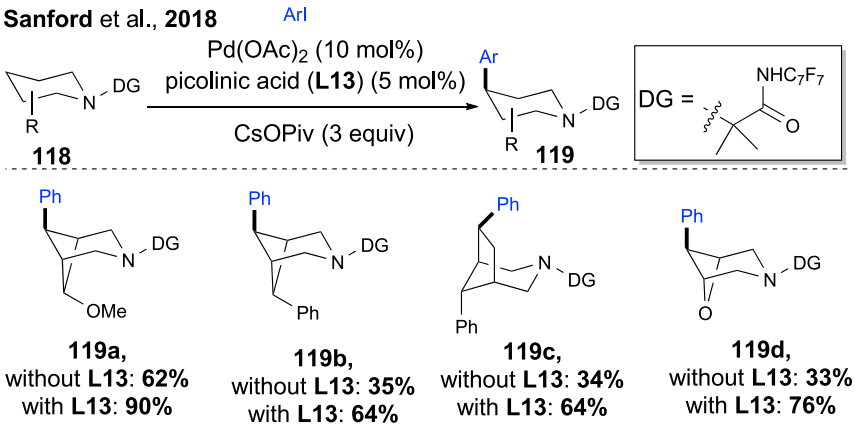
to kinetic and thermodynamic factors (Scheme 101, a1–a6).[65] Consequently, there have been many successful examples of Pd-catalyzed C(sp^3)–H activation reactions via five-membered palladacycle intermediates, although reports on direct C(sp^3)–H functionalization via a six-membered palladacycle are infrequent.

C–H arylation

In 2020, Ge and co-workers reported the first Pd-catalyzed site-selective γ-C(sp^3)–H arylation reaction of aliphatic and benzoheteroaryl aldehydes (Scheme 102).[65] The authors used an external ligand in combination with a TDG to promote the formation of six-membered palladacycle intermediates. In this process, the external ligand coordinates with the Pd catalyst and promotes the C–H bond cleavage step. However, the TDG contributes through reversible binding to the substrate, which coordinates to a metal center and helps deliver it on a targeted C–H bond through an appropriate spatial arrangement, enabling selective C–H activation via the formation of a cyclometalated species. This strategy has numerous advantages; it does not require the use of pre-functionalized starting materials, it helps avoid the use of stoichiometric organometallic reagents, and it does not demand additional steps to



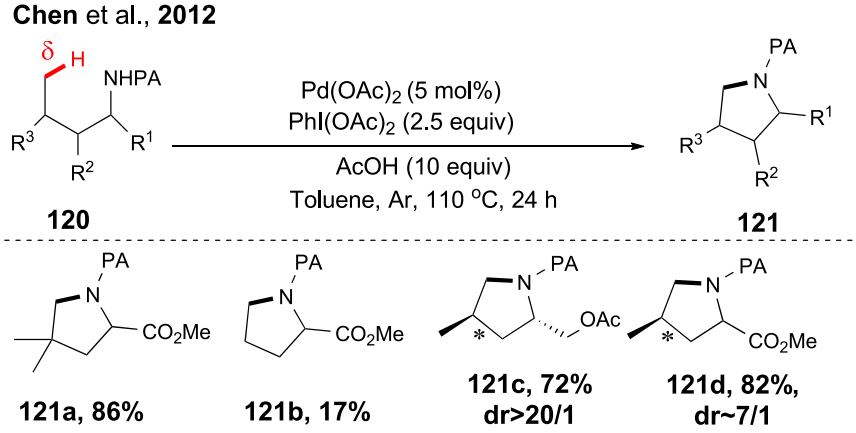
Scheme 79. The late-stage C–H arylation of varenicline



Scheme 80. Pd-catalyzed γ-C(sp^3)–H arylation of alicyclic amines using 2-picolinic acid as a ligand

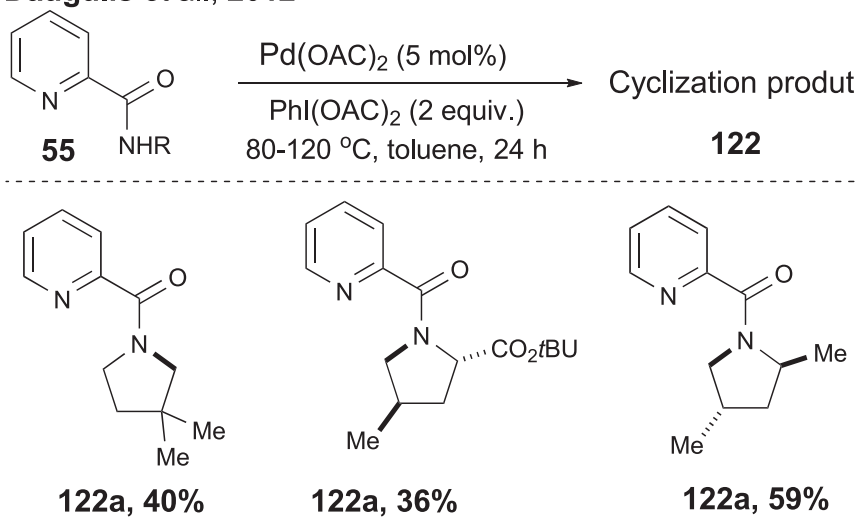
construct and remove DGs. Specifically, L-phenylalanine(**TDG2**) was used as a novel TDG, and 3-nitro-5-(trifluoromethyl)pyridin-2-ol(**L14**) was employed as an external ligand (Scheme 102). This highly selective γ-arylation reaction displayed high functional-group tolerance and a broad substrate scope. A tentative mechanism was proposed (Scheme 103); first, condensation of aliphatic aldehyde **151a** with **TDG2** generates the imine intermediate **151A**, which upon coordination with the Pd catalyst and subsequent external ligand **L14**-promoted γ-C–H bond activation forms the [6,5]-bicyclic Pd complex **151C**. Then, oxidative addition of **151C** with an aryl iodide affords the Pd(IV) species **151D**. Finally, reductive elimination of **151D** and ligand dissociation yields the γ-arylated product **152a**.

Later work by Yu expanded the scope to primary aldehyde substrates without α-substitution by modifying the reaction conditions (Scheme 104).[66] However, the scope remained limited. The β-substitution is required. Otherwise, the mixture of γ/β-arylation products would occur. Moreover, the methylene γ-C(sp^3)–H arylation of aldehydes is less efficient, affording a 20% yield (**152g**). Furthermore, for two or more methyl γ-C(sp^3)–H contains in the substrate, forming mono- and di-arylated products.



Scheme 81. Synthesis of pyrrolidines by Pd-catalyzed intramolecular amination of δ-C(sp^3)–H bonds

Daugulis et al., **2012**

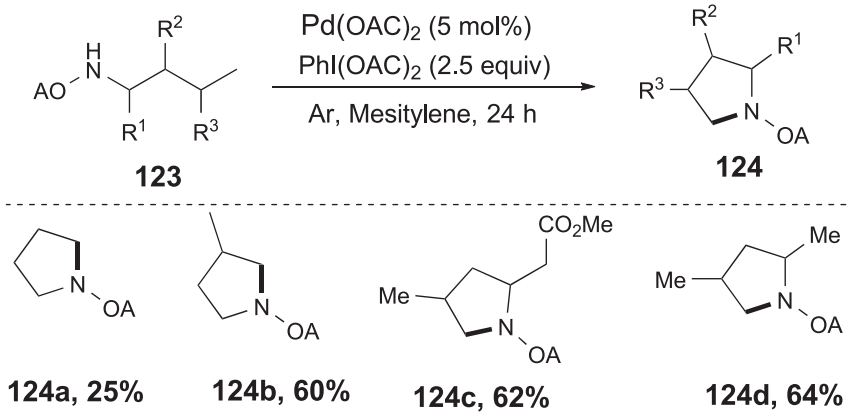


Scheme 82. Pd-catalyzed δ-C(sp^3)–H/N–H cyclization reaction

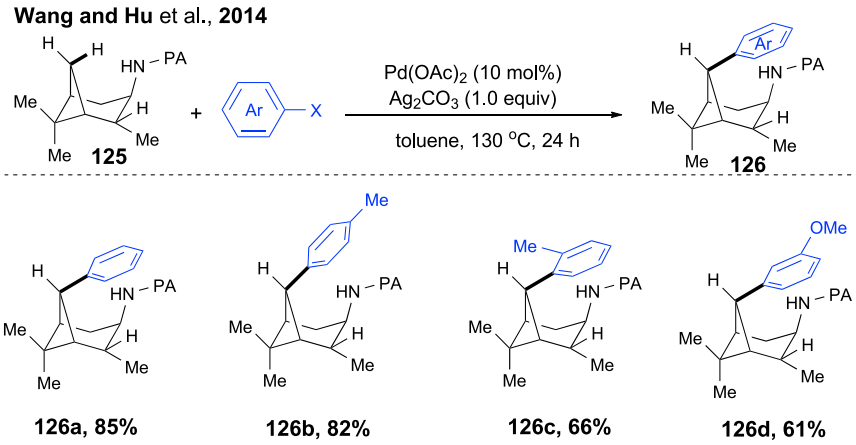
It was found that the scope of aldehydes remained limited under current reaction conditions. Further studies aimed at resolving this challenging issue would greatly improve the substrate scope and the synthetic applicability of these methods. Additionally, more active benzylic γ-C(sp^3)–H functionalization has been achieved in recent years. Yu et al. outlined a Pd(II)-catalyzed C(sp^3)–H arylation reaction of 2-methylbenzaldehydes for the first time using an amino acid ligand, glycine, as a TDG (Scheme 105).[67] This reaction exhibited a broad substrate scope for 2-alkylbenzaldehydes as well as (hetero)aryl iodides with high functional-group compatibility. More importantly, with a chiral amino acid, L-*tert*-leucine as a TDG, the enantioselective γ-C(sp^3)–H arylation of 2-ethylbenzaldehydes could be effectively achieved (Scheme 106). In addition, the methylene C(sp^3)–H bond on a longer side chain could also be functionalized to produce the desired product with a good enantiomeric ratio.

After the above studies, Hu, Kim, Zhang, and Li further reported the Pd(II)-catalyzed C(sp^3)–H arylation reaction of 2-methylbenzaldehydes by using different

Yao and Zhao et al., **2014**



Scheme 83. Pd-catalyzed intramolecular δ-C(sp^3)–H/N–H cyclizations to synthesize pyrrolidines

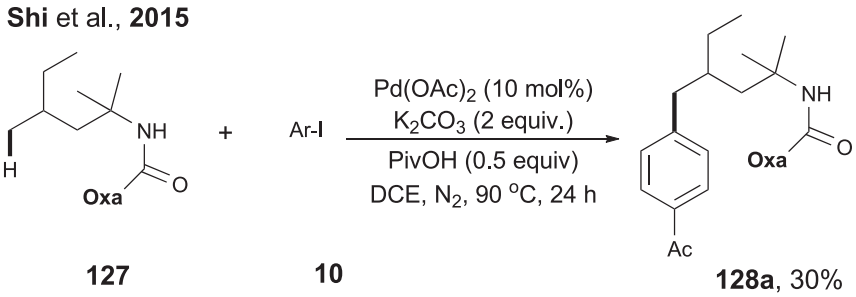


Scheme 84. Pd-catalyzed arylation of 3-pinanamine with aryl halide

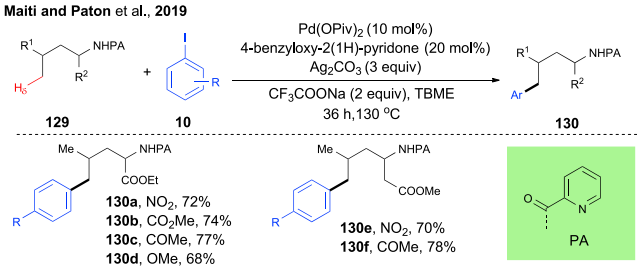
TDGs, including acetohydrazide (**TDG3**), hydroxy amino amide (**TDG4**), and semicarbazide (**TDG6**) (Scheme 107).[68–71] These reactions displayed a broad substrate scope and tolerated a variety of reactive functional groups. In 2020, Bhat and coworkers reported an efficient and straightforward method of TDG-enabled direct γ-C(sp^3)–H arylation of 3-methylheteroarene carbaldehydes (Scheme 107).[72] In the work, (S)-2-amino-3-methylbutanoic acid (L-valine) was used as a transient ligand and a variety of β-benzyl-substituted five-membered heterocyclic carbaldehydes were obtained in good to excellent yields. In spite of the success achieved by introducing more active benzylic- and methyl-heteroarenes C(sp^3)–H bonds, the great restriction to the substrates severely hamper the efficacy and compatibility of the reactions.

C–H enantioselective fluorination

In 2018, Yu and co-workers further disclosed a C(sp^3)–H enantioselective fluorination reaction of 2-ethylbenzaldehydes by using a chiral amino acid-derived diethyl amide as a TDG (Scheme 108).[73] The palladacycle intermediate **159aa** was successfully isolated through the reaction between the pre-formed imine **159** and stoichiometric $Pd(OAc)_2$ at 70°C (Scheme 109). In this study, the bulky amino amide TDG group was found to play a vital role in achieving high enantioselectivity and accelerating C–F reductive elimination. Various substituted 2-(1-fluoroethyl)benzaldehydes were efficiently synthesized with good enantiomeric ratios and moderate to good yields under standard conditions. Unfortunately, 2-ethylbenzaldehydes with electron-donating aromatic substituents did not afford any fluorinated products. For example, only esterification product



Scheme 85. Pd-catalyzed arylation of δ-(sp^3)–H bonds of amides



Scheme 86. Pd-catalyzed δ-C(sp^3)–H arylation of amino acids

158 with very low ee values were obtained when substrate bearing an electron-donating-OMe group. The author speculates that 158 is produced by the quinone methide-type intermediate, which undergoes a nucleophilic addition with $C_6F_5CO_2H$.

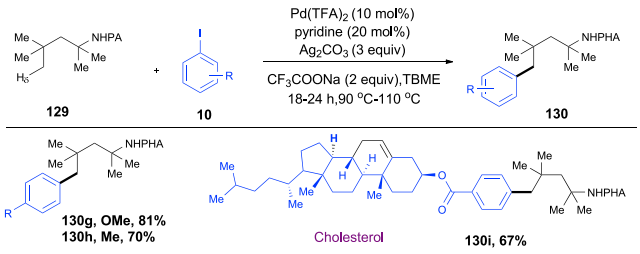
The TDG-assisted transition-metal-catalyzed site-selective C(sp^3)–H arylation and enantioselective fluorination of aldehydes have been reported already. However, these reactions mainly rely on employing benzylic C–H bonds and specific substrates specific substrates with α/β-substitution. Future development pathways involve more γ-C(sp^3)–H functionalization examples of aliphatic aldehydes using various strategies. It is also important to invistigate the enantioselective functionalization of aliphatic aldehydes using chiral amino acids as a TDG.

TDG-assisted γ-C(sp^3)–H functionalization of ketones

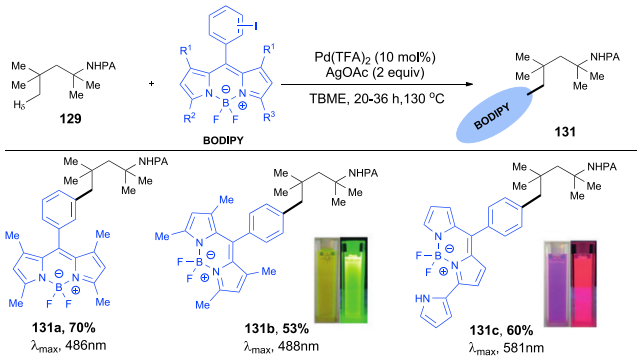
Ketones are key intermediates in chemical synthesis and ubiquitous structural skeletons in numerous natural products, biologically active compounds, pharmaceuticals, and agrochemical molecules.[67] In the past decade, C(sp^3)–H functionalization has emerged as a powerful synthetic strategy to construct and derivatize ketones.[67] Especially, Pd-catalyzed direct β-C(sp^3)–H functionalization of ketones through a thermodynamically favored five-membered metallacycle intermediate has been extensively studied. In contrast, Pd-catalyzed direct γ-C(sp^3)–H functionalization of ketones is particularly rare as this process requires the formation of a less favorable six-membered palladacycle intermediate.

C–H arylation

In 2016, Yu and co-workers demonstrated a single example of Pd(II)-catalyzed γ-C(sp^3)–H arylation of 4,4-dimethylpentan-2-one by using glycine as a TDG (Scheme 110).[67] In the presence of $Pd(OAc)_2$, AgTFA, glycine, and a 3:1 mixture of HFIP and AcOH as solvent, γ-arylated products were obtained in a 61% yield and about 4:1 ratio of mono- to di-olefinated products (Scheme 110). Notably



Scheme 87. Pd-catalyzed δ-C(sp^3)–H arylation of aliphatic amines



Scheme 88. BODIPY labeling of δ-C(sp^3)–H bonds of amines

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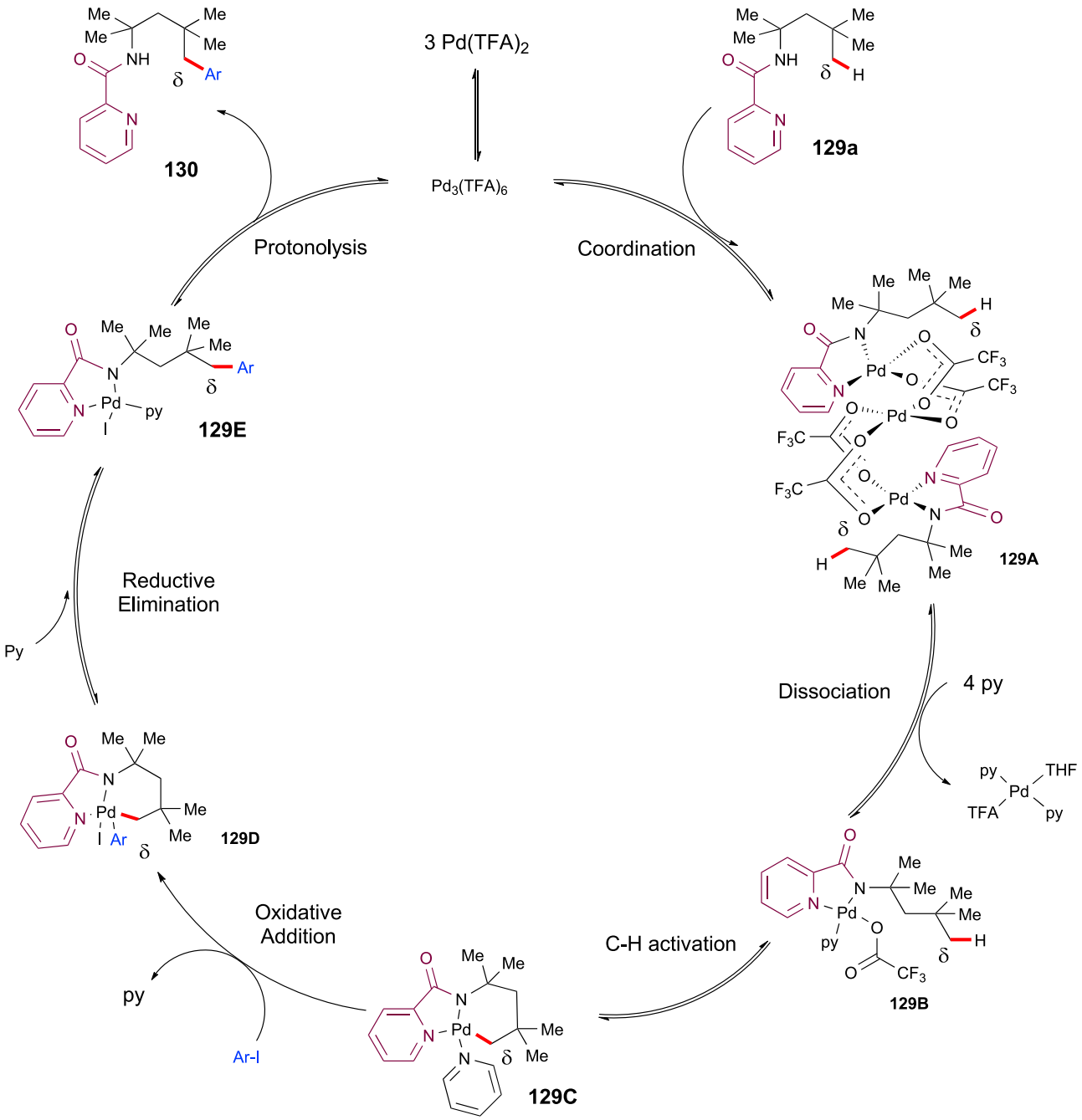
however, for ketones without a β-quaternary center, γ-functionalization was not successful.

The TDG-assisted γ-C(sp^3)–H functionalization of ketones has been generally less explored than that of aldehydes. Only a single example of Pd(II)-catalyzed γ-C(sp^3)–H arylation of 4,4-dimethylpentan-2-one has been achieved with glycine as a TDG so far. Encouraging more efforts to develop additional γ-C(sp^3)–H functionalization examples of ketones via the TDG strategy is needed.

TDG-assisted γ- and δ-C(sp^3)–H functionalization of amines. The TDG-enabled γ-C(sp^3)–H functionalization process has emerged as an effective synthetic strategy and has received significant interest among scientists in chemical research. This method is particularly efficient because it does not require the additional steps associated with the installation and removal of the DGs.[67]

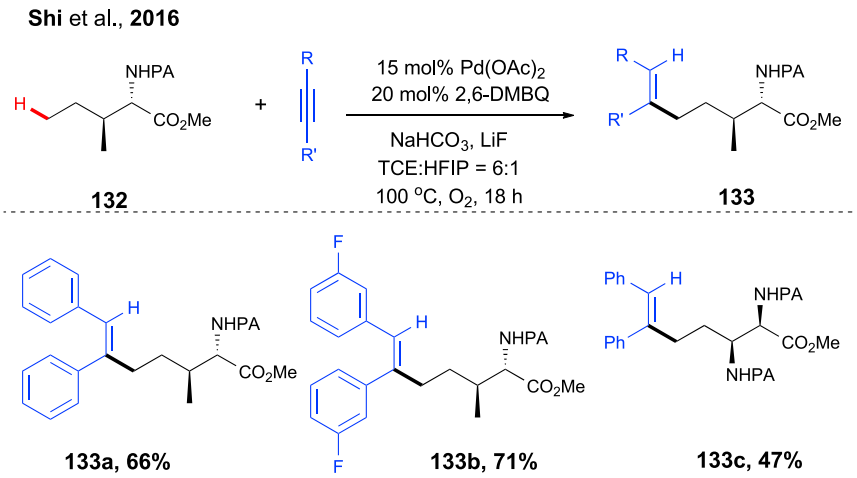
C–H arylation. In 2016, Dong and co-workers disclosed Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic primary amines using stoichiometric quinoline-8-carbaldehyde as ligand and aryliodonium salts as coupling partners (Scheme 111).[74] Concurrently, the Ge group also reported a similar γ-arylation of primary amines using catalytic amounts of glyoxylic acid as a ligand and aryl iodides as a coupling partners (Scheme 112).[75] To gain insight into the reaction mechanism, they synthesized a pyridine derivative of a potential palladacycle derivative and suggested it to be the intermediate in the reaction. Furthermore, they proposed a plausible catalytic cycle (Scheme 113); first, the condensation of primary amine **164** with glyoxylic acid generates the imine intermediate **164A**, which, upon coordination with the Pd catalyst and subsequent ligand exchange, forms the Pd complex **164B**. Cyclopalladation of **164B** produces the [5,5]-bicyclic Pd complex **164C**, probably via a concerted metalation-deprotonation (CMD) process. Then, oxidative addition of Pd intermediate **164C** with an aryl iodide affords the Pd(IV) species **164D**. Finally, reductive elimination of **164D** followed by ligand dissociation yields the γ-arylated product 165 and regenerates transient ligand glyoxylic acid.

Subsequently, the Yu, Kamenecka, and Murakami groups demonstrated the use of either 2-hydroxynicotinaldehyde, salicylaldehyde, or 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde as a transient ligand for this transformation (Schemes 114, 115, and 116).[76–78] Impressively, secondary C(sp^3)–H bonds of primary amines were effectively arylated with 2-hydroxynicotinaldehyde or salicylaldehyde, significantly improving the substrate scope and the synthetic application of the



Scheme 89. Mechanistic for the δ-C(sp^3)–H arylation of substrate 129a

method. In 2018, Young and co-workers successfully achieved the same process using CO_2 in the form of dry ice as a TDG (Scheme 117).[79] In this reaction, it was hypothesized that carbon dioxide reversibly reacts with aliphatic amines to produce carbamates that coordinate with the Pd catalyst, upon which the carbamate salt intermediate undergoes an irreversible CMD step to give rise to a cyclopalladated intermediate. The primary KIE value of 3.2 was observed in the intermolecular competition reaction, indicating that the C–H cleavage of the amines is involved in the rate-determining step. In addition, Bull and

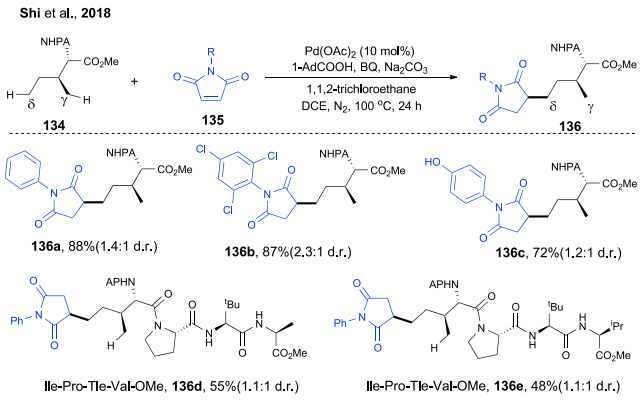


Scheme 90. Pd-catalyzed δ-C(sp^3)–H alkenylation of aliphatic amines

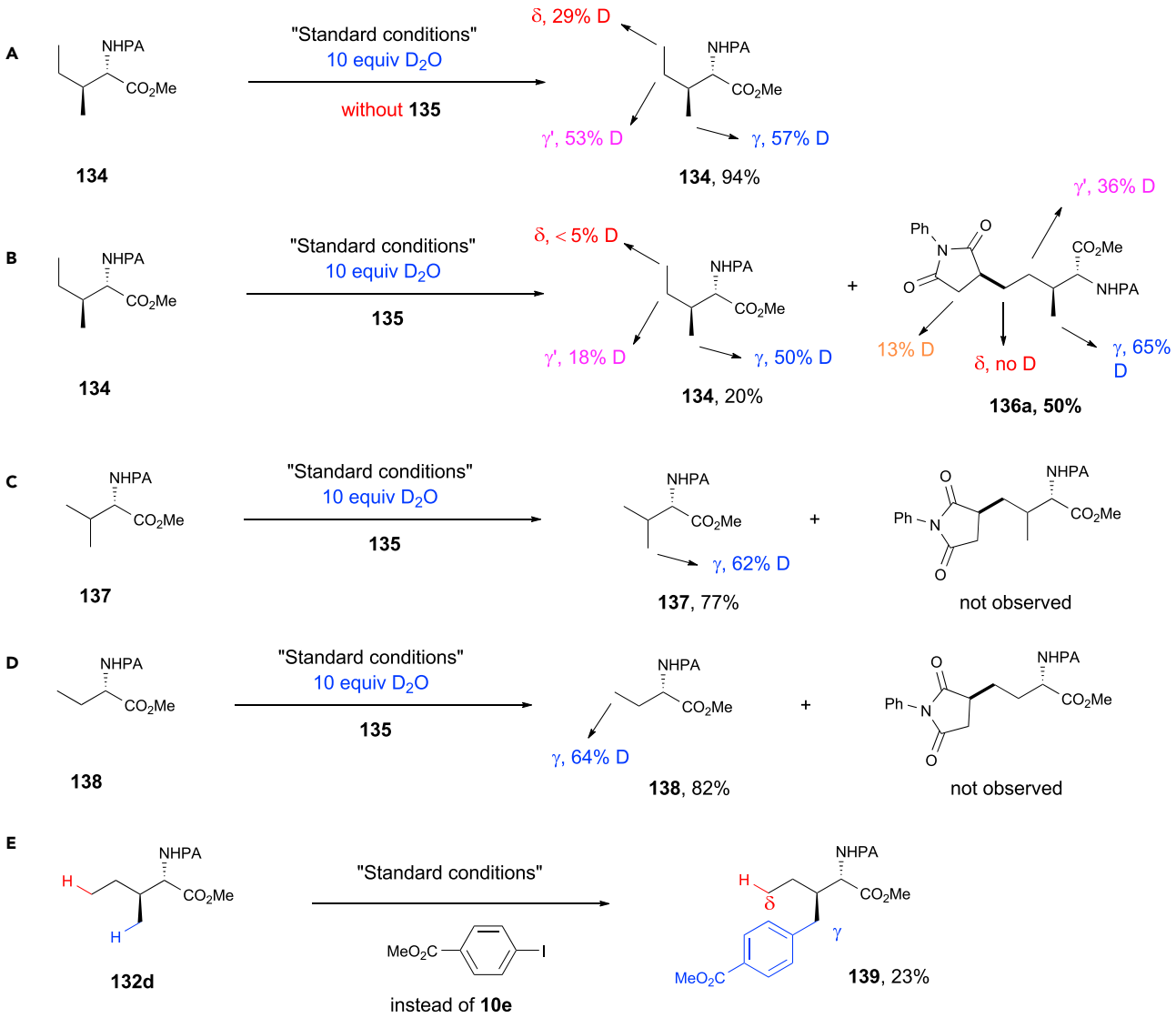
co-workers developed a commercially available alkyl acetal as a novel TDG for the γ-arylation of amines (Scheme 118).[80] A wide range of aryl iodides were tolerated under these given conditions.

C–H heteroarylation. In 2018, Yu and co-workers described a Pd(II)-catalyzed γ-methylene C(sp^3)–H heteroarylation of aliphatic amines by using 5-(trifluoromethyl)pyridin-2-ol(**L16**) as an external ligand in combination with TDG10 (Schemes 119 and 120).[81] This pyridine ligand plays a critical role in the reaction as it coordinates with, and effectively stabilizes the Pd catalyst, and lowers the activation energy of the C–H bond-cleavage step. Using this method, a wide range of medicinally important heteroaryl iodides and previously unreactive heteroaryl bromides could effectively react with aliphatic amines to produce the corresponding heteroarylated products in good yields.

C–H acyloxylation and alkoxylation. In 2020, the same group developed Pd-catalyzed γ-C(sp^3)–H acyloxylation and alkoxylation of free amines by using *N*-fluoro-2,4,6-trimethylpyridiniumtetrafluoroborate as a [F$^+$] bystanding oxidant and 2-hydroxylnicotinaldehyde as the TDG (Schemes 121 and 122).[82]



Scheme 91. Pd-catalyzed δ-C(sp^3)–H alkylation of amino acids and peptides



Scheme 92. Mechanistic investigations of Pd-catalyzed site-selective δ-C(sp^3)–H alkylation of amino acids and peptides with maleimides using PA as a DG

Standard conditions: substrate (0.10 mmol), Pd(OAc)2 (10 mol %), 1-adamantanecarboxylic acid (0.2 equiv), BQ (0.3 equiv), Na_2CO_3 (2.0 equiv), followed by addition of anhydrous 1,1,2-trichloroethane (1.0 mL), 100°C, 24 h.

(A) The substrate **134** has been deuterated under standard reaction conditions in the absence of **135**.

(B) In contrast, **136a** was obtained in a 50% yield in the presence of **135**.

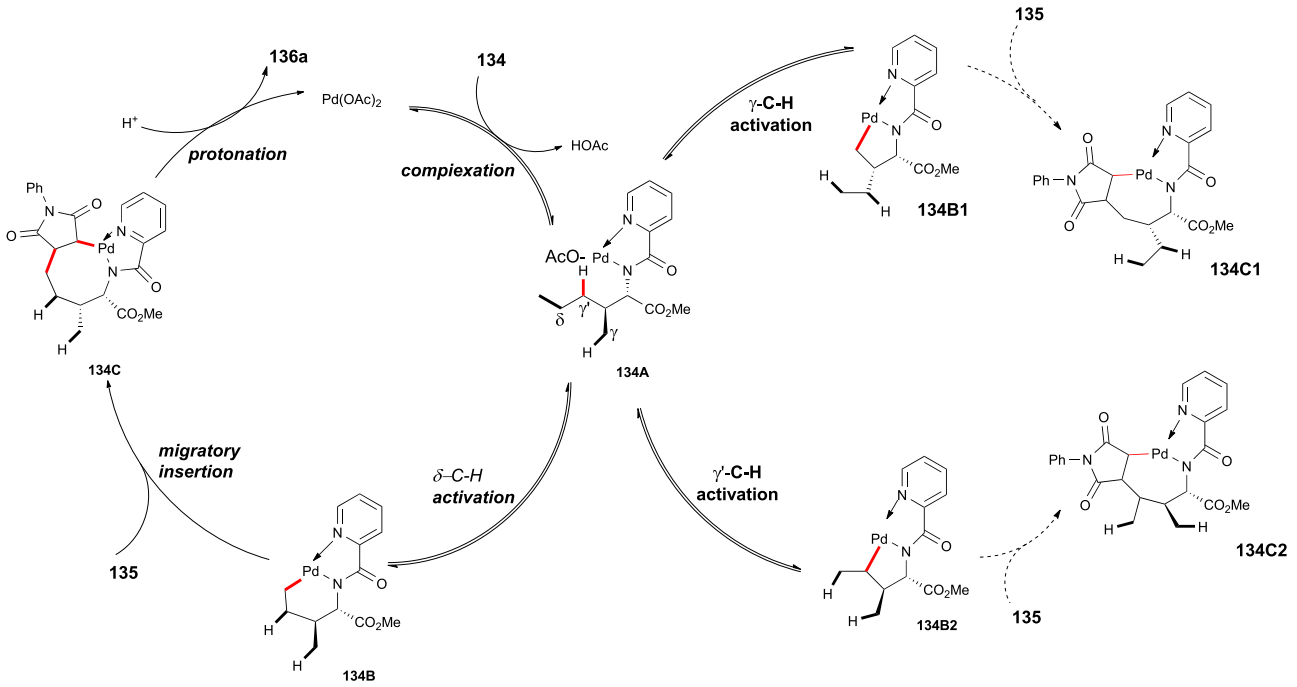
(C) The γ-alkylation product did not appear under **137** as a substrate.

(D) The γ-alkylation product did not appear under **138** as a substrate.

(E) The γ-arylated product **139** was detected when methyl 4-iodobenzoate was instead of maleimide **135**.

C–H arylation. Recently, the TDG strategy was developed for the γ-C(sp^3)–H arylation of secondary amines. In 2018, the Young group achieved γ-C(sp^3)–H arylation of secondary amines using CO_2 as a TDG group (Scheme 123).[79] It is noteworthy that this reaction displays excellent chemoselectivity. For a variety of benzylic amines, the reaction takes place exclusively at the γ-C(sp^3) position rather than on the C(sp^2)–H bond on the arene.

C–H arylation. In 2018, Yu group demonstrated the Pd(II)-catalyzed δ-arylation of alkyl amines with aryl iodides as the coupling partners by using the TDG strategy (Scheme

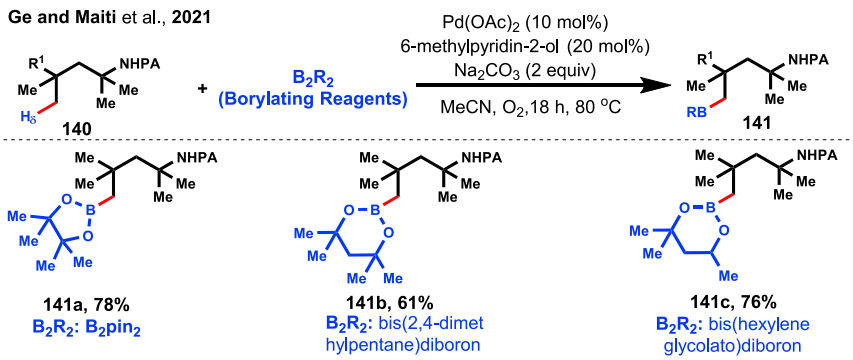


Scheme 93. A plausible mechanism for the formation of 136a

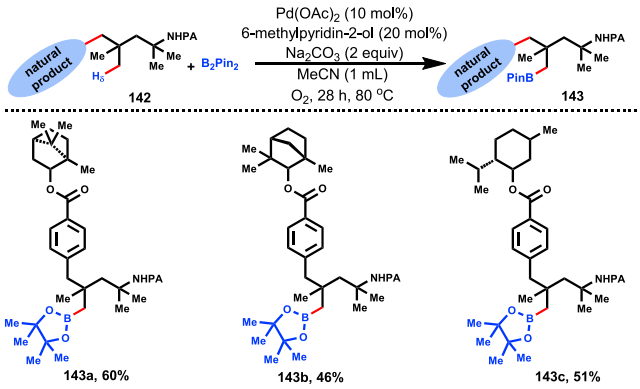
124).[81] In this reaction, the TDG coordinates with Pd(II) via the kinetically favored five-membered chelate, hence activating the δ-C(sp^3)–H bonds. TDG11 was used as a TDG and 5-nitropyridin-2-ol was employed as an external ligand. A series of protecting group free alkyl amines can react with a vast variety of aryl iodides to supply the desired δ-C(sp^3)–H arylation products with moderate to good yields and diastereoselectivity.

Dong developed the Pd-catalyzed δ-arylation of 2-*tert*-butyl-aniline-derived substrates by using quinoline-8-carbaldehyde as a TDG and diaryl iodonium salts as coupling partners (Scheme 125).[74]

Although the TDG-assisted γ- and δ-C(sp^3)–H functionalization of aliphatic amines has developed rapidly, the scopes of the reactions are limited, and the Pd-catalyst loading (10–15 mol %) is costly. Using 2-pyridone-based ligands as strongly coordinating X-type ligands promotes the formation of reactive Pd(II) precursors and



Scheme 94. Pd-catalyzed δ-C(sp^3)–H borylation of aliphatic amines

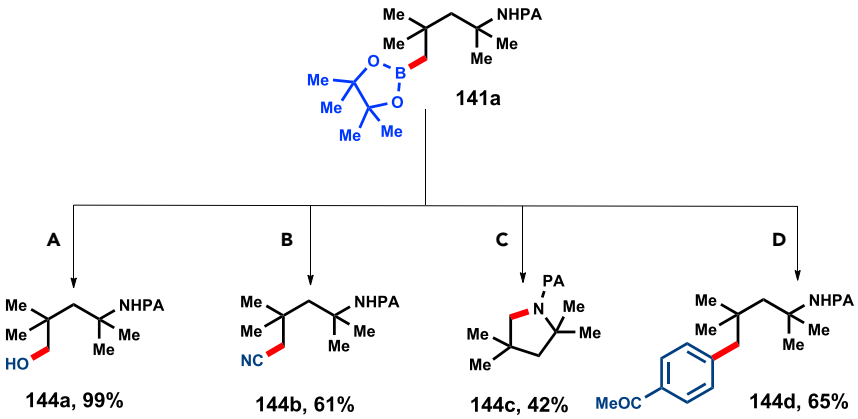


Scheme 95. δ-Borylation of aliphatic amines containing natural products

accelerates C–H activation in many cases. Further advances in the TDG-assisted γ- and δ-C(sp^3)–H functionalization of aliphatic amines requires the development of additional innovative and efficient approaches and the further extension of the reaction scopes.

NATIVE-FUNCTIONAL-GROUP-DIRECTED γ- AND δ-C(sp^3)–H FUNCTIONALIZATION

Despite the improved reactivity obtained by incorporating well-designed directing auxiliaries, the requirement of including additional steps for the association of the DGs and their subsequent removal after the desired operation has taken place severely hampers the efficacy and compatibility of such reactions. A preferred alternative solution is the utilization of TDGs that are both installed and removed *in situ*. Even more preferred would be a method that does not need any auxiliaries or TDGs altogether. The native functional group present in the aliphatic molecules (acid, amine, etc.) can serve as the chelating group for site-selective C(sp^3)–H functionalization, providing better step and atom economy. Such strategy was considered an



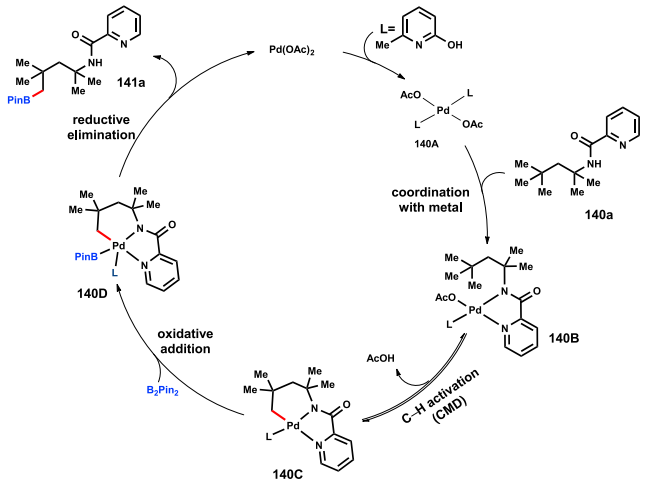
Scheme 96. Synthetic transformations of the δ-borylated amines

(A) Oxidation-H_2O_2, aqueous buffer (pH 7), THF, RT, 2 h.

(B) Cyanation-**141a** (0.1 mmol), CuCN (0.1 mmol), K_2CO_3 (0.30 mmol), and DMF (2 mL), 60°C, 4 h.

(C) *N*-Heterocylization-**141a** (0.1 mmol), O_2 (ballon), $Cu(OAc)_2$ (10 mol %), and CH_2Cl_2 (1 mL), 40°C, 12 h.

(D) Suzuki reaction-**141a** (0.1 mmol), $Pd(OAc)_2$ (10 mol %), X-Phos (40 mol %), 1-(4-iodophenyl) ethan-1-one (0.2 mmol), K_3PO_4 (2 equiv), toluene (2 mL), and N_2,120°C, 30 h.

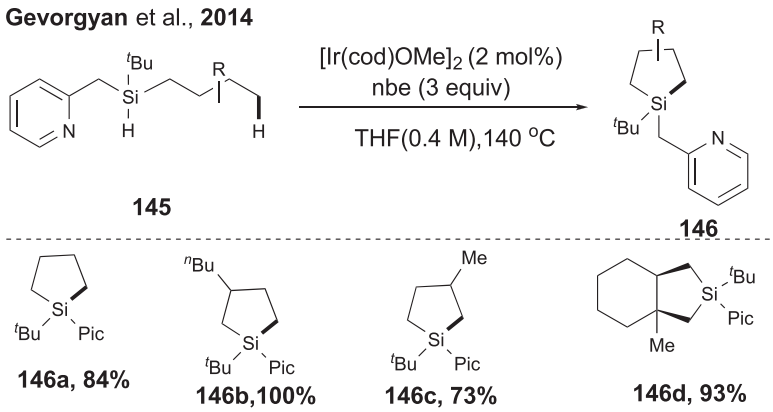


Scheme 97. Plausible reaction mechanism for the formation of 141a

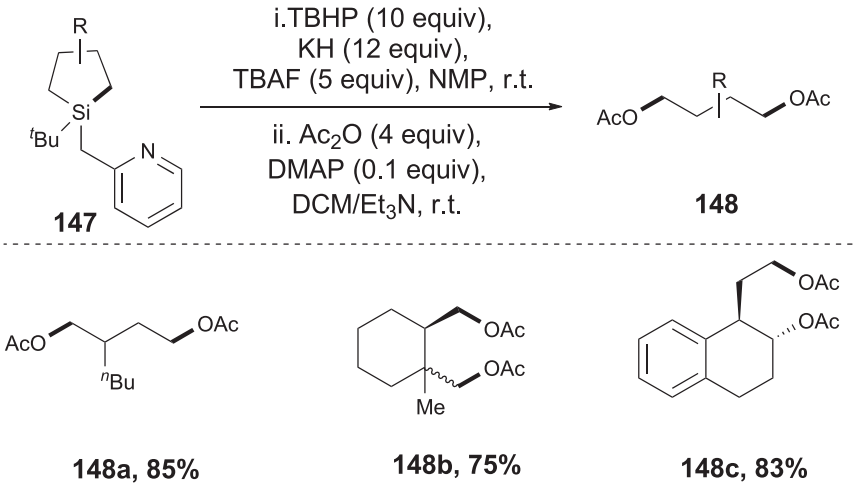
ideal approach that would make C(sp^3)–H functionalization reactions more efficient and practical for application in organic synthesis chemistry. In recent years, transition-metal-catalyzed native-functional-group-directed γ- and δ-C(sp^3)–H functionalization has progressed to a great extent in aliphatic compounds.

Carboxy-group-directed γ-C(sp^3)-H functionalization

Although the conversion of carboxylic acids to their corresponding amides significantly enhances their directing abilities, such conversion requires additional installation and removal steps, compromising the overall efficiency of the process. Therefore, there has been a need for the development of a more direct method that utilizes carboxylic acids as immediate DGs. Over the past decade, the direct β-C(sp^3)–H functionalization of the free carboxylic acid has been rapidly developed with a five-membered palladacycle.[1,83–86] In contrast, the corresponding direct γ-C(sp^3)–H functionalization remains underdeveloped. The direct γ-C(sp^3)–H functionalization of the free carboxylic acid requires the formation of the thermodynamically less stable six-membered metallacycle intermediate. Hence, the use of suitable ligands and the careful fine-tuning of the reaction conditions are required to overcome this issue.



Scheme 98. Ir-catalyzed C–H silylation of an unactivated δ-C(sp^3)–H bond

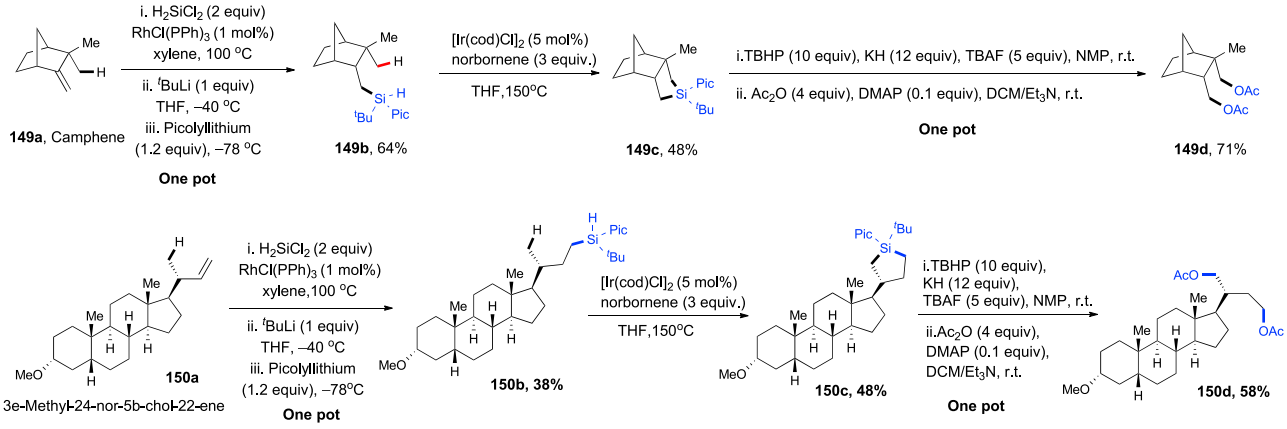


Scheme 99. Conversion of silacycle intermediates 147 into 1,4-diol derivatives 148

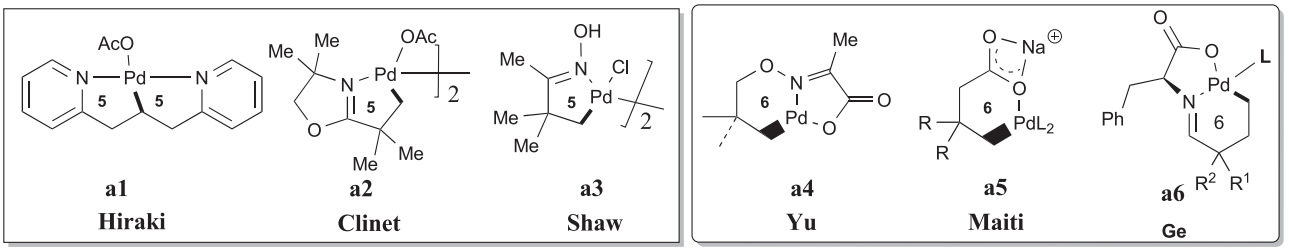
C–H arylation

In 2019, the Maiti group reported a direct ligand-enabled Pd-catalyzed γ-C(sp^3)–H arylation of free aliphatic acid.[87] N–Ac–Gly–OH (**L17**; Scheme 126) was found to be the most effective ligand for this transformation, whereas other ligands (such as, pyridine-, quinoline-, and phosphine-based ligands) did not prove effective. This regioselective functionalization displayed broad substrate scope and high functional-group tolerance under standard reaction conditions. Notably, a variety of natural product containing aryl iodides, including menthol and fenchyl alcohol iodides, could be effectively utilized as coupling partners (Scheme 127). A plausible mechanism is depicted in Scheme 128; first, the aliphatic acid coordinates to the Pd species, and the resulting complex undergoes alkali-metal-ion-assisted γ-C–H bond activation to form the six-membered palladacycle intermediate **181A**. Then, oxidative addition of the Pd intermediate **181A** with the aryl iodide produces the Pd(IV) species **181B**. Finally, reductive elimination of **181B** generates the γ-arylated product **182** and reproduces the Pd catalyst.

Concurrently, the Shi group disclosed Pd-catalyzed ligand-enabled γ-C(sp^3)–H arylation of *tert*-leucine and its derived peptides via a thermodynamically less stable



Scheme 100. 1,4-Oxygenation of alkene-containing natural products and derivatives

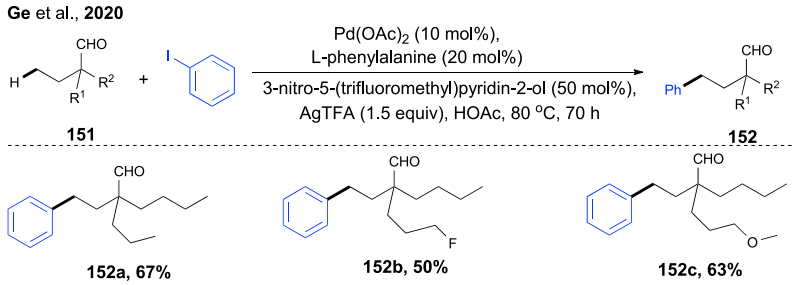


Scheme 101. Examples of five- and six-membered-ring Pd intermediates

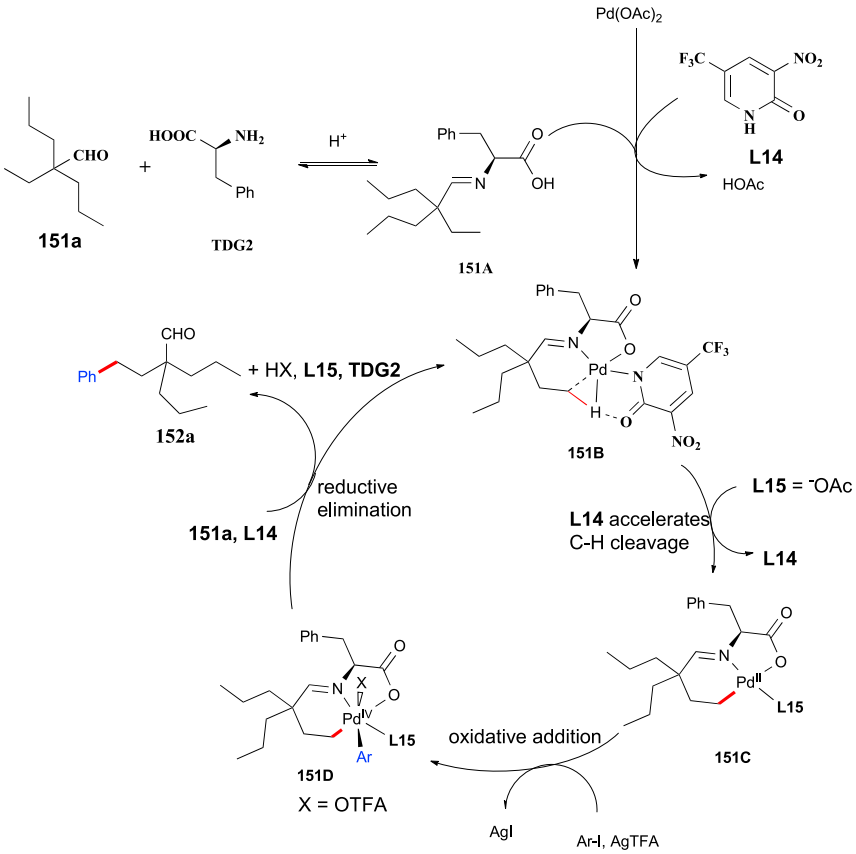
six-membered palladacycle intermediate (Schemes 129 and 130).[88] The amino acid ligand plays an important role in promoting the reaction. After screening a series of ligands, Ac–Tle–OH was proven to be most effective. Both electron-withdrawing and electron-donating group-substituted aryl iodides were compatible with this reaction and were found to afford the desired products in good yields. Notably, late-stage C(sp^3)–H functionalization of peptides was successfully accomplished using this strategy.

C–H olefination

In 2020, the same strategy was further utilized by the Gemmeren group, who developed ligand-enabled γ-C(sp^3)–H olefination of free carboxylic acids via a less favored six-membered palladacycle (Scheme 131).[89] *N*-Ac-β-alanine proved to be the optimal ligand, whereas other ligands such as pyridone, pyridine, anthranilic acid derivatives, and other amino acid-derived ligands provided compromised results. Although the yields were modest and the diastereoselectivity was moderate, this reaction exhibited a broad substrate scope for both free carboxylic acids and olefins. However, carboxylic acids without a quaternary center at the β-position were not compatible because of the absence of the Thorpe-Ingold effect. The results of the competition and in parallel experiments revealed that the C(sp^3)–H bond cleavage is the rate-limiting step of this process. In a tentatively proposed mechanism (Scheme 132), the aliphatic acid coordinates with the Pd(II) species. Subsequently, an alkali metal ion assists γ-C–H bond activation forming a six-membered palladacycle intermediate **187B**, which then undergoes a sequence of ligand exchange, carbopalladation, β-H elimination, and de-coordination to yield the product in its non-cyclized form (**188**-open). Finally, upon cyclization, the lactone product 188 is formed. Subsequently, the Yu group also reported a Pd-catalyzed γ-C(sp^3)–H olefination of free carboxylic acids by using Ac–Phe–OH as a key ligand (Scheme 133).[20]



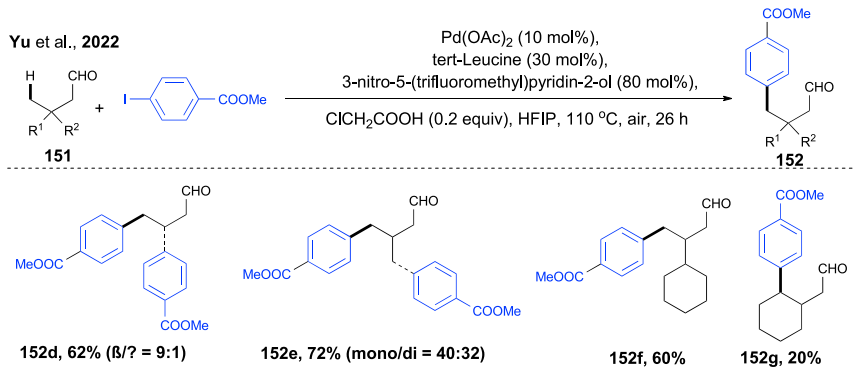
Scheme 102. Pd-catalyzed site-selective γ-C(sp^3)–H arylation reaction of aldehydes with aryl iodides



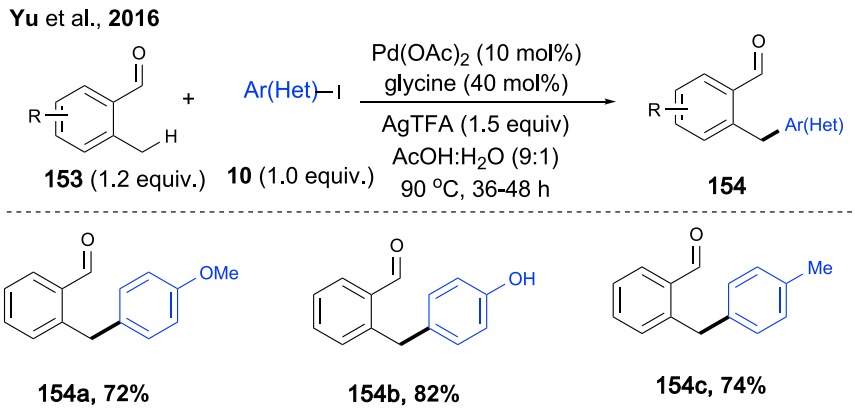
Scheme 103. Plausible reaction mechanism for Pd-catalyzed γ-C(sp^3)–H arylation of aldehydes

C–H hydroxylation

Lactones widely exist in a variety of bioactive natural products and pharmaceuticals. Transition-metal-catalyzed C(sp^3)–H functionalization of acids proved to be an effective method for constructing lactone (Scheme 134).[90–93] In 2001, Sames and co-workers reported the first platinum-catalyzed selective hydroxylation of α-amino acids in water. Using this strategy, five-membered lactones were obtained, albeit in poor yields.[90] In 2006, the Chang group expanded the substrate scope to encompass 2-methylbenzoic acids, forming benzolactones with moderate yields.[91] In 2011, the Martin group reported Pd-catalyzed C(sp^3)–H lactonization of



Scheme 104. Pd-catalyzed site-selective γ-C(sp^3)–H arylation of primary aldehydes without α-substitution



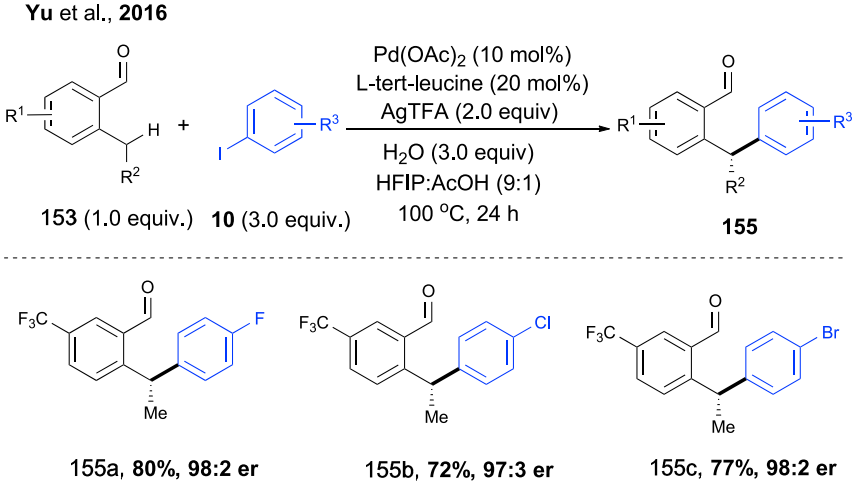
Scheme 105. Pd-catalyzed benzylic C(sp^3)–H arylation of aldehydes

2-methylbenzoic acids by using commercially available N-protected amino acids as ligands to produce the corresponding benzolactones in moderate to good yields.[92] Further reports by Yu expanded the scope of this transformation to include 2-methylbenzoic acid and 3-bromo-2-methylbenzoic acid using molecular oxygen as oxidant.[93]

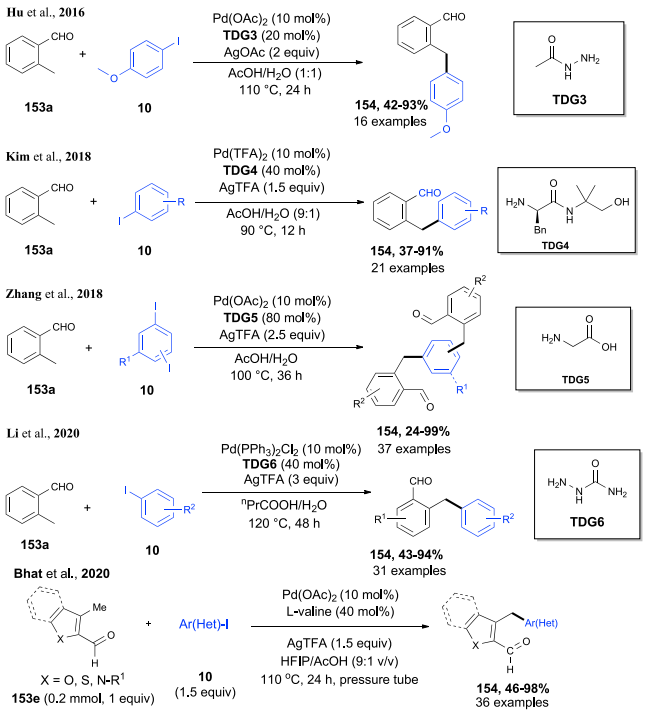
The transition-metal-catalyzed γ-C(sp^3)–H arylation, olefination, and hydroxylation of free aliphatic acids have been developed recently. However, these reactions rely heavily on the use of specific biased substrates that lack accessible proximal C–H bonds, and hence non-quaternary aliphatic acids are almost ineffective in these protocols. Further advances in the carboxy-group-directed γ-C(sp^3)–H functionalization require the exploration of more influencing external ligands design and subsequent extension of the scopes of the reactions to encompass non-quaternary aliphatic acids.

Free-amine-directed γ-C(sp^3)–H functionalization of primary amines

Monoamine-Pd complexes were found effective at catalyzing aliphatic γ-C(sp^3)–H bond functionalization of aliphatic amines through Pd-assisted C–H cleavage.



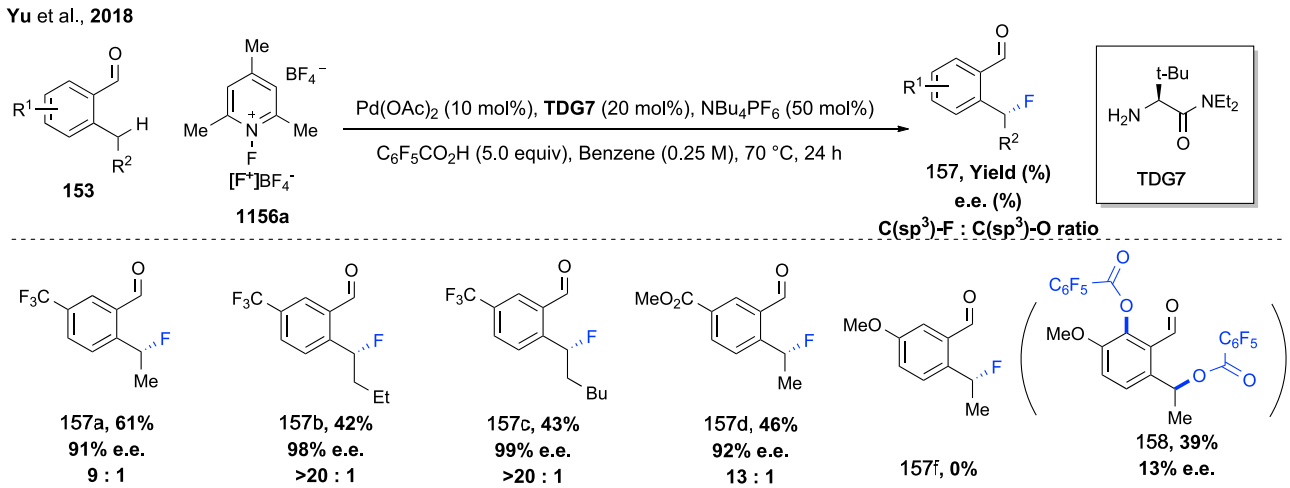
Scheme 106. Pd-catalyzed enantioselective benzylic C(sp^3)–H arylation of aldehydes



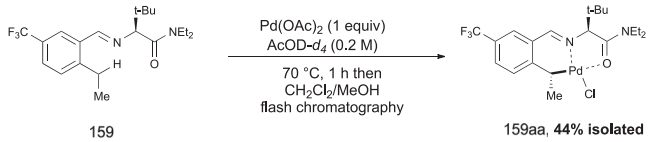
Scheme 107. Pd-catalyzed benzylic C(sp^3)–H arylation of aldehydes using a TDG

C–H acetoxylation

In 2017, Shi and co-workers disclosed NH_2-directed γ-acetoxylation of primary aliphatic amines with $PhI(OAc)_2$ as an oxidant and acetic acid as a solvent (Scheme 135).[94] Protonation of amines plays an important role in this study as it enhances their stability toward oxidative and electrophilic reagents, which in turn improves the amino group tolerance under harsh reaction conditions. Notably, the chemoselectivity of the reaction was also enhanced upon protonation. Substrates containing various functional groups were tolerated and afforded desired the products in moderate yields. A plausible reaction mechanism was proposed; first, under acidic



Scheme 108. Pd-catalyzed enantioselective benzylic C(sp^3)–H fluorination of aldehydes

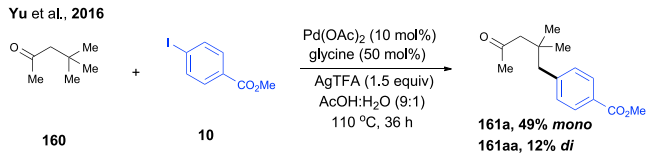


Scheme 109. Synthesis of bicyclic palladacycle 159aa

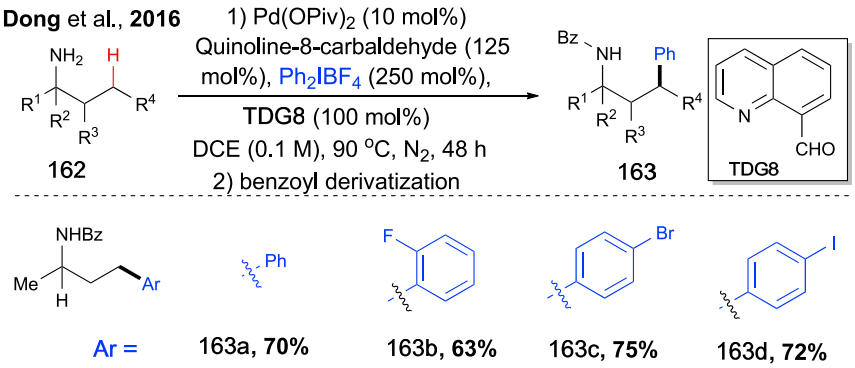
conditions, the primary amine coordinates with the Pd(II) catalyst to generate the intermediate **190A**, which then undergoes C–H bond activation to give rise to the five-membered palladacycle **190B**. Subsequently, the oxidative addition of **190B** with $PhI(OAc)_2$ forms the Pd(IV) species **190C**. Then, reductive elimination of **190C** generates the Pd(II) intermediate **190D**. Finally, upon *in situ* protection of the amino group, the desired product is obtained (Scheme 136).

C–H arylation

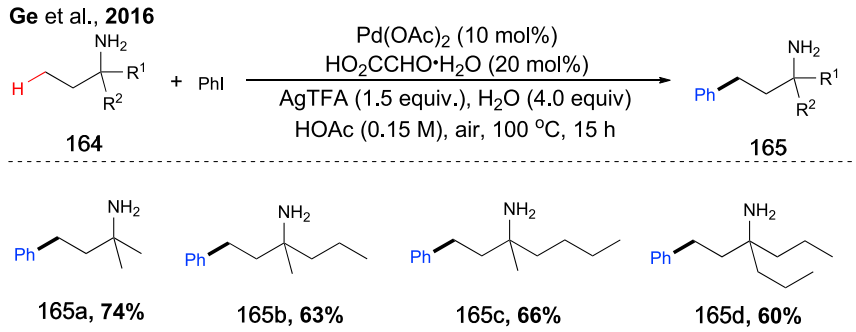
In 2019, Yao and co-workers reported a Pd-catalyzed NH_2-directed γ-C(sp^3)–H arylation of α-amino esters using diaryliodonium triflates as arylation reagents (Scheme 137).[95] Ag_2O was employed as an additive as it was found to enhance the reaction results. In this study, a primary KIE of 5.0 was observed, implying that the C–H cleavage step is involved in the rate-determining step. A plausible mechanism was proposed (Scheme 138); first, a silver-amine complex **191A** is generated by the combination of the AgOAc complex with the amine. Subsequently, complex **191A** reacts with $Pd(OAc)_2$ to form the Pd(II)-amine complex **191B**, which then undergoes C–H bond activation to afford the five-membered palladacycle **191C**. Subsequently, AgOAc-facilitated oxidative addition of the Pd intermediate **191C** with Ar_2IOTf (OTf, trifluoromethanesulfonate) forms the Pd(IV) species **191D**, which upon reductive elimination produces the desired product. The same group further developed Pd-catalyzed native amine-directed γ-C(sp^3)–H arylation of amino acids and peptides using aryl iodides as arylation reagents



Scheme 110. Pd-catalyzed γ-C(sp^3)–H arylation of 4,4-dimethylpentan-2-one



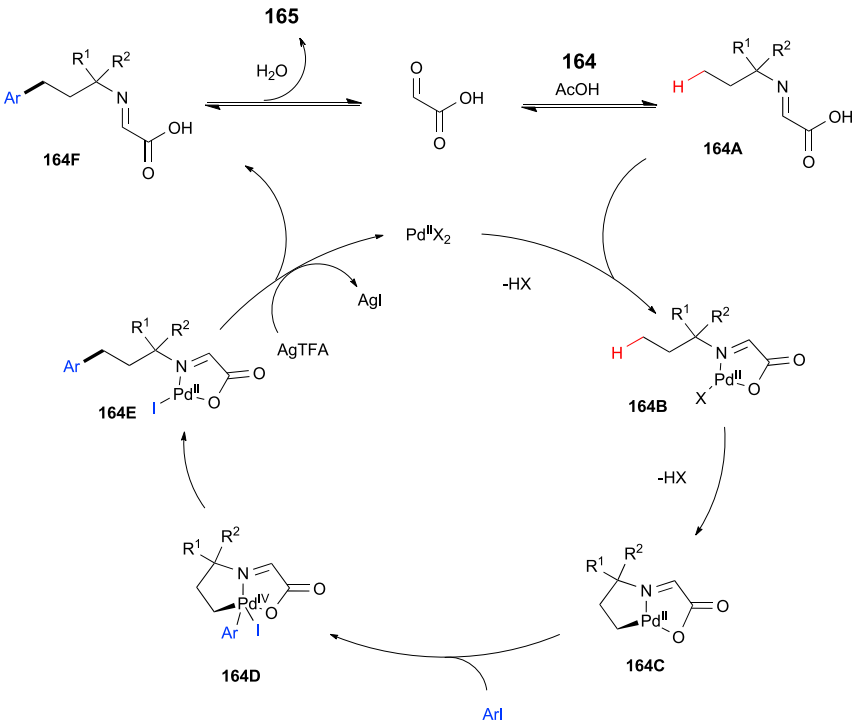
Scheme 111. Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic primary amines with quinoline-8-carbaldehyde as a ligand



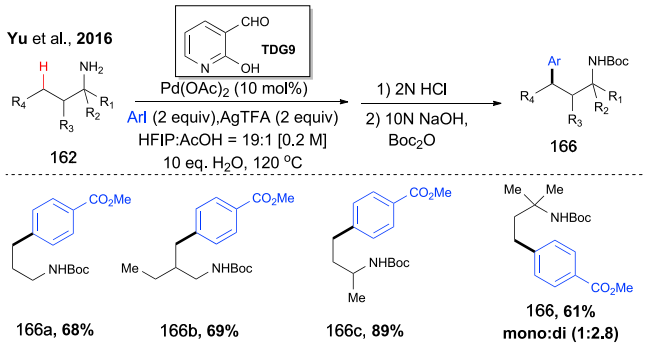
Scheme 112. Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic primary amines with glyoxylic acid as a ligand

(Scheme 139).[96] The authors found that the use of AgOAc and TfOH as additives significantly improved reactivity. Notably, this reaction displayed evident applicability as D-(+)-menthol, and the fluorescent 1,8-naphthalimide was successfully installed onto dipeptides by this method. Additionally, the same technique could be used to synthesize the trigeminal peptide (Scheme 140). Although the substrate scope of this approach was limited at the time, the range of amine substrates has been expanded since. Under modified reaction conditions, free-amine-directed γ-C(sp^3)–H arylation of a variety of primary aliphatic amines was successfully achieved (Scheme 141).[97]

In 2020, the Yu group developed a Pd-catalyzed enantioselective γ-C(sp^3)–H functionalization reaction of cyclopropylmethylamines (Scheme 142).[98] Upon



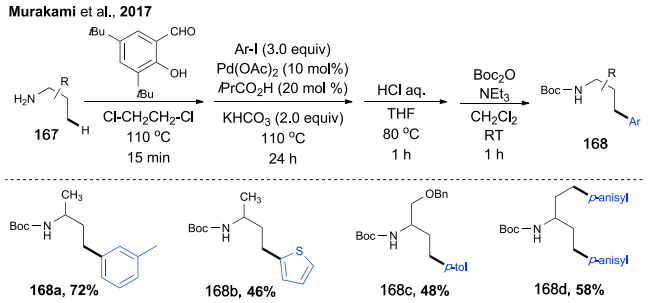
Scheme 113. A plausible reaction mechanism for Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic primary amines



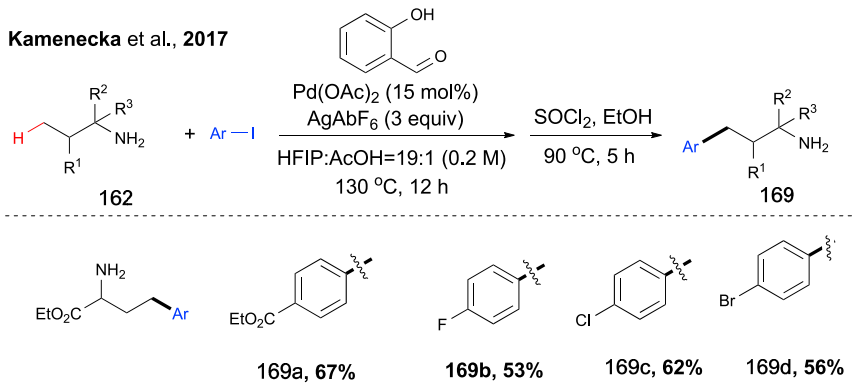
Scheme 114. Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic primary amines with 2-hydroxynicotinaldehyde as a ligand

coordination of the thioether ligand to the Pd catalyst, the requisite mono(amine)-Pd(II) intermediate is formed, enabling the enantioselective C–H activation of the amine substrates. A series of chiral γ-arylated/γ-olefinated free amines, and γ-lactams were obtained in moderate to good yields.

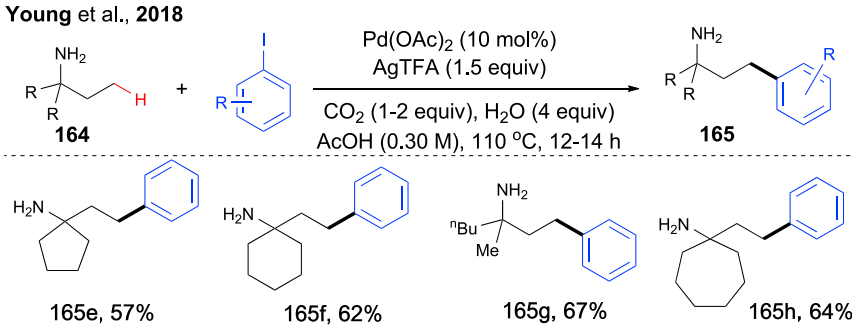
The NH_2-directed γ-C(sp^3)–H arylation and acetoxylation of primary amines have already been accomplished. However, these reactions are based on the blocking strategy via the use of structurally specific substrates, leading to limited scope of substrates. Further advances in the free-amine-directed γ-C(sp^3)–H functionalization of primary amines require the development of effective external ligands



Scheme 115. Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic primary amines with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde as a ligand

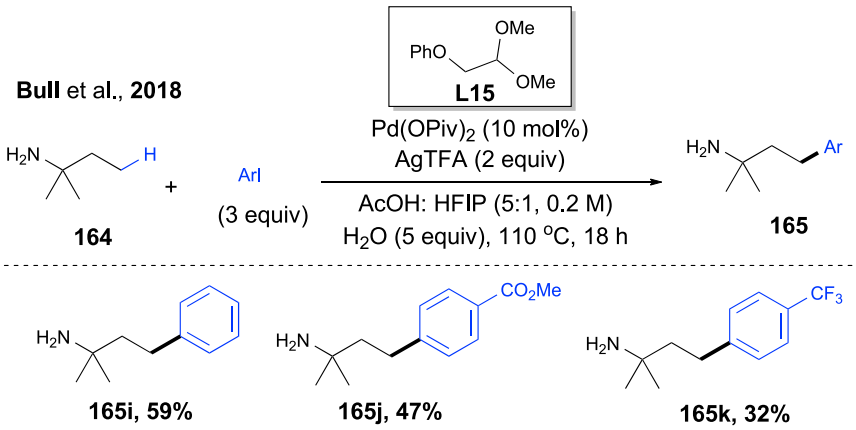


Scheme 116. Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic primary amines with salicylaldehyde as a ligand

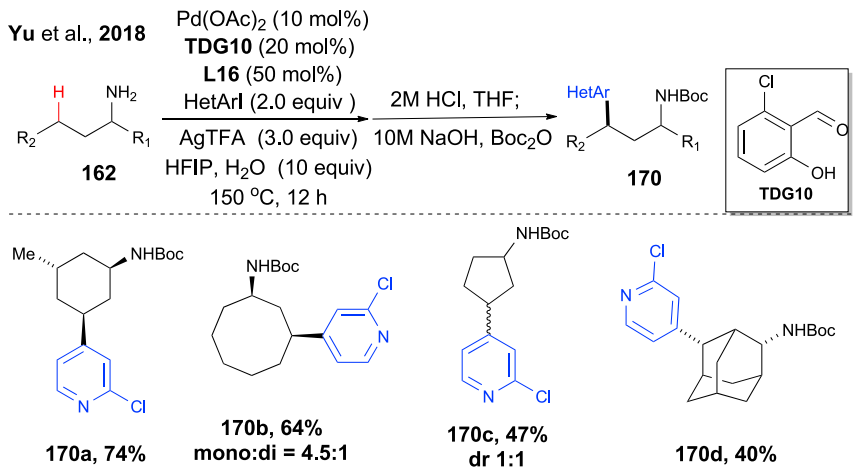


Scheme 117. Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic amines using CO_2 in the form of dry ice as a TDG

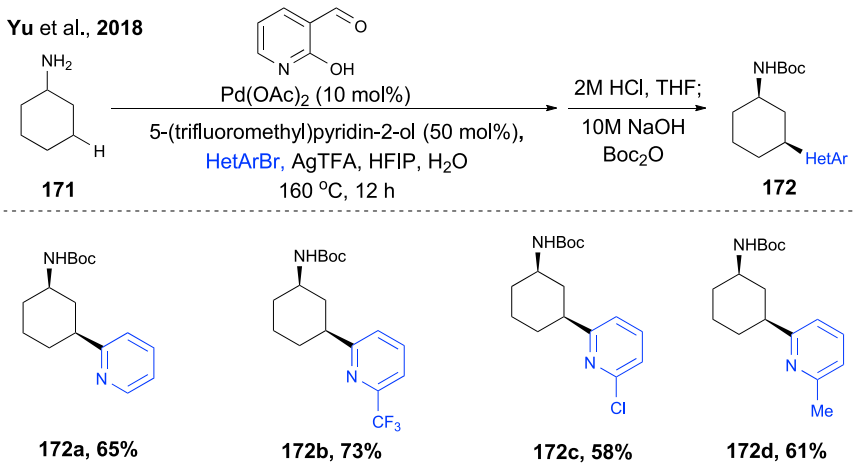
and further extension of the scopes of the reactions. Efforts toward the development of efficient catalytic enantioselective functionalization methodologies are also needed.



Scheme 118. Pd-catalyzed γ-C(sp^3)–H arylation of aliphatic primary amines with alkyl acetals as a ligand



Scheme 119. Pd(II)-catalyzed γ-methylene C(sp^3)–H heteroarylation of aliphatic amines



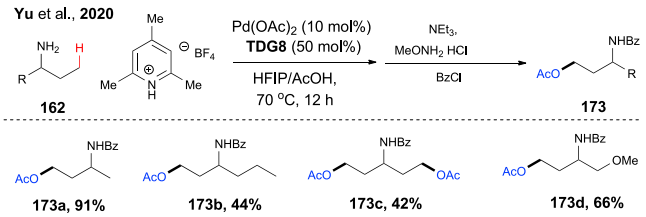
Scheme 120. Pd(II)-catalyzed γ-methylene C(sp^3)–H heteroarylation of cyclohexanamine

γ-C(sp^3)–H functionalization of secondary amines

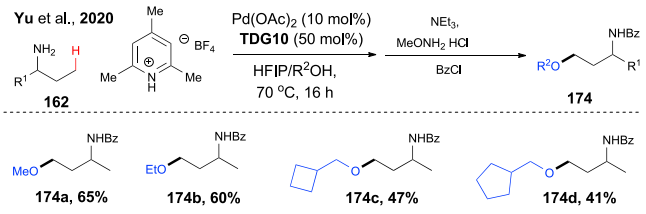
Secondary amines are important substrates in C–N bond-forming reactions. Considerable efforts have been devoted to the construction and the derivatization of these molecules. Among various synthetic methods, transition-metal-catalyzed C(sp^3)–H bond functionalization of secondary amines has become one of the most efficient approaches.[4]

C–H acetoxylation

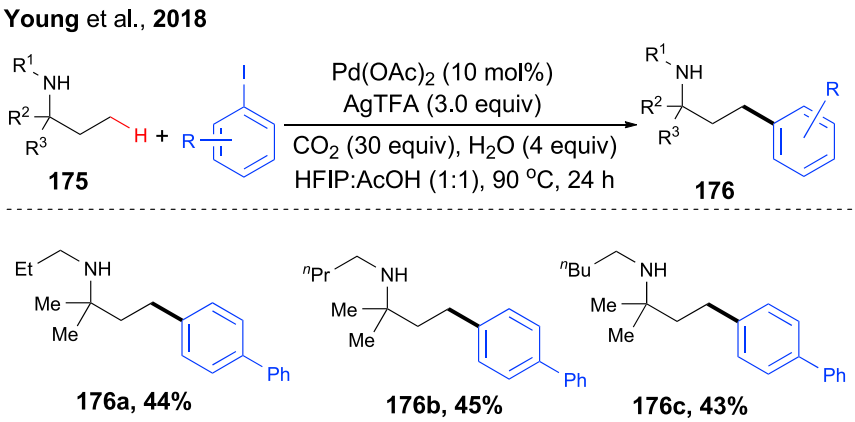
In 2015, the Gaunt group outlined a Pd-catalyzed direct γ-C(sp^3)–H functionalization reaction of amino alcohols (Schemes 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, and 156).[99] Using PhI(OAc)$_2$ as an oxidant, the reaction selectively produced the γ-acetoxylated products in satisfactory yields (Scheme 143). The reaction proved tolerant to a broad range of functional groups, including alkyl, aryl, protected hydroxyl, carbonyl functional groups,



Scheme 121. Pd-catalyzed γ-C(sp^3)–H acyloxylation of free amines

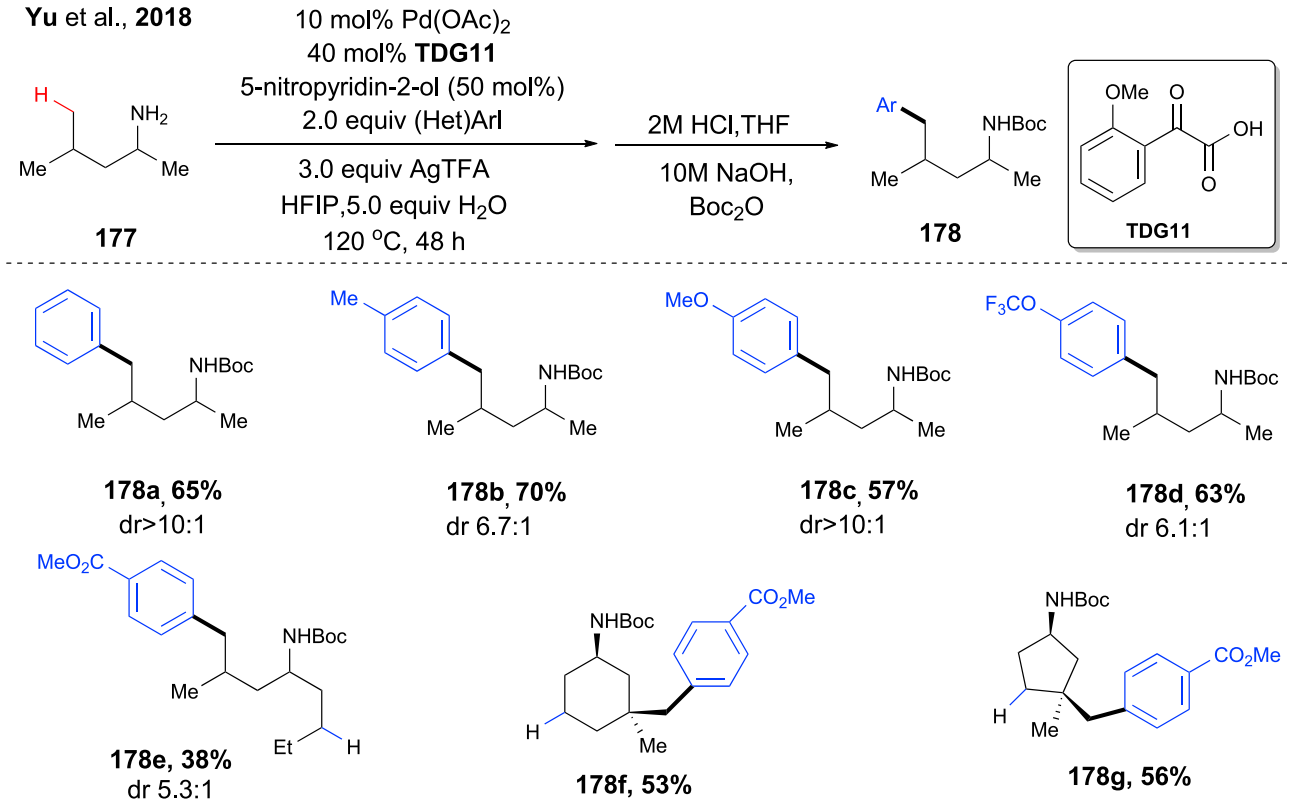


Scheme 122. Pd-catalyzed γ-C(sp^3)–H alkoxylation of free amines

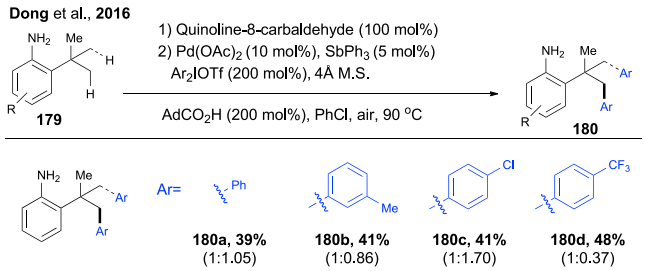


Scheme 123. Pd-catalyzed γ-C(sp^3)–H arylation of secondary amines using CO_2 in the form of dry ice as a transient ligand

and nitrogen-containing heterocycles. In 2019, the same group also reported a Pd-catalyzed γ-C(sp^3)–H acetoxylation reaction of a class of cyclic alkyl amines using $PhI(OAc)_2$ as an oxidant (Scheme 144).[100] Compared with previous studies, as shown in Scheme 139, the substrate scope was successfully extended from amino alcohol derivatives to encompass morpholinones. DFT studies suggested that a dissociative ionization mechanism is the main pathway for the carbon–oxygen reductive elimination.



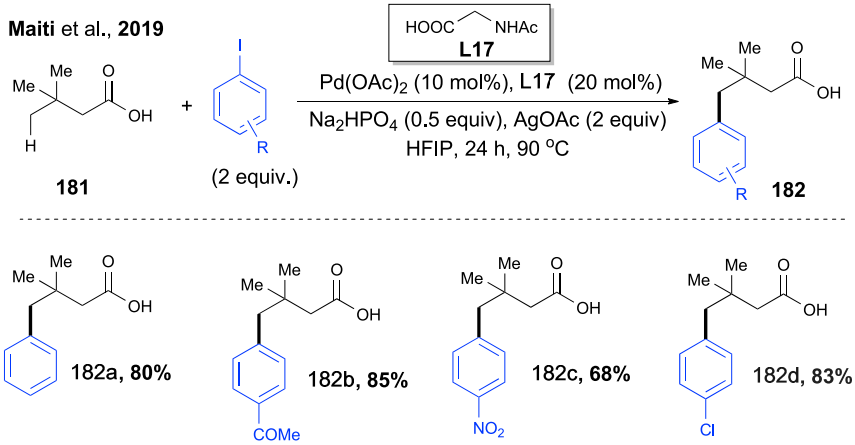
Scheme 124. Pd(II)-catalyzed δ-arylation of alkyl amines with aryl iodides



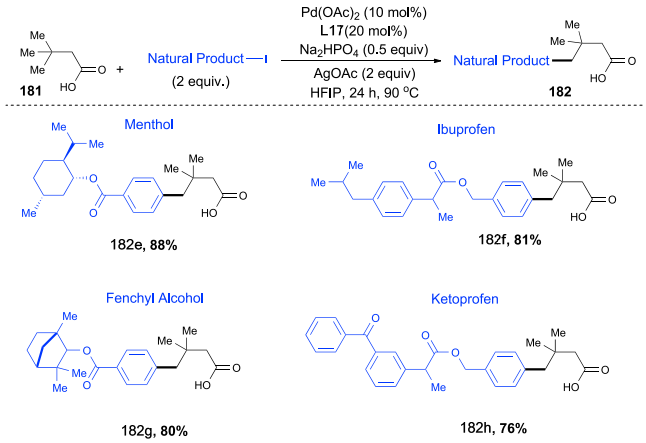
Scheme 125. Pd-catalyzed δ-arylation of 2-*tert*-butyl-aniline-derived substrates

C–H arylation

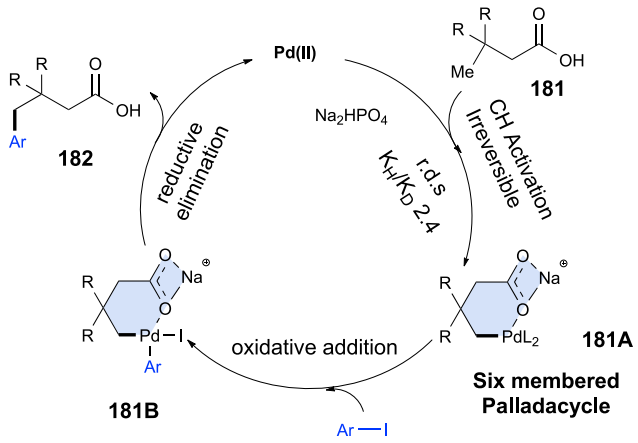
Additionally, the Pd-catalyzed γ-C(sp^3)–H arylation of amino alcohol derivatives was achieved with Ar(Mes)–I–OTf as an aryl source under slightly modified reaction conditions (Scheme 145). In 2019, the same group demonstrated a Pd-catalyzed γ-C(sp^3)–H arylation reaction of secondary alkylamines using an *ortho*-carboxylate substituted aryl halide as an aryl-transfer reagent (Scheme



Scheme 126. Ligand-enabled Pd-catalyzed γ-C(sp^3)–H arylation of free aliphatic acids



Scheme 127. γ-C(sp^3)–H arylation of free aliphatic acids using natural products containing aryl iodides as a coupling partner

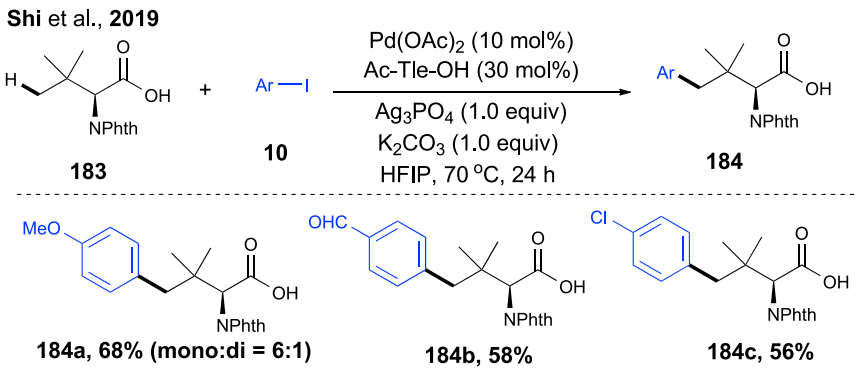


Scheme 128. A plausible mechanism for Pd-catalyzed γ-C(sp^3)–H arylation of free aliphatic acids

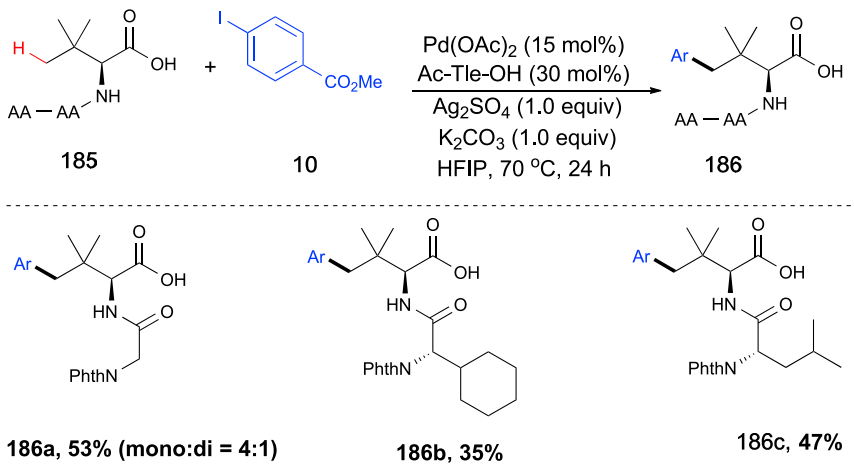
146).[101] The carboxylic acid functionality was found to promote the oxidative addition of halobenzoic acids to the alkylamine-derived palladacycles. The authors proposed a plausible reaction pathway (Scheme 147); the intermediate 211A undergoes ligand exchange with *o*-iodobenzoic acid to generate intermediate 211B, which, upon oxidative addition, produces the bis-palladacyclic γ-aminoalkyl Pd^{IV} species 211C. Subsequently, 211C experiences AgI-mediated iodide-to-carboxylate ligand exchange followed by pyridine-displacing carboxylate binding and a series of geometric isomerizations to generate the hydrogen bond-stabilized Pd^{IV} intermediate 211D. Finally, 211D endures decarboxylation, concerted 1,2-arylpalladium migration, and reductive elimination to yield the seven-membered palladacycle (211E).

C–H carbonylation

Furthermore, carbonylation of amino alcohol derivatives to generate pyrrolidinones was made possible through the use of CO as a carbonyl source (Scheme 148). Later, the authors extended the substrate scope to include a range of structurally and functionally diverse amines to access 4,5-disubstituted γ-lactams in synthetically useful yields and good diasteroselectivity under slightly modified reaction conditions (Scheme 149).[102] They were also able to optimize the reaction conditions to achieve these transformations in good yields with spiro compound 217 (Scheme 150).[103]



Scheme 129. Pd-catalyzed ligand-enabled γ-C(sp^3)–H arylation of *tert*-leucine

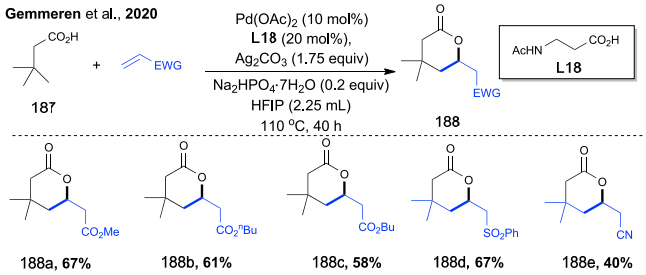


Scheme 130. Pd-catalyzed γ-C(sp^3)–H arylation of peptides

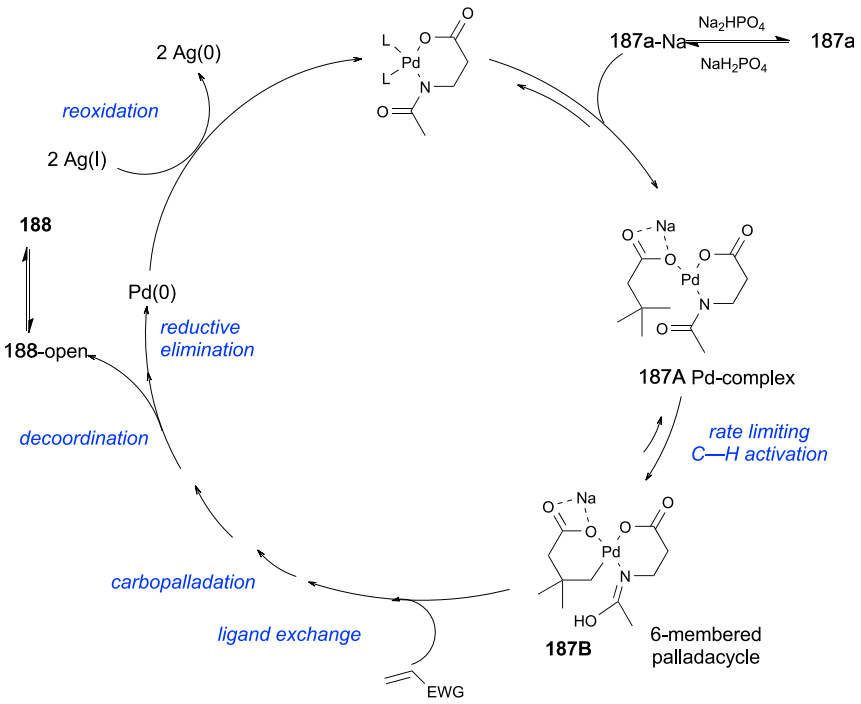
C–H alkenylation and cyclization

Moreover, the authors further modified the reaction conditions to obtain pyrrolidines through a γ-alkenylation reaction followed by intramolecular aza-Michael addition (Scheme 151). The core of this strategy, which applies to all four functionalization reactions, is the temporary conversion of catalytically incompatible primary amino alcohols to hindered secondary amines, which are capable of sterically promoting Pd-catalyzed γ-C(sp^3)–H activation. Furthermore, the same group expanded the substrate scope of the alkenylation reaction to encompass diverse olefins under milder conditions (Scheme 152).[104] A variety of acrylates, α,β-unsaturated ketones, amides, and acrolein were efficiently coupled to secondary amines **221a** to afford the corresponding products in good yields with Ac–Gly–OH as an optimal ligand. Interestingly, the sequential processes of C–H amination, ring-opening, C–H alkenylation, followed by intramolecular cyclization provided the bicyclic product **221d** in 55% yield. To explore the synthetic applications of the products resulting from this sequential functionalization, the bicyclic compound **221e** was successfully modified to afford the highly functionalized pyrrolidine derivative **222** (Scheme 153).[104]

The authors proposed a working hypothesis and a plausible mechanism for these transformations (Schemes 154 and 155); first, the amino alcohol **206** and acetate ligand coordinate with the Pd catalyst to generate intermediate **int-I**, which is then transformed into the bis(amine) Pd(II) complex (**int-II**). There is a reversible balance between the two species, **int-I** and **int-II**, but the balance is more inclined



Scheme 131. The ligand-enabled γ-C(sp^3)–H olefination of free carboxylic acids

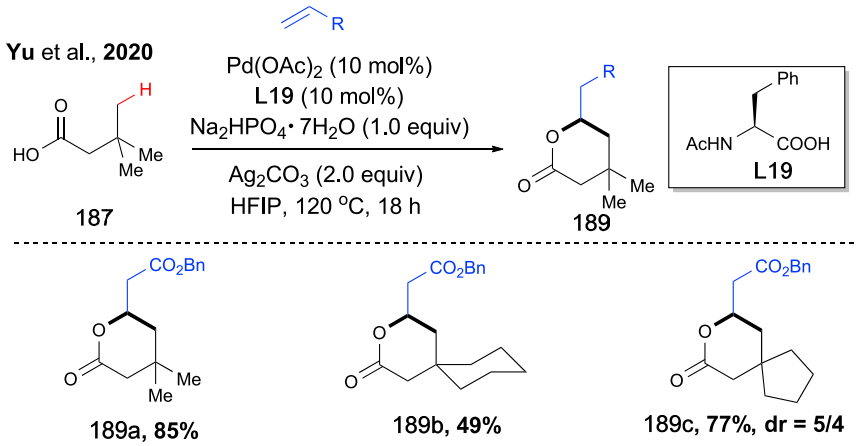


Scheme 132. A plausible mechanism for γ-C(sp^3)–H olefination of free carboxylic acids

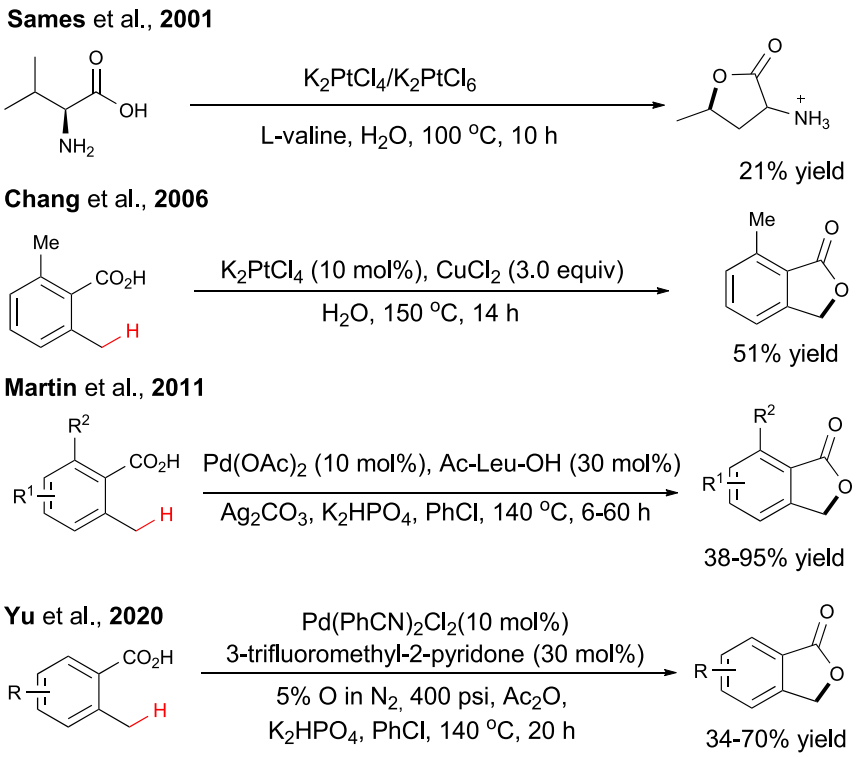
toward **int-I** according to theoretical calculations. Afterward, **int-I** undergoes C–H bond activation to form intermediate **int-III**. Finally, the desired products are obtained upon reductive elimination. This hypothesis was further supported by trial experiments and theoretical calculations. An illustrative catalytic cycle for the γ-acetoxylation reaction is represented in Scheme 155.

C–H amination

In 2018, the Gaunt group reported a Pd(II)-catalyzed γ-C(sp^3)–H amination reaction of cyclic alkyl amines to produce highly substituted azetidines using a benziodoxole tosylate as an oxidant (Scheme 156).[105] The authors found that the combination of benzoxazole tosylate and AgOAc is critical in controlling the selective reductive elimination

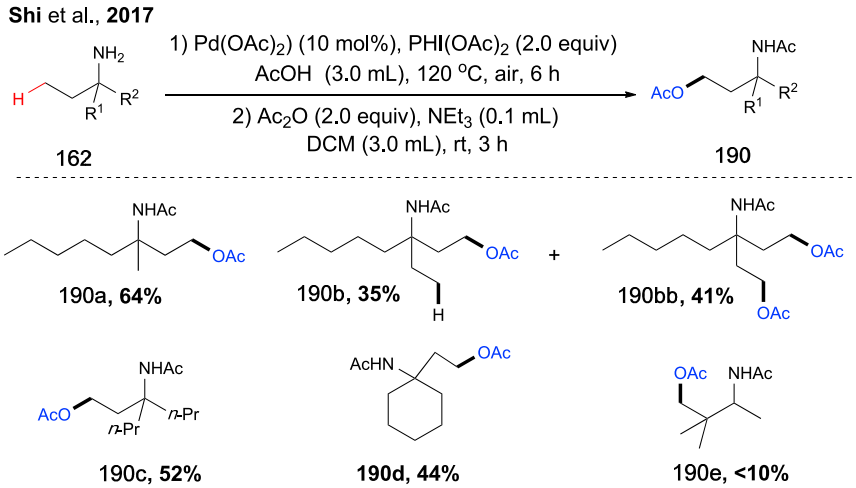


Scheme 133. Pd-catalyzed γ-C(sp^3)–H olefination of free carboxylic acids

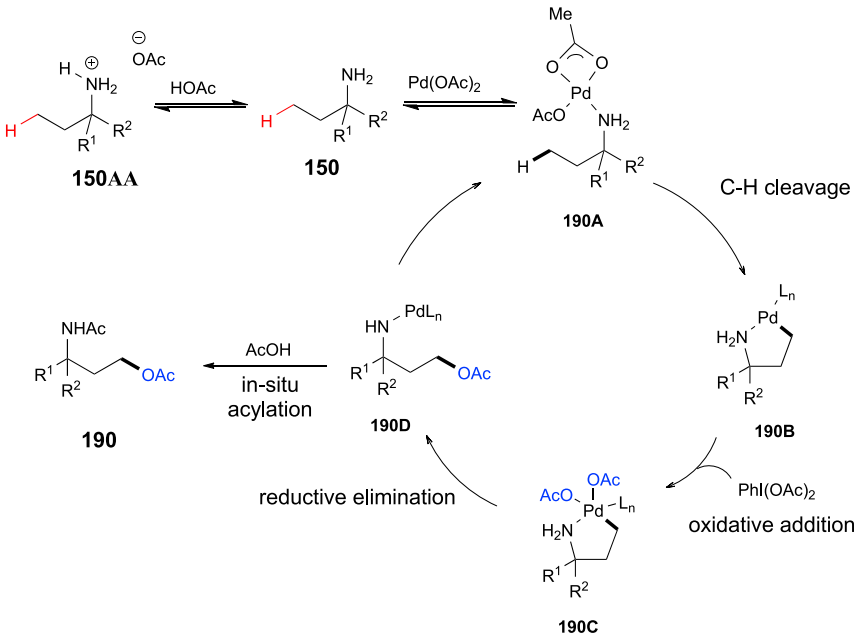


Scheme 134. Transition-metal-catalyzed C(sp^3)–H functionalizations of acids to build cyclic esters

pathway. A range of functionalized morpholinone derivatives were found to be effective substrates in this reaction. A tentative mechanism was proposed (Scheme 157); first, amine **223** coordinates to the Pd species to generate intermediate **223A**, which undergoes oxidative tosylate transfer to afford the aminoalkyl Pd(IV) complex (**223B**). Subsequently, dissociation of the OTs (*p*-toluenesulfonyl) group from **223B** produces the octahedral Pd(IV) intermediate **223C**, which, upon reductive elimination, forms the γ-amino tosylate **223D**. Finally, intramolecular cyclization of **223D** via an S_N2 process yields the azetidine product **225**.



Scheme 135. NH_2-directed γ-C(sp^3)–H acetoxylation of primary aliphatic amines

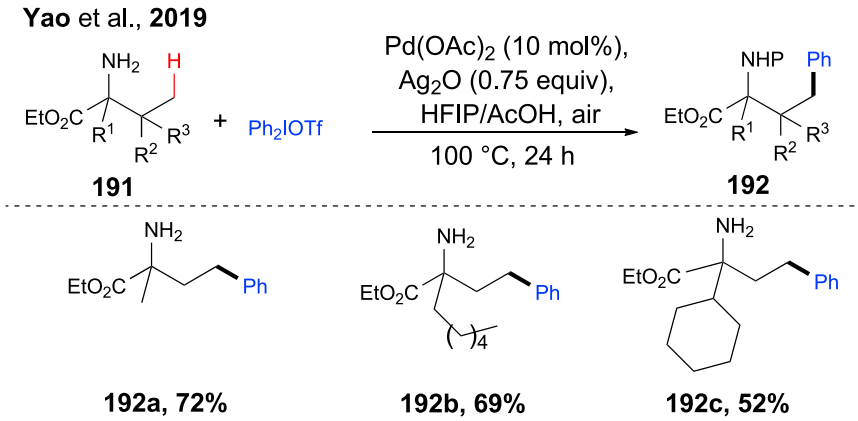


Scheme 136. A plausible reaction mechanism for NH_2-directed γ-C(sp^3)–H acetoxylation of primary aliphatic amines

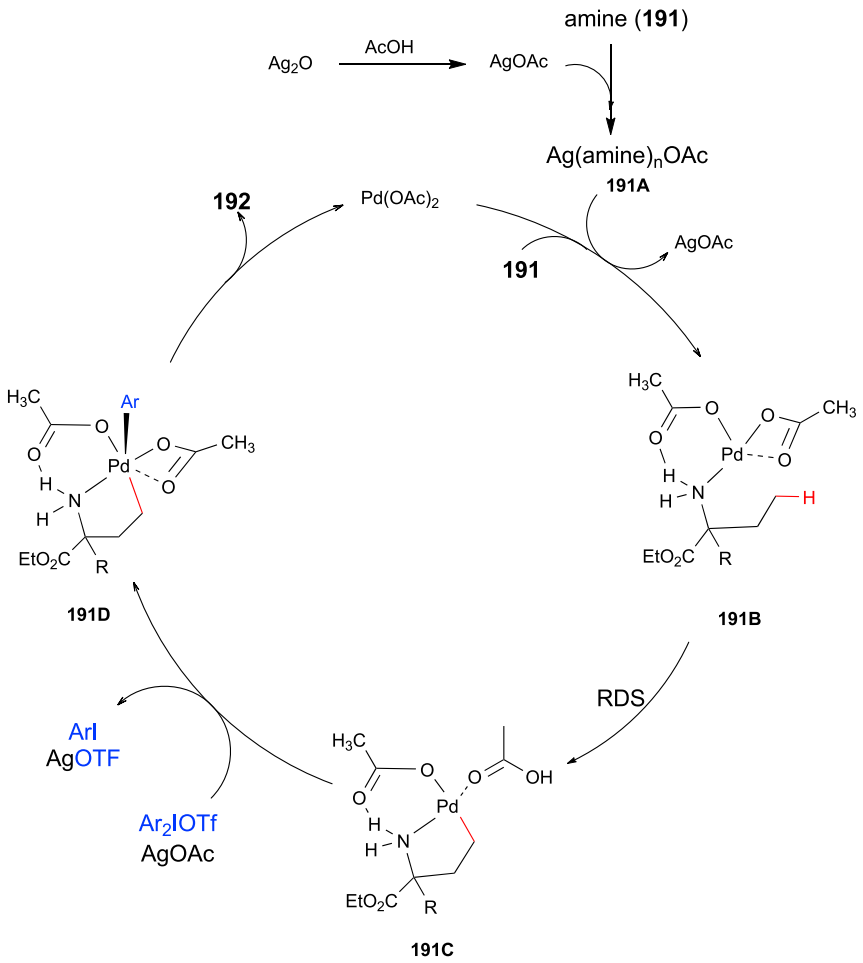
Although the transition-metal-catalyzed γ-C(sp^3)–H functionalization of secondary amines has developed rapidly, the majority of reactions rely on the utilization of specific substrates. Hence, the scopes of the reactions are limited, and common secondary amines are not compatible with such catalytic systems. The development of more effective catalysts and ligands designs and incorporating systems compatible with secondary amines would greatly enhance the applicability of these strategies and could lead to important accomplishments in the synthesis of natural products and complex pharmaceutical drugs.

γ-C(sp^3)–H functionalization of tertiary amines

Late-stage functionalization is especially valuable in the context of the development of pharmaceutical agents as it enables the efficient and straightforward synthesis of



Scheme 137. Pd-catalyzed NH_2-directed γ-C(sp^3)–H arylation of α-amino esters

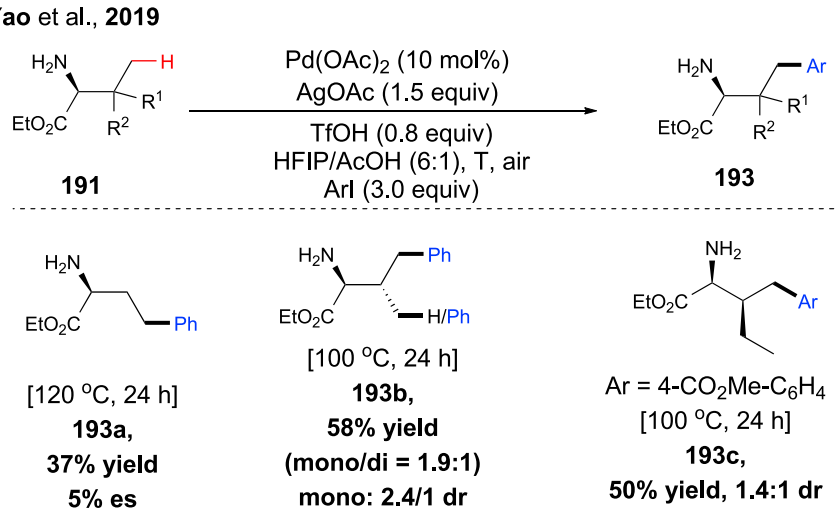


Scheme 138. Plausible mechanism for Pd-catalyzed NH_2-directed γ-C(sp^3)–H arylation

drugs and prodrugs analogs to optimize their pharmacokinetic properties.[106] Tertiary amines are of great research interest to organic and medicinal chemists as they widely exist in biologically active molecules and functional materials.[4] Although a variety of synthetic strategies have been reported for the synthesis of tertiary amines, approaches for the late-stage functionalization of these molecules are rare. The transition-metal-catalyzed C–H bond functionalization is considered to be a powerful method for the late-stage functionalization of natural products and biologically active molecules.[106]

C–H arylation

In 2020, the Gaunt group reported a Pd(II)-catalyzed γ-C(sp^3)–H arylation reaction of tertiary amines by using aryl-boronic acids as coupling partners (Scheme 158).[106] In the presence of $Pd(OAc)_2$, *N*-acetyl *t*-leucine, Ag_2CO_3, benzoquinone, in NMP (1-methyl-2-pyrrolidinone), various substituted aryl- and heteroaryl-boronic acids were successfully introduced into the tertiary amine framework to deliver the desired products in good yields. Notably, the reaction was applied to the tricyclic antidepressant (Surmontil), enabling late-stage diversification into γ-(hetero) aryl tertiary alkylamine derivatives (Scheme 159). A possible mechanism was proposed (Scheme 160); first, tertiary alkylamine **226** and the amino acid ligand coordinate with the Pd



Scheme 139. Pd-catalyzed native amine-directed γ-C(sp^3)–H arylation of amino acids and peptides

catalyst to give rise to **226A**. Subsequently, ligand promoted γ-C–H bond activation forms the [5,5]-bicyclic Pd complex **226B**, which undergoes *trans*-metalation with phenylboronic acid to form intermediate **226C**. Finally, the reductive elimination of **226C** generates the desired product **227a** alongside Pd(0), which is oxidized by Ag(I) to regenerate the Pd(II) catalyst.

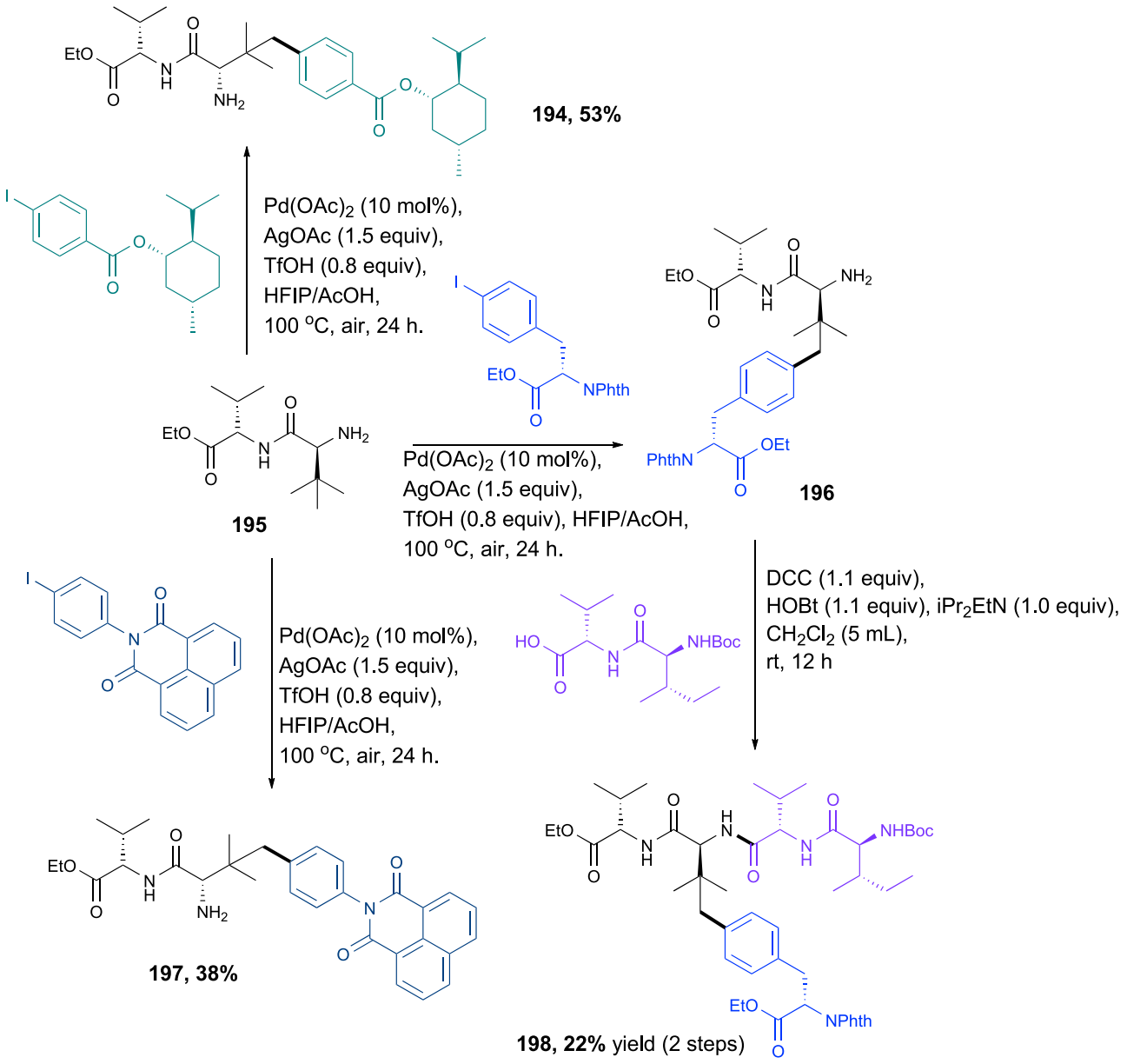
Only arylation examples of tertiary amines have been developed via Pd(II)-catalyzed so far. The scope of γ-C(sp^3)–H functionalization of tertiary amines is limited, and there is plenty of room for improvement. Further advances in the γ-C(sp^3)–H functionalization of tertiary amines require the design of effective ligands and application of these techniques in the modification of natural products.

Free-amine-directed δ-C(sp^3)–H functionalization of primary amines

C–H arylation

In general, free amines are not good substrates for Pd-catalyzed C–H bond activation reactions due to the generation of stable bis-amine Pd complexes. In 2019, Bannister employed weak acid to aid in the dissociation of the bis-amine Pd complexes. They disclosed the Pd-catalyzed arylation of unactivated δ-C(sp^3)–H bonds of free primary aliphatic amines with a broad range of aryl iodides using acetic acid as the reaction solvent and NH_2 as a native DG (Scheme 161).[107] The addition of 2-nitrobenzoic acid was useful for improving yields in the transformation. This reaction was compatible with a wide range of functional groups of aryl iodides and proceeded with high δ-position-selectivity of aliphatic amines. The efficiency of this protocol was showcased by the arylation of a variety of free primary amines with adjacent quaternary centers and/or with alpha esters. Furthermore, the authors proved the free amino group plays as a native DG because N-acylated substrate **230a-Ac** was not an effective substrate. Acetic acid was further demonstrated to aid in the dissociation of the stable bis-amine Pd complex by a control experiment (Scheme 162B).

Unfortunately, the single example of NH_2-directed δ-C(sp^3)–H arylation of primary amines to date is exclusive to primary quaternary amines. Further advances in the

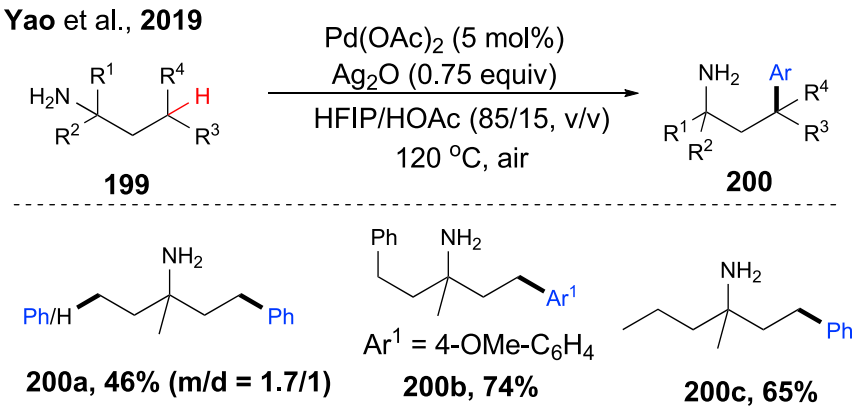


Scheme 140. Synthetic applications of Pd-catalyzed native amine-directed γ-C(sp^3)–H arylation of amino acids and peptides

free-amine-directed δ-C(sp^3)–H functionalization of primary amines require the development of effective external ligands and further extending the scopes of the reactions to non-quaternary primary amines.

Silicon-based directed δ-C(sp^3)–H functionalization

Organosilicon compounds have attracted great research interest in recent years because of their potential applications in material science, medicinal chemistry, and agroscience. Although metal-catalyzed silylation of C–H bonds has achieved significant progress over the past two decades, the development of enantioselective silylation of unactivated C(sp^3)–H bonds is still highly sought after.

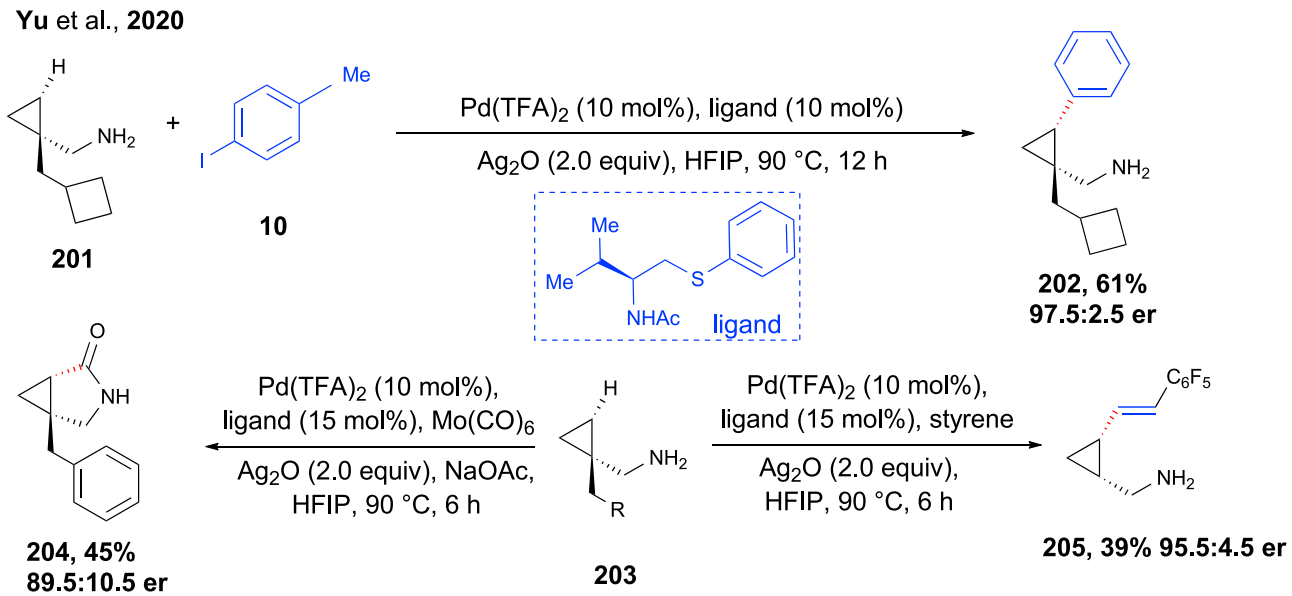


Scheme 141. Pd-catalyzed free-amine-directed γ-C(sp^3)–H arylation of primary aliphatic amines

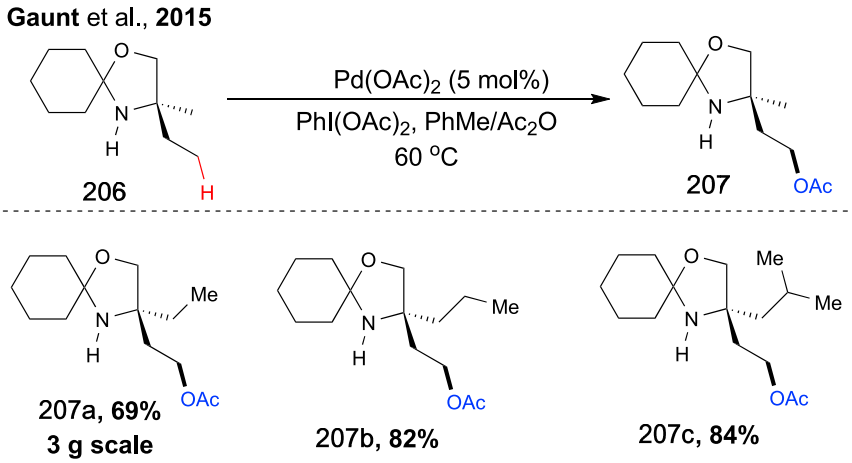
C–H silylation

In 2017, Hartwig described an elegant enantioselective intramolecular silylation reaction of methyl C–H bonds to afford dihydrobenzosiloles in high yields with excellent enantioselectivities in the presence of an Ir catalyst and chiral dinitrogen ligands (Scheme 163),[108] albeit with a limited substrates scope. To demonstrate the potential applications of the protocol, a gram scale of the silylation product was synthesized under standard conditions, and the C–Si bond in the enantioenriched dihydrobenzosiloles was transformed to C–Cl, C–Br, C–I, and C–O bonds in a series of functional products (Scheme 164). The reaction proved effective for the late-stage C–H enantioselective silylation of a biologically active natural product, dehydroabietic acid derivative (**243**; Scheme 165).

The scope of enantioselective intramolecular silylation is rather limited. Further advances in silicon-based directed δ-C(sp^3)–H functionalization require extending the scopes of reaction and its utilization in the synthesis of complex biologically active molecules



Scheme 142. Pd-catalyzed enantioselective γ-C(sp^3)–H functionalizations of cyclopropylmethylamines



Scheme 143. Pd-catalyzed direct γ-C(sp^3)–H acetoxylation of amino alcohols

INSERTION

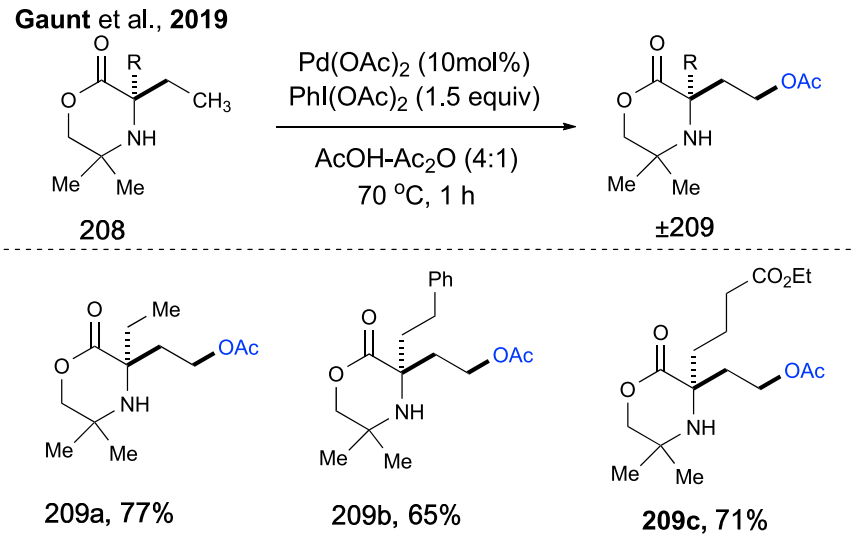
Nitrene insertion

C–H cyclization

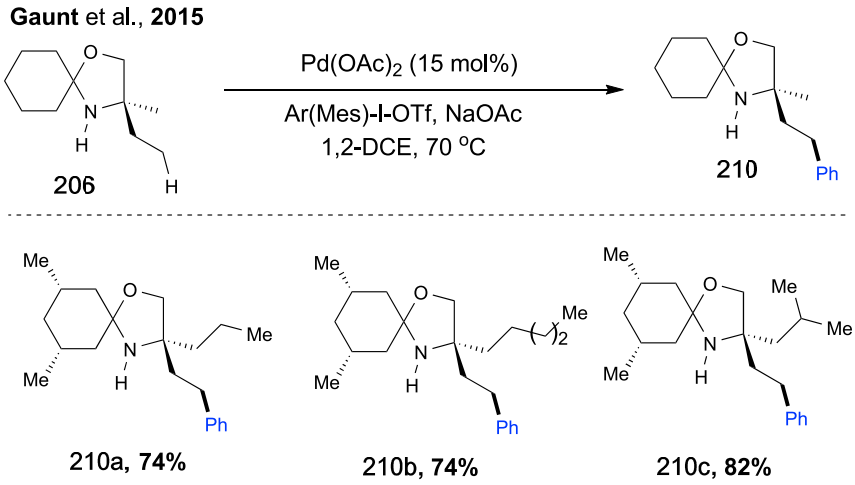
Metal-mediated carbene or nitrene insertion into aliphatic C–H bonds is a unique strategy for γ-C(sp^3)–H functionalization of alcohols. In 2001, Du Bois and co-workers developed Rh(II)-catalyzed oxidative cyclization of carbamates to afford 1,3-difunctionalized amine derivatives (Scheme 166).[109] In this study, a Rh nitrenoid inserts into the γ-C–H bond of sulfamates to afford the corresponding six-membered ring products. Various sulfamate esters were efficiently transformed selectively into six-membered oxathiazinanes. The reaction exhibited a broad substrate scope, and a variety of functional groups were tolerated under the standard reaction conditions.

C–H amination

In 2009, the White group used the same strategy of Pd-catalyzed nitrene insertion into aliphatic C–H bonds to achieve the γ-C(sp^3)–H functionalization of masked



Scheme 144. Pd-catalyzed γ-C(sp^3)–H acetoxylation reaction of a class of cyclic alkyl amines

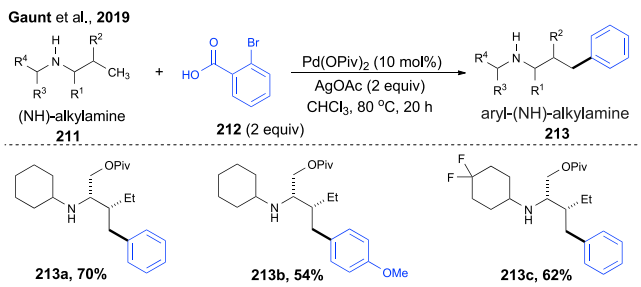


Scheme 145. Pd-catalyzed direct γ-C(sp^3)–H arylation of amino alcohols

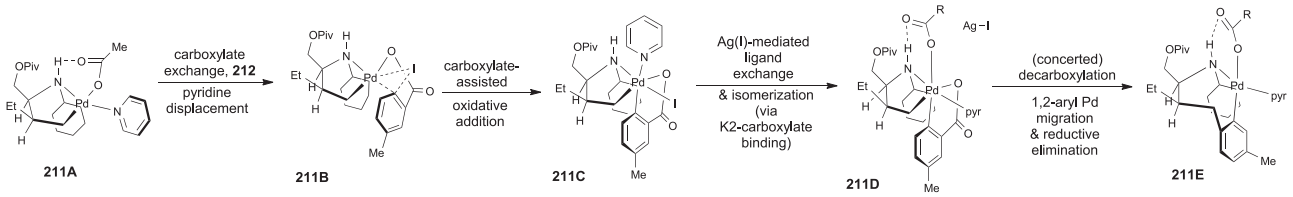
alcohols (Scheme 167).[110] 1,2-Bis(phenylsulfinyl)ethane Pd(II) acetate was used as a catalyst, and phenylbenzoquinone (PhBQ) was employed as an oxidant in this study. A series of cyclic carbamates were obtained under mild reaction conditions in good yields and diastereoselectivity. In this process, the use of electron-deficient nosyl-substituted carbamates was found to play a critical role in promoting the C–H functionalization. Notably, the *N*-nosyl group could be easily removed by PhSH/K_2CO_3 under mild conditions to afford the free oxazinanone.

C–H diarylation

Recently, Young et al. demonstrated a Pd-catalyzed γ,γ′-diarylation of free alkenyl amines to construct Z-selective alkenyl amines by interrupted chain walking (Scheme 168).[111] The scope of the reaction proved broad in that it tolerated a variety of cyclic branched and linear secondary and tertiary alkenylamines in moderate to good yields. Further mechanistic studies revealed that the amine could facilitate direct arylation at the γ-position, and the cascade reaction undergoes β-hydride elimination and selectively chain walk to produce a new terminal olefin. A plausible mechanism was proposed (Scheme 169); first, Pd was reduced by free amine to form Pd nanoparticles. Then, Pd nanoparticles addition with amine produces intermediate **250A**. Subsequently, oxidative addition of **250A** with an aryl iodide affords the Pd intermediate **250B**, which then undergoes γ-selective migratory insertion into the olefin to produce intermediate **250C**. Following this, regioselective β-hydride elimination and oxidative addition with a second equivalent of aryl iodide generates



Scheme 146. Pd-catalyzed γ-C(sp^3)–H arylation of secondary alkylamines



Scheme 147. Plausible mechanism for Pd-catalyzed γ-C(sp^3)–H arylation of secondary alkylamines

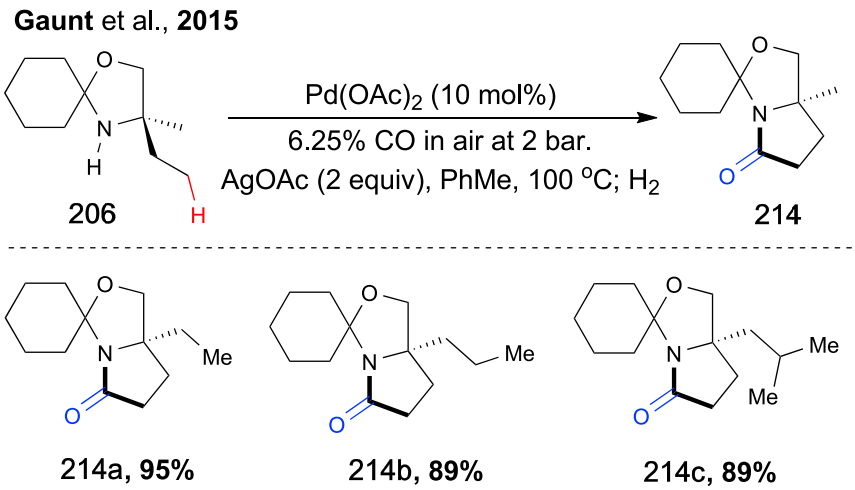
intermediate **250E**. Further selective insertion and reductive elimination yield the product and regenerate the Pd nanoparticle catalyst.

Insertion is a unique strategy for γ-C(sp^3)–H functionalization. Examples of γ-C(sp^3)–H functionalization via insertion are characterized by superb functional-group compatibility under mild reaction conditions, albeit with moderate yields. Further advances in these protocols require applications in the late-stage functionalization of natural products.

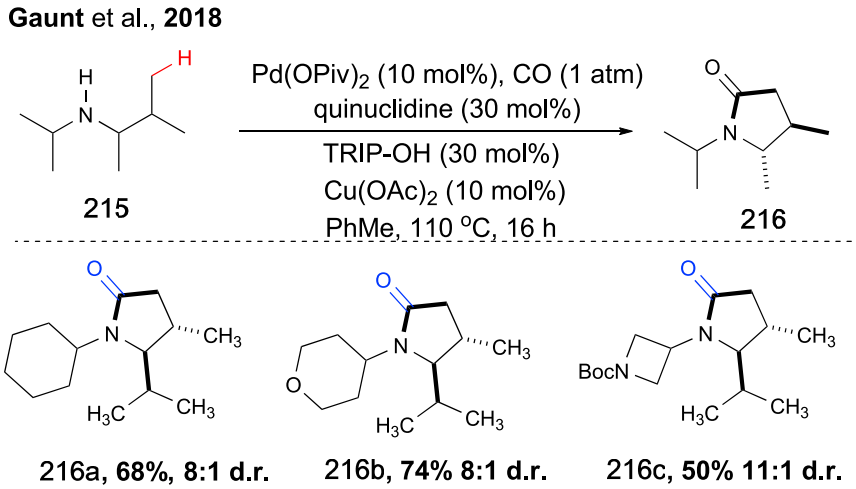
NON-COVALENT INTERACTION

C–H borylation

Using the strategy of non-covalent interactions to achieve remote site-selectivity C(sp^3)–H functionalization reactions has aroused great interest among organic scientists because it not only has high site selectivity but also avoids the extra steps for the installation and removal of DGs. Rather, the strategy utilizes non-covalent interactions to control the selectivity. It is different from the auxiliary-assisted C–H functionalization in that it does not need to form the corresponding conventional metallacycle intermediate (five-, six-, or seven-membered) in the reaction. Recently, Sawamura and co-workers used this strategy to develop a highly enantioselective modular Ir-catalyzed borylation of γ-C(sp^3)–H bonds in aliphatic secondary and tertiary amides and esters (Scheme 170).[112] In this study, an enzyme-like structural cavity was formed by modular assembly of an Ir center, a chiral monophosphite ligand, a urea-pyridine-based hydrogen-bond receptor ligand (**RL**), and pinacolatoboryl groups (Figure 2). The cavity binds the substrate via multiple non-covalent interactions, and γ-C(sp^3)–H borylation takes place subsequently. The [Ir(OMe)(cod)]$_2$ was used as a catalyst, and monophosphite (**R**, **R**)-**L*** and urea-pyridine **RL** were

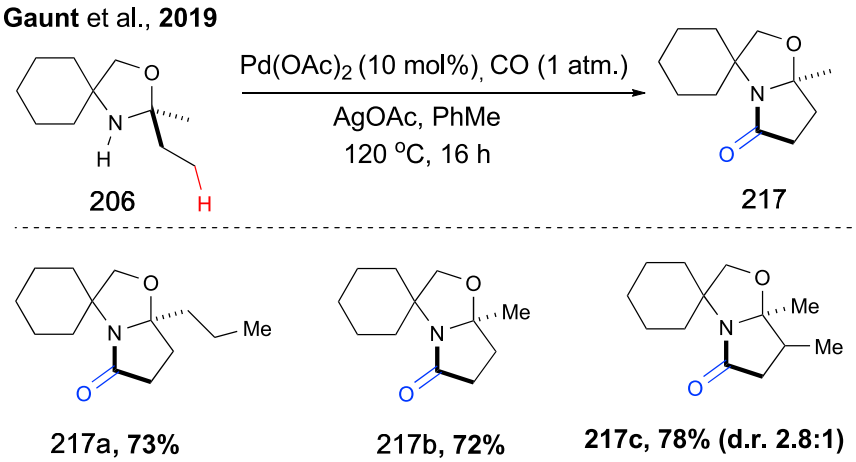


Scheme 148. Pd-catalyzed direct γ-C(sp^3)–H carbonylation of amino alcohols

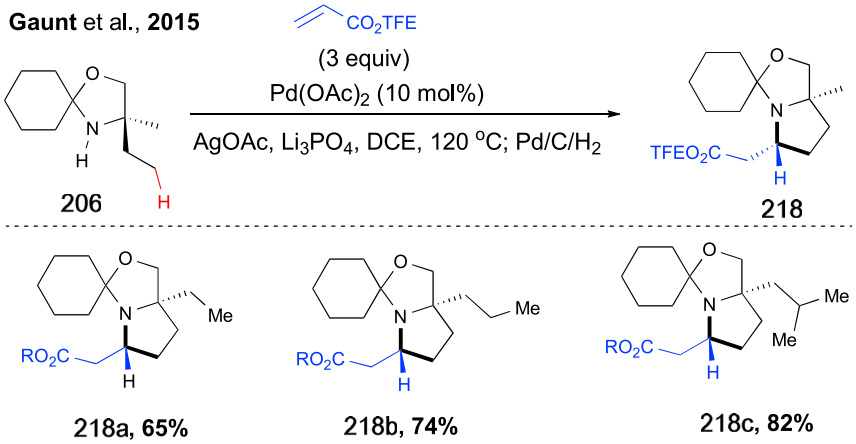


Scheme 149. Pd-catalyzed γ-C(sp^3)–H carbonylation of secondary amines

employed as the chiral ligand and receptor ligand, respectively. To illustrate the importance of ligands, the authors conducted a series of comparison experiments (Scheme 171). When 1-cyclohexyl-3-(2-(pyridin-3-yl)phenyl)urea was used as a hydrogen-bond receptor ligand, product **253a** was obtained in 99% yield and 99.9% ee; in contrast, the selectivity and yields of the reaction were not good with other hydrogen-bond receptor ligands (**RL2**–**RL4**). In addition, control experiments showed that no product was detected in the absence of the chiral phosphite ligand or **RL**, and 2,6-lutidine was very important for the enhanced reactivity and enantioselectivity of the reaction. Under the optimized reaction conditions, various amides and esters were borylated at the γ-position to deliver the desired products in good to excellent yields with high enantioselectivity (up to 98% ee). The Ir center, a chiral monophosphite ligand, an achiral urea-pyridine receptor ligand, and pinacolatoboryl groups effectively combined to form a chiral C–H activation catalyst. Furthermore, the corresponding secondary alcohols were obtained with highly enantioselectivity under oxidative conditions. To demonstrate the practicality and



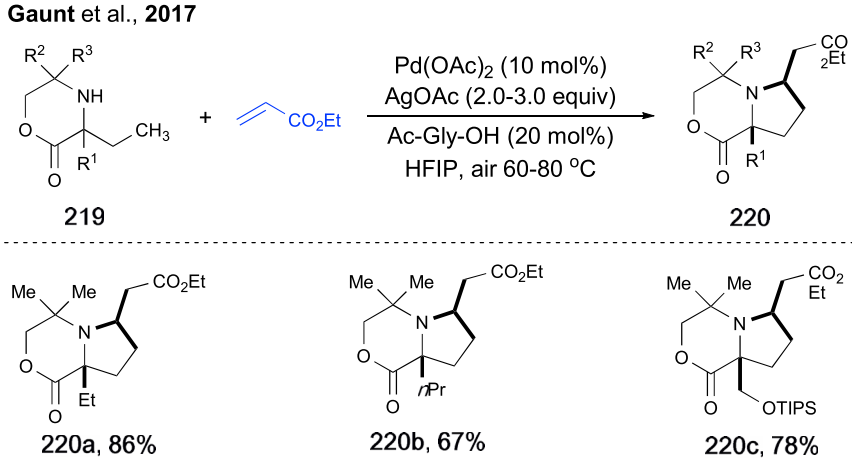
Scheme 150. A series of γ-lactams were obtained by Pd-catalyzed γ-C(sp^3)–H carbonylation reaction



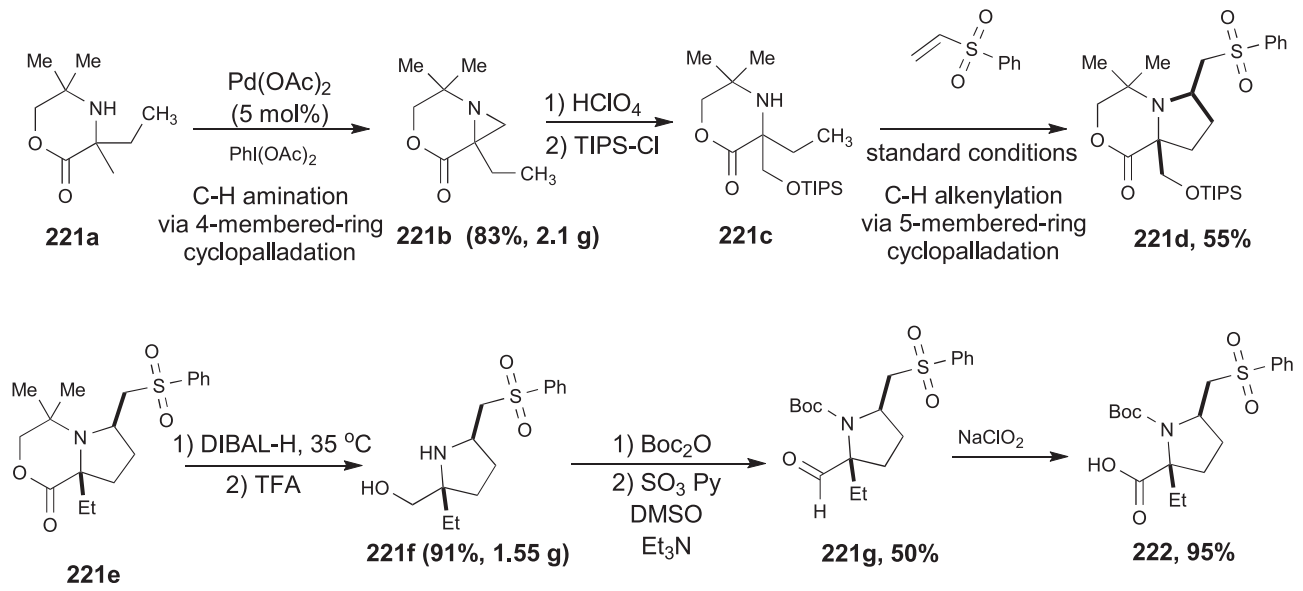
Scheme 151. Pd-catalyzed direct γ-C(sp^3)–H alkenylation of amino alcohols

efficiency of this borylation protocol, the authors successfully conducted a gram-scale reaction by using a low loading (1 mol %) of the Ir-L* catalyst, giving (R)-**253b** (1.32 g, 83%) from **252b** without erosion of the enantioselectivity (Scheme 172). Subsequently, the pharmacologically interesting γ-alkyl-γ-aminobutyric acid (GABA) derivative [(R)-**255**] was easily obtained by the amination of (R)-**253b** (Scheme 173). Furthermore, quantum chemical calculations demonstrated that an enzyme-like structural cavity formed, and multiple non-covalent interactions participated in the reaction.

In addition to transition-metal catalysis, organic molecules were employed as catalysts for the functionalization of alkenyl C–H bonds, as demonstrated by Sigman and Toste in 2016. They reported a chiral phosphoric-acid-catalyzed fluorination of allylic alcohols to obtain allylic fluoride in high enantioselectivity (Scheme 173).[113] The aryl boronic acids played an important role and were used as TDGs in the protocol. A series of mechanistic experiments have shown that a lone pair-π interaction between the phosphate and the substrate ligated aryl boronic acids led to stereoselectivity control (Scheme 174).

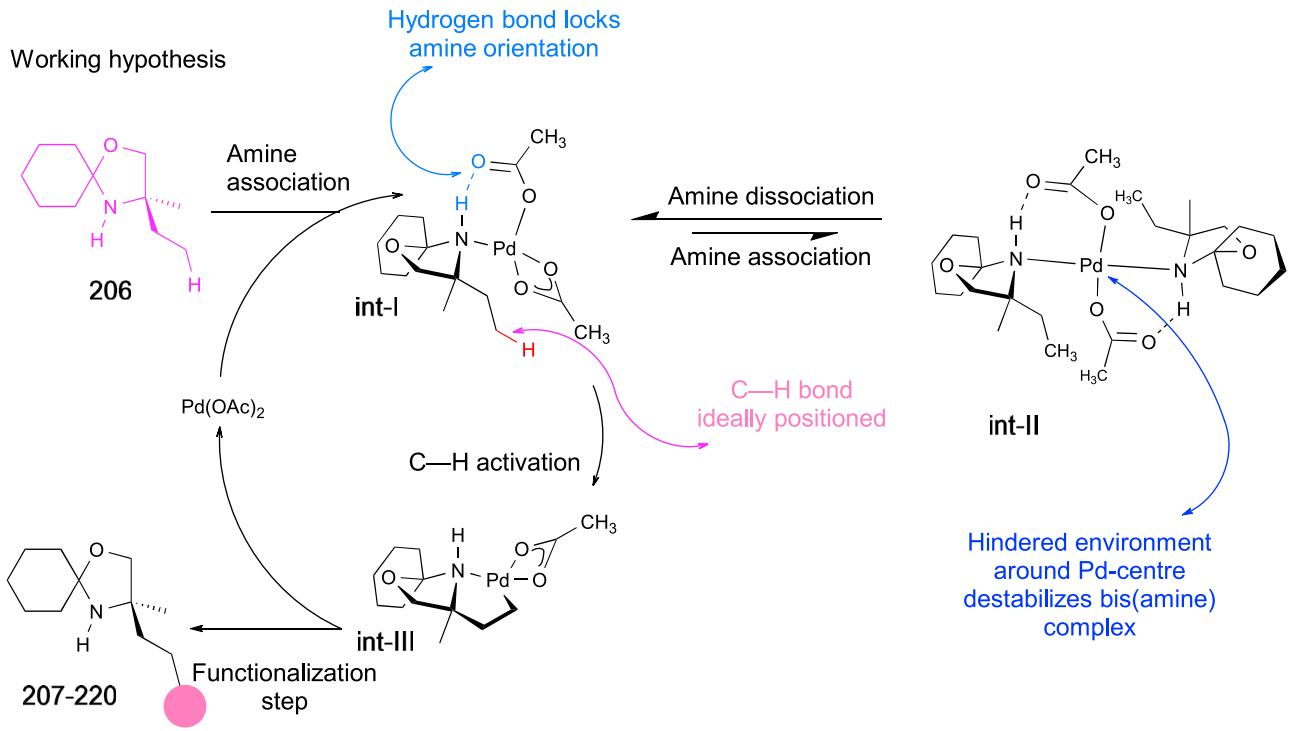


Scheme 152. Pd-catalyzed direct γ-C(sp^3)–H alkenylation and cyclization of secondary amines

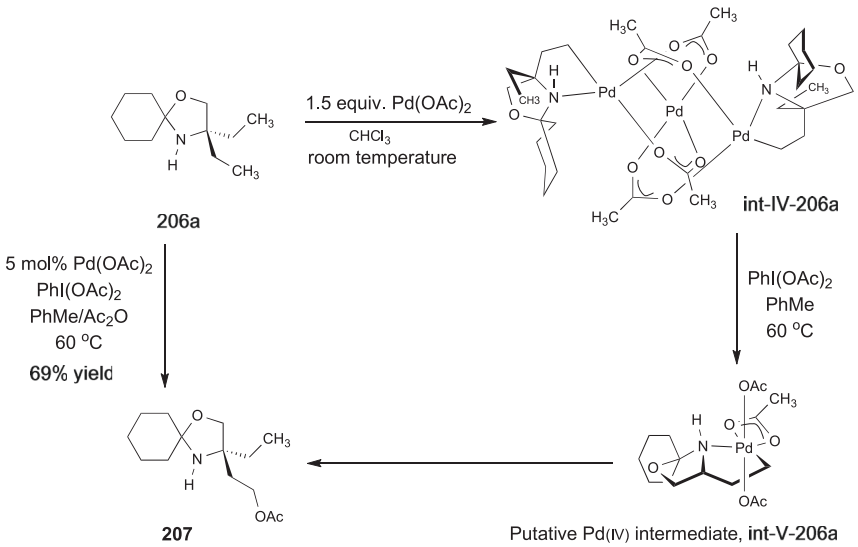


Scheme 153. Synthetic applications of Pd-catalyzed direct γ-C(sp^3)–H alkenylation and cyclization

Non-covalent interaction is a practical strategy for γ-C(sp^3)–H functionalization with high yields and excellent enantioselectivity under mild reaction conditions. It is needed to design new supramolecular catalysts by taking advantage of non-covalent interactions, such as reversible Lewis acid and Lewis base interactions, hydrogen bonding, hydrophobic interactions, and coulombic interactions.



Scheme 154. Working hypothesis for the C–H activation strategy



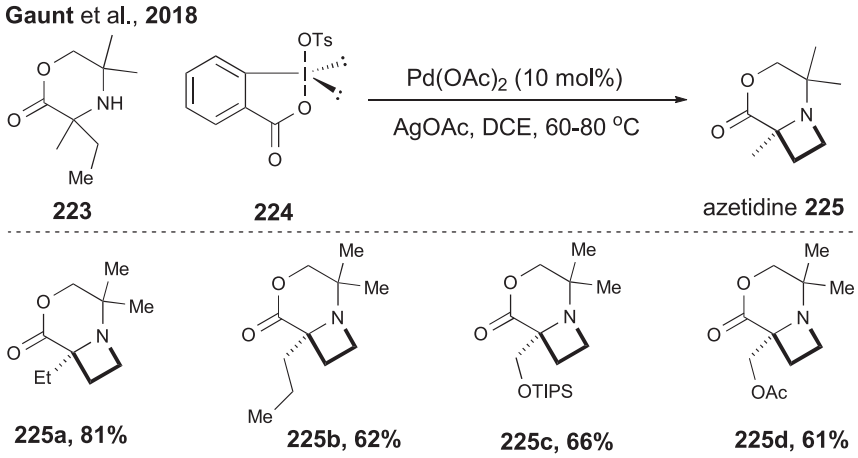
Scheme 155. Plausible mechanism for Pd-catalyzed γ-C(sp^3)–H acetoxylation of amino alcohols

Further advances in the protocol are required to develop more enantioselective functionalization reactions and to continue to find uses for these methods in synthesis.

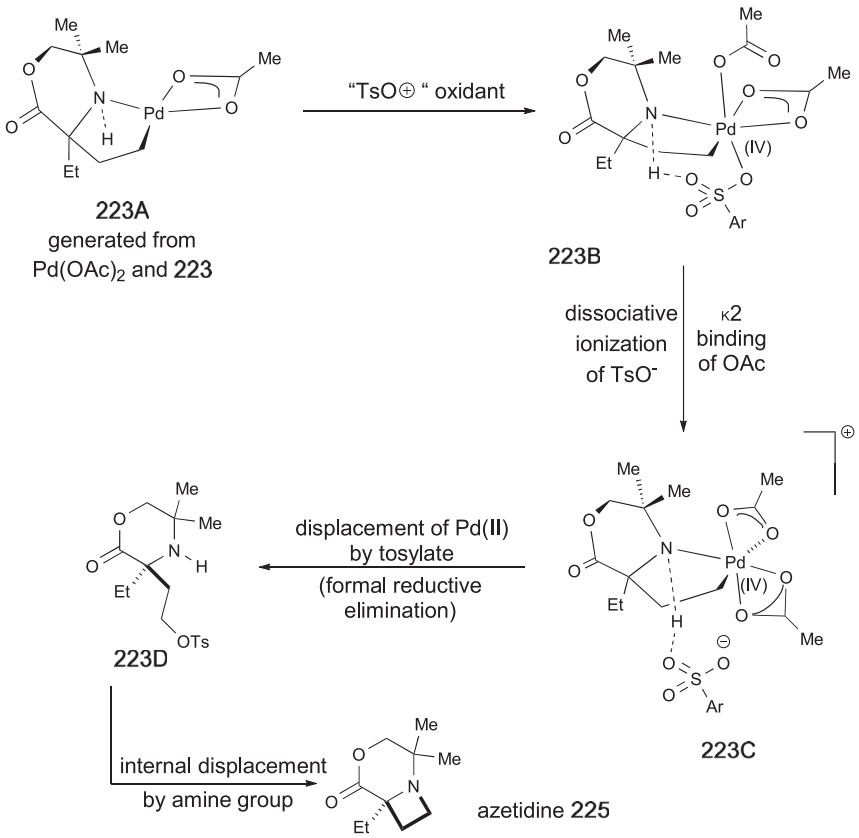
C–H OXIDATION AND HYDROXYLATION

The Kanai group disclosed a different methylene C(sp^3)–H oxygenation reaction of aliphatic alcohols by using a radical *N*-oxyl directing activator via cobalt catalysis in 2016 (Scheme 175).[114] Various oxidation-sensitive functional groups were tolerated under the mild reaction conditions.

Amino acids and peptides with preservation of α-center chirality was reported by White and co-workers in 2016 (Scheme 176).[115] Small-molecule Fe catalysts Fe(PDP) (C1) and Fe(CF$_3$PDP) (C2) displayed high functional-group tolerance in amide-rich peptide settings. A series of amino acids and peptides were successfully



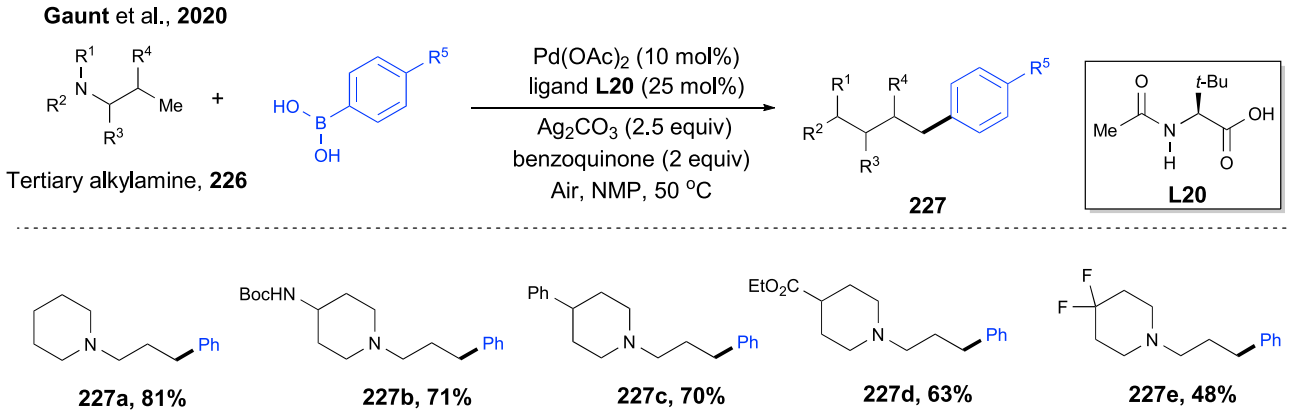
Scheme 156. Pd(II)-catalyzed γ-C(sp^3)–H amination of cyclic alkyl amines



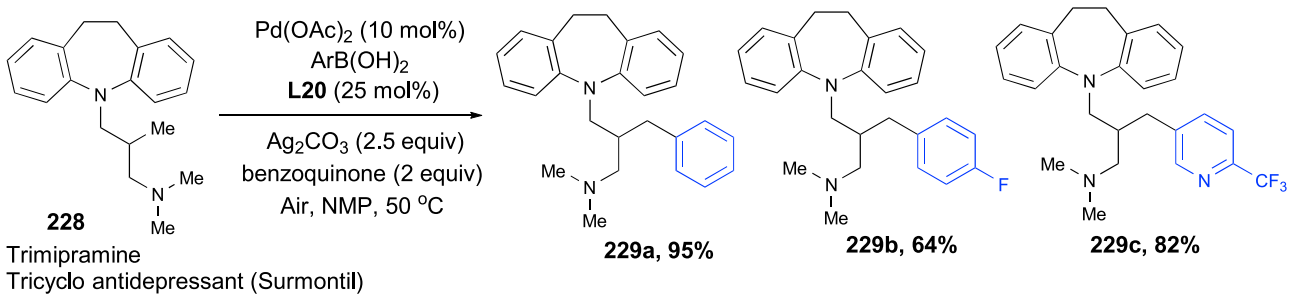
Scheme 157. Plausible mechanism for Pd(II)-catalyzed γ-C(sp^3)–H amination of cyclic alkyl amines

oxidized to the corresponding oxo products with high regioselectivity and good yields while preserving α-center chirality.

In 2017, Sigman, Bois, and co-workers reported ruthenium-catalyzed C–H hydroxylation of C(sp^3)–H bonds (Scheme 177).[116] In this work, *cis*-[(dtbpy)$_2$RuCl$_2$] was employed as an effective catalyst, and H_5IO_6 was used as a terminal oxidant. A variety of N-containing substrates were successfully hydroxylated under this system in good



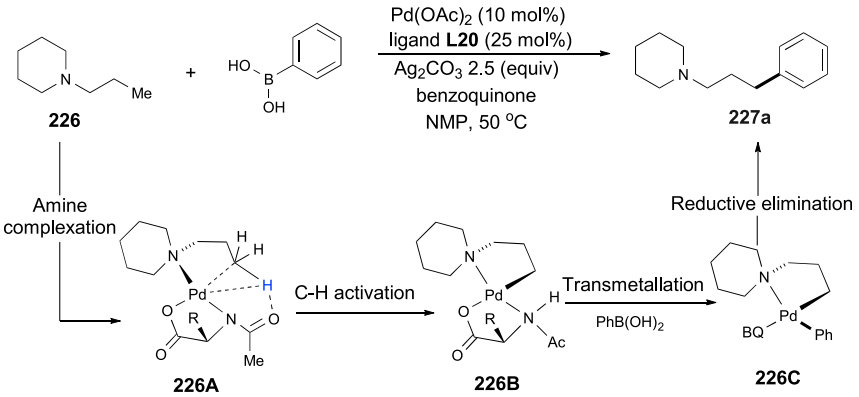
Scheme 158. Pd-catalyzed γ-C(sp^3)–H arylation of tertiary amines



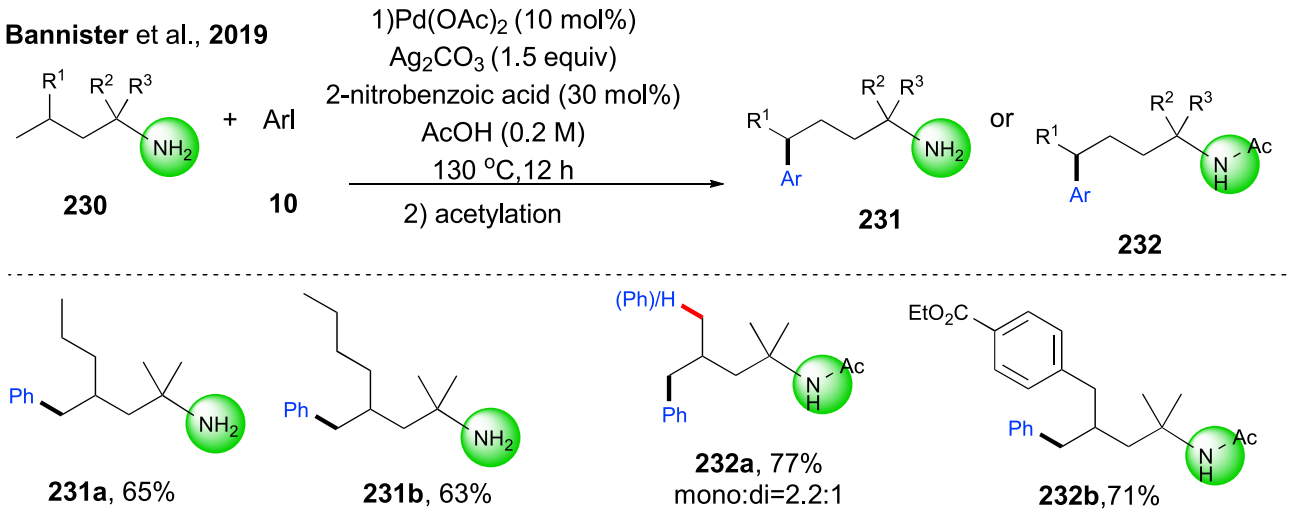
Scheme 159. Late-stage arylation of trimipramine

yields. Notably, oxidation of the chiral tertiary center provided evidence that this reaction is stereospecific (Scheme 178).

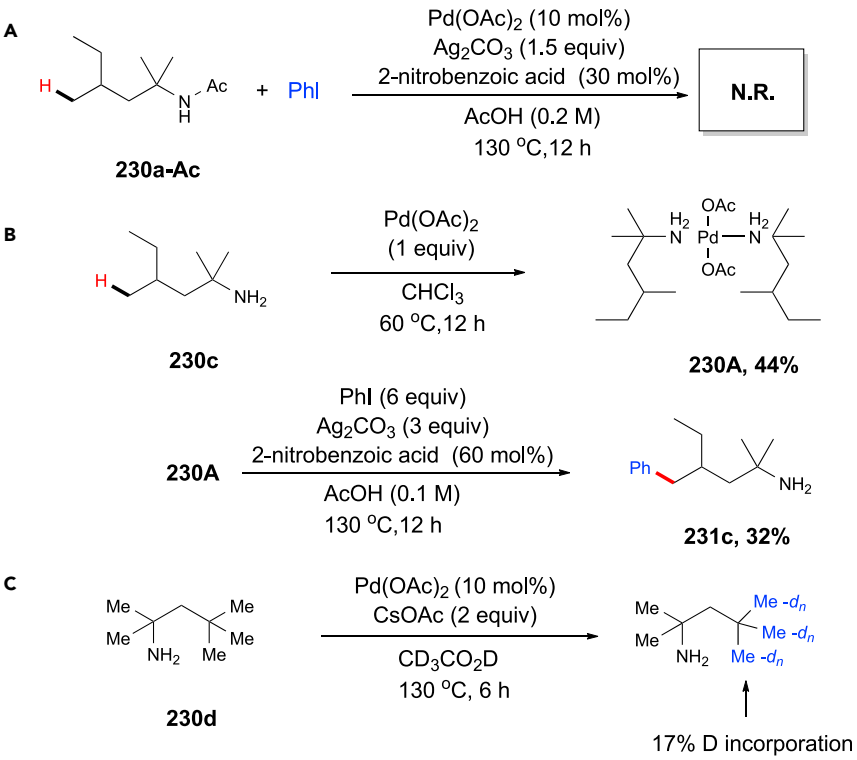
Very recently, Du Bois and Sigman disclosed an operationally simple protocol for site-selective oxidation of remote aliphatic C–H bonds by using an acid-stable, bis(bipyridine)Ru catalyst (Scheme 179).[117] Based on a series of experiments, the



Scheme 160. Plausible mechanism for Pd-catalyzed γ-C(sp^3)–H arylation of tertiary amines



Scheme 161. Pd-catalyzed arylation of unactivated δ-C(sp^3)–H bonds of free primary aliphatic amines



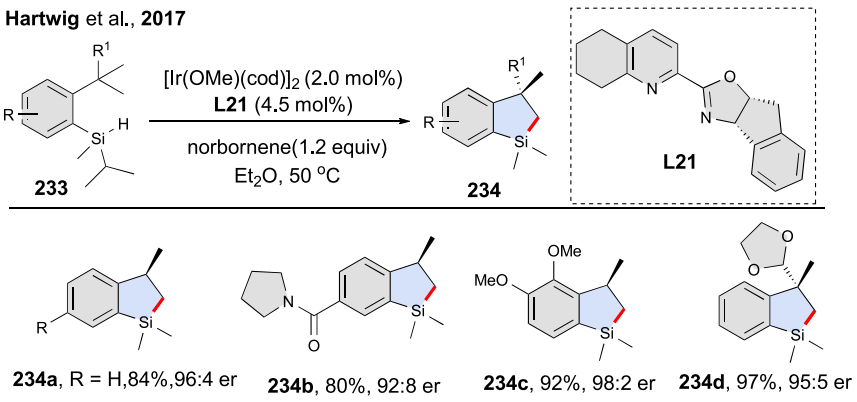
Scheme 162. Control experiments for the Pd-catalyzed arylation of unactivated δ-C(sp^3)–H bonds of free primary aliphatic amines.

(A) N-Acylated substrate **230a**–Ac did not react with PhI under standard conditions.

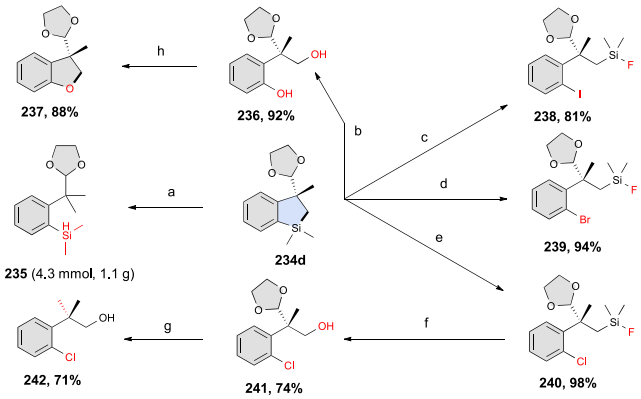
(B) The substrate amine **230c** reacted with $Pd(OAc)_2$ to produce bis-palladium intermediate **230A**. Next, the intermediate reacted with PhI to give product **231c** under standard conditions.

(C) Treatment of substrate **230d** with $Pd(OAc)_2$ (10 mol %) in CD_3CO_2D obtained 17% deuterium incorporation at the methyl groups.

authors have demonstrated that judicious selection of protecting groups for alcohol substrates could improve product selectivity. In addition, strong hydrogen bonding between substrates and solvent could enhance site selectivity under a strongly acidic reaction condition. Through this protocol, selective oxidation of distal 2° C–H bonds occurs in moderate to high yields.



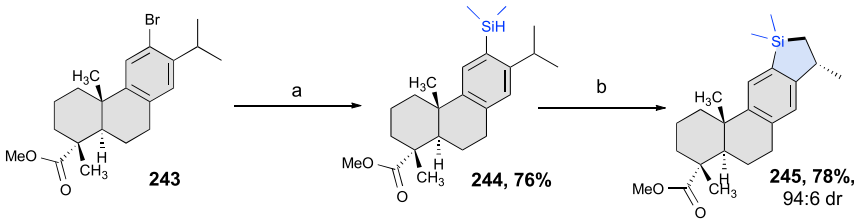
Scheme 163. Ir-catalyzed enantioselective silylation of C(sp^3)–H bonds



Scheme 164. Transformations of the enantioenriched dihydrobenzosiloles

Reaction conditions: (A) $[Ir(cod)OMe]_2$ (0.50 mol %), L21 (1.1 mol %), nbe, Et_2O, 50°C; (B) ^{t}BuOOH, ^{t}BuOK, TBAF; (C) NIS, AgF, MeCN; (D) NBS, AgF, MeCN; (E) NCS, AgF, MeCN; (F) ^{t}BuOOH, KH, TBAF; (G) HCl, THF/H_2O; and (H) DEAD, PPh_3, THF.

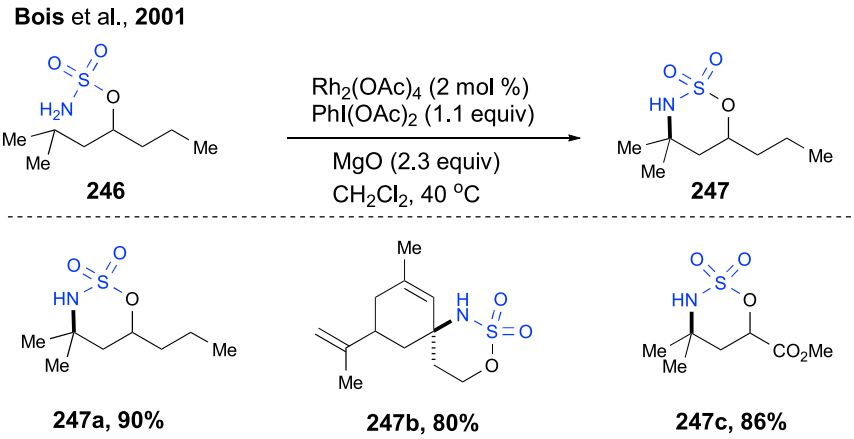
An interesting report by Bietti and Costas in 2020 described an enantioselective γ-C(sp^3)–H oxidation of free carboxylic acids that affords γ-lactones (Schemes 180 and 181).[118] In this study, either (S,S)-Mn(TIBSpdp) or (S,S)-Mn(pdp) was used as a catalyst, whereas hydrogen peroxide was employed as an oxidant. Coordination of the carboxylic acid to the catalyst proved to provide enough rigidity for high enantioselectivity and γ site selectivity. The authors found that the addition of a Brønsted acid effectively



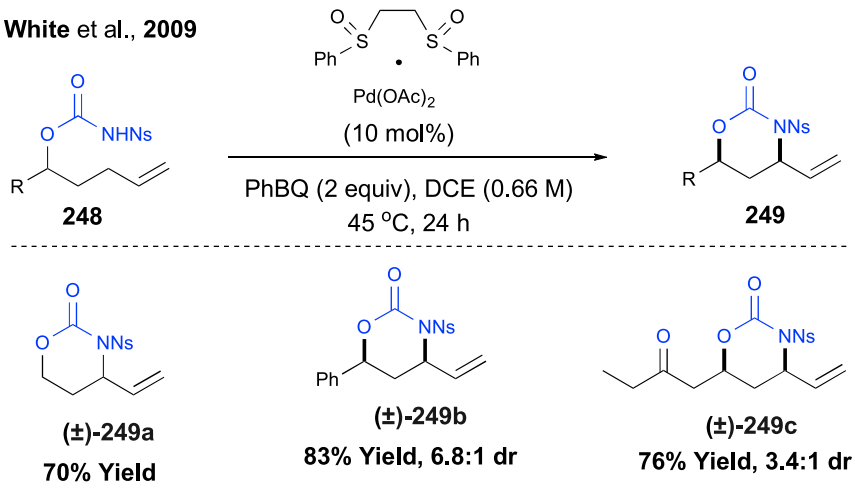
Scheme 165. Diastereoselective silylation of the C(sp^3)–H bond of dehydroabietic acid derivative

(A) Mg, THF, and Me_2SiHCl.

(B) $[Ir(cod)OMe]_2$/**L21**, nbe, Et_2O.



Scheme 166. Rh(II)-catalyzed oxidative cyclization of carbamates



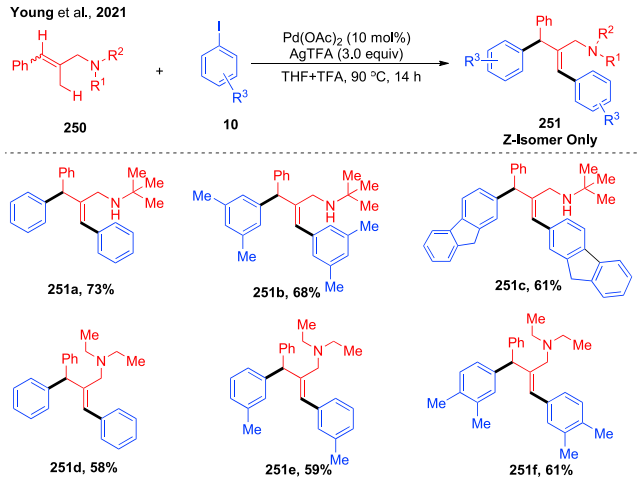
Scheme 167. Pd-catalyzed γ-C(sp^3)–H functionalization of masked alcohols

shortens reaction times. A series of γ-lactones were obtained in good yields and high enantiomeric excess (up to 99%) under mild conditions.

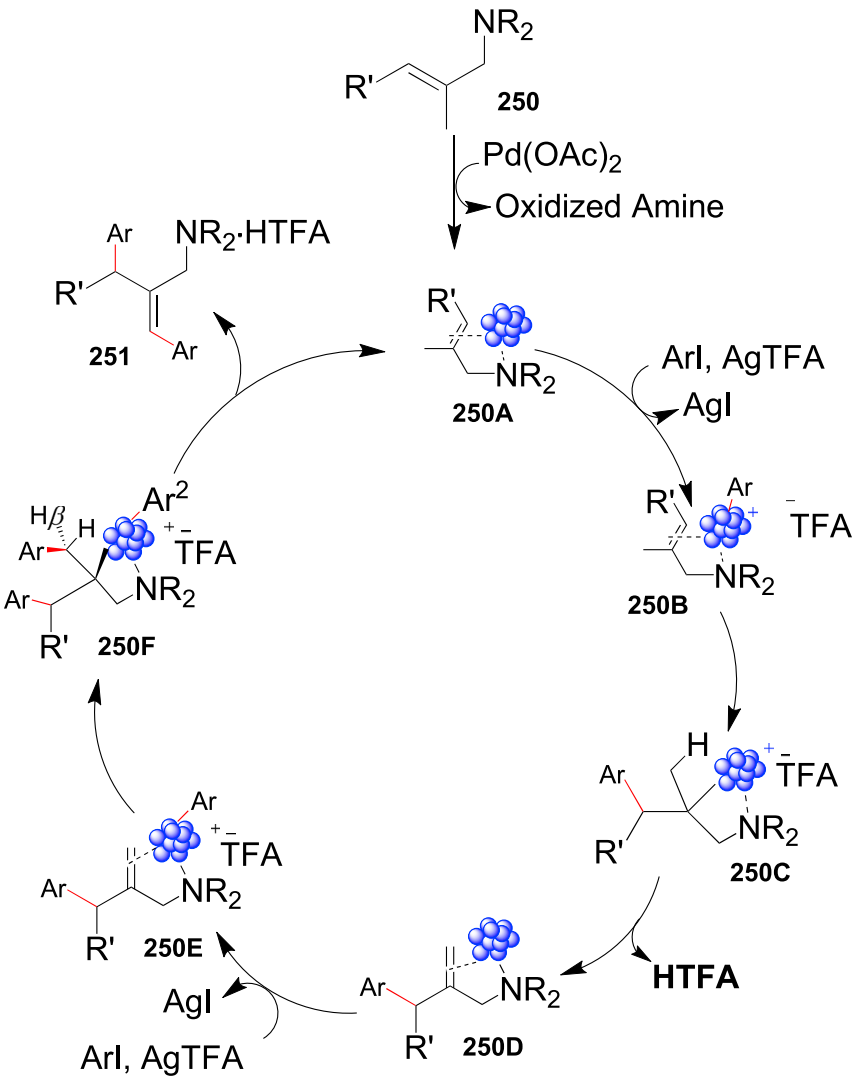
The selective remote C(sp^3)–H oxidative/hydroxylation is an important target in molecular synthesis since many biologically relevant molecules contain oxidized hydrocarbons. Transition-metal-catalyzed remote C(sp^3)–H oxidative/hydroxylation functionalization reactions are often characterized by moderate yields and mild reaction conditions. Further advances in these protocols are required before they could be applied in the synthesis of biologically relevant molecules.

HYDROGEN-ATOM TRANSFER

In recent years, radical-mediated 1,*n*-HAT has emerged as an attractive synthetic strategy and has aroused great interest among scientists. This method shows great selectivity toward distal C(sp^3)–H bonds.[119]



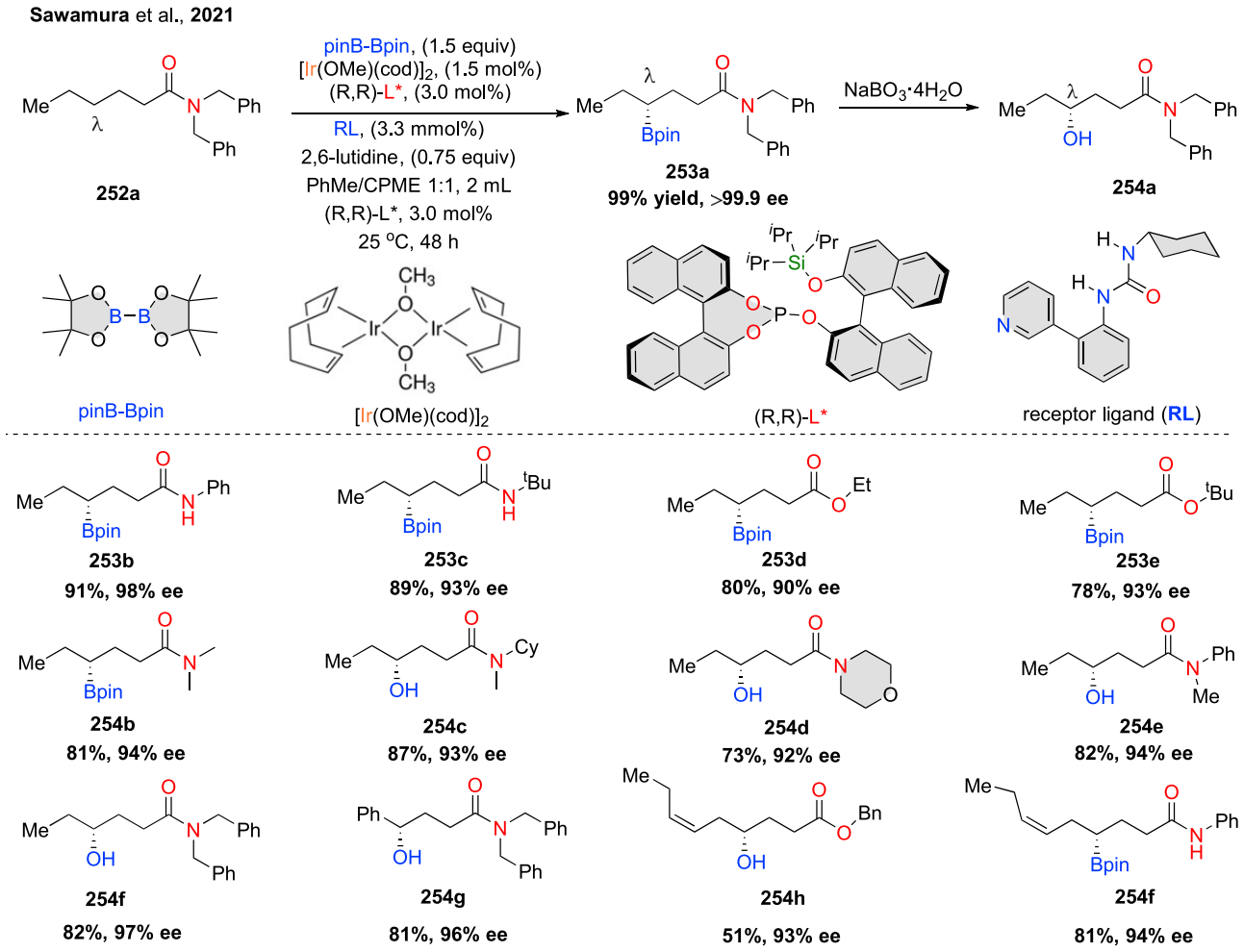
Scheme 168. Pd-catalyzed γ,γ′-diarylation of free alkenyl amines via interrupted chain walking to synthesize *Z*-selective alkenyl amines



Scheme 169. The proposed mechanism of Pd-catalyzed γ,γ′-diarylation of free alkenyl amines to synthesize *Z*-selective alkenyl amines

C–H desaturation

In 2017, Gevorgyan devised a general, efficient, and site-selective visible-light-induced Pd-catalyzed β-/γ-, γ-/δ-, and δ-/ε-desaturation of aliphatic alcohols by using the easily installable and removable Si-auxiliaries (Schemes 182 and 183).[120] A series of valuable allylic, homoallylic, and bis-homoallylic alcohols have been obtained in good yields and high regioselectivity under mild conditions. Mechanistic studies show that the reaction undergoes a visible-light-induced formation of a hybrid Pd-radical intermediate capable of the HAT process. A plausible mechanism was proposed in Scheme 184. Upon induction with visible light, the *in-situ*-generated Pd(0) complex is excited into the active Pd(0)* species, which then engages in a single electron transfer (SET) with alkyl iodide **274** to form alkyl hybrid intermediate **274A**. Next, radical species **274A** triggers a 1,*n*-HAT (n = 5–7) to afford translocated alkyl hybrid Pd-radical species **274B**, which then undergoes a direct abstraction of the β-hydrogen atom by Pd(I) (**274B** → **275** or **276** [path A]) or a



Scheme 170. The Ir-catalyzed highly enantioselective borylation of γ-C(sp^3)–H bonds in aliphatic amides and esters

β-hydride elimination to produce the alkene **275** or **276** and regenerate the Pd catalyst (path B).

The following year, the same group extended the scope to aliphatic amines by using the same strategy. A series of valuable enamines, as well as allylic and homoallylic amines, have been produced in moderate to good yields by visible-light-induced Pd-catalyzed remote desaturation of aliphatic amines (Scheme 185).[121]

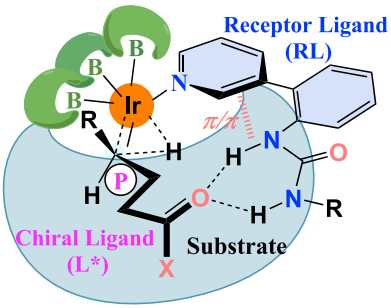
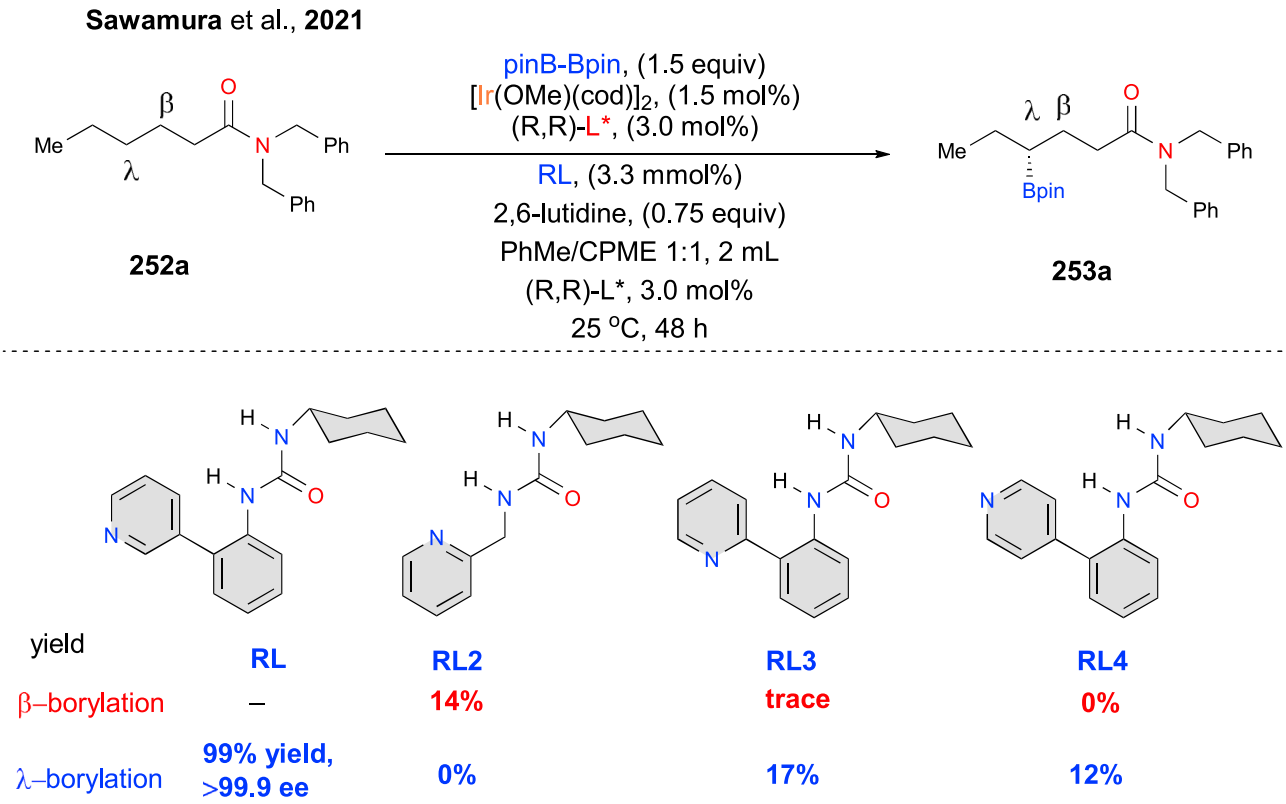


Figure 2. An enzyme-like structural cavity formed by modular assembly of an Ir center, a chiral monophosphite ligand, a urea-pyridine-based hydrogen-bond receptor ligand (RL), and pinacolatoboryl groups

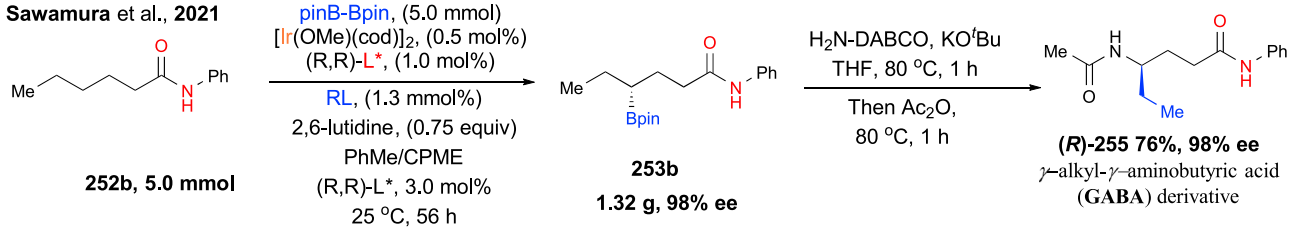


Scheme 171. Comparative experiments for different hydrogen-bond receptor ligands

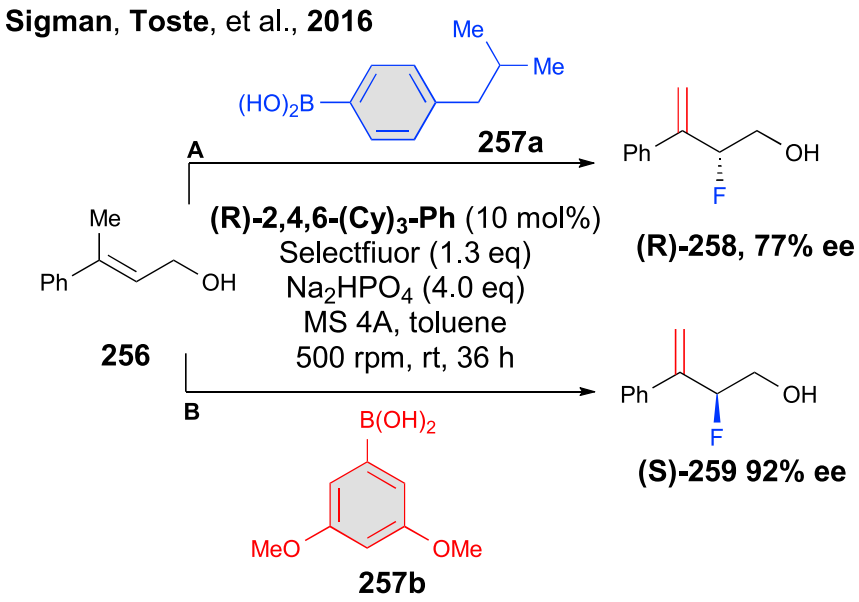
The protocol uses easily installable/removable aryl iodide-containing tethers as auxiliaries. It is noteworthy that this method is very practical and could be performed on a gram scale. The valuable homoallylic amine **278e** can be obtained in nearly quantitative yield over the three steps by this method (98%, 1.46 g) (Scheme 186).

C–H arylation

In fact, significant achievements have been made in the γ-C(sp^3)–H functionalization of ketones via a radical 1,5-HAT. In 2017, the Nevado group developed the first example of visible-light-mediated 1,5-HAT of iminyl radicals, producing a wide variety of elaborated ketones (Scheme 187).[122] In their study, Ir(ppy)$_3$ (1 mol %) was found to be an effective photoactivator, and a 4:1 ratio of CH_3CN:H_2O was proven to be the optimal solvent system in the presence of AcOH as an additive. The γ-C(sp^3)–H functionalization of a series of ketones was achieved under these mild,

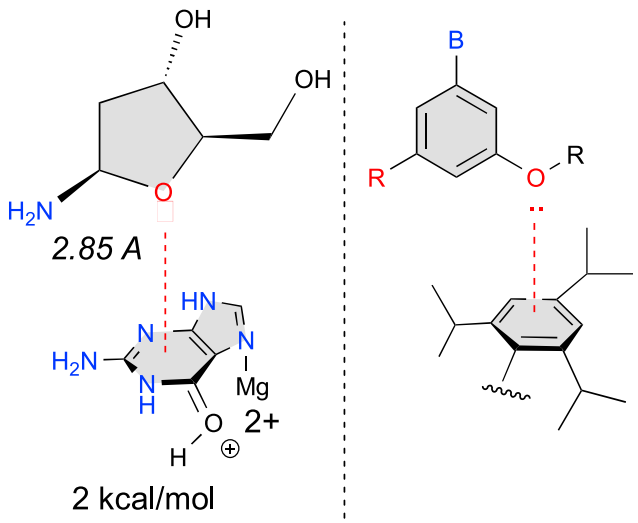


Scheme 172. Gram-scale preparation of 253b and its derivatizations γ-alkyl-γ-aminobutyric acid (GABA) derivative [(R)-255]

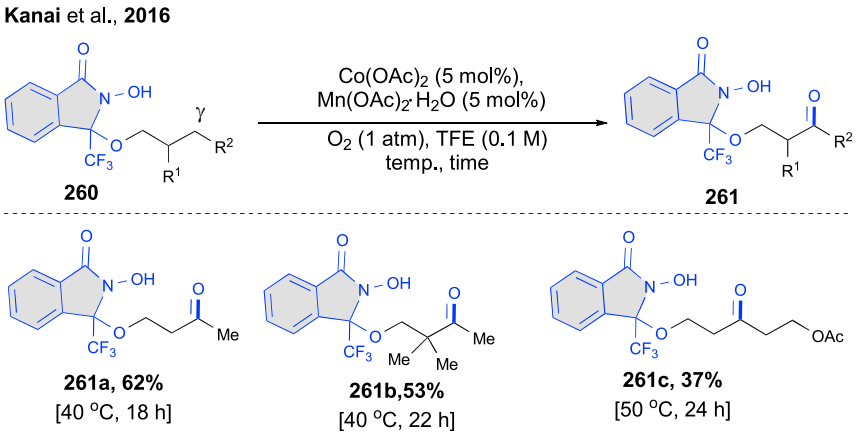


Scheme 173. The (R)-2,4,6-(Cy)$_3$-Ph-catalyzed enantioselective fluorination of allylic alcohols with different aryl boronic acids

redox neutral conditions. A plausible mechanism was proposed (Scheme 188); first, upon irradiation with 34 W blue LED, Ir(III) is excited to Ir(III)*, which then gives 1e$^-$ to the acyl oxime **279a** with the concomitant cleavage of the NO bond. Subsequently, iminyl radical **279A** and oxidized photocatalyst (Ir(IV)) are generated *in situ*. Then, the iminyl radical **279A** undergoes a 1,5-HAT to produce carbon-centered radical **279B**, which undergoes intramolecular homolytic aromatic substitution via a Minisci-type reaction to give rise to intermediate **279C**. Following this, the intermediate **279C** is oxidized by Ir(IV) to form imine **279D** and regenerate the photocatalyst Ir(III). Finally, **279D** is hydrolyzed by AcOH/H_2O to yield the ketone product **280a**.



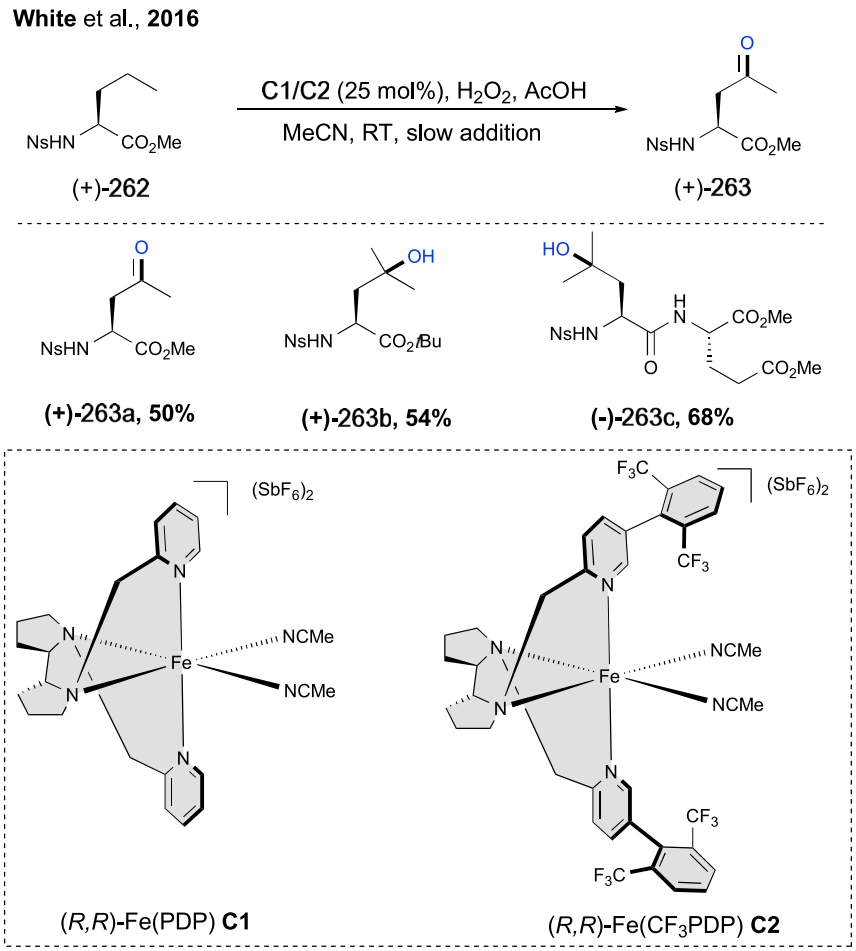
Scheme 174. The qualitative description of potential lone pair-π interaction between aryl boronic acids and chiral phosphoric acids



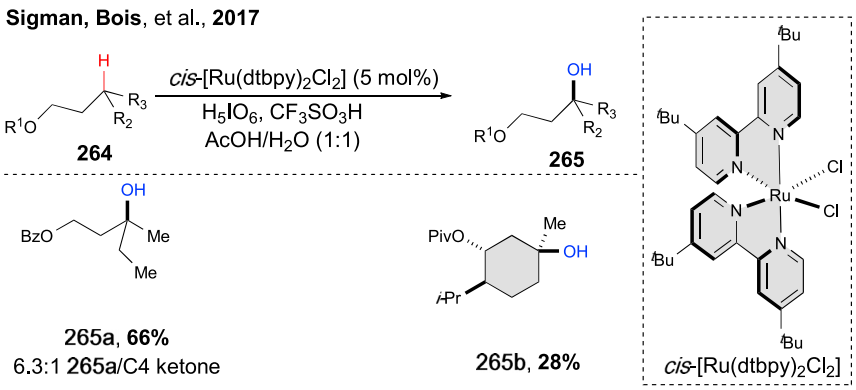
Scheme 175. The methylene C(sp^3)–H oxegynation of aliphatic alcohols

C–H bromination

Furthermore, the 1,5-HAT strategy was implemented to achieve selective bromination of γ-methylene C(sp^3)–H bonds of aliphatic amides by the Yu group in 2017



Scheme 176. Iron-catalyzed remote C(sp^3)–H oxidative functionalization of amino acids and peptides



Scheme 177. Ruthenium-catalyzed C–H hydroxylation of C(sp^3)–H bonds

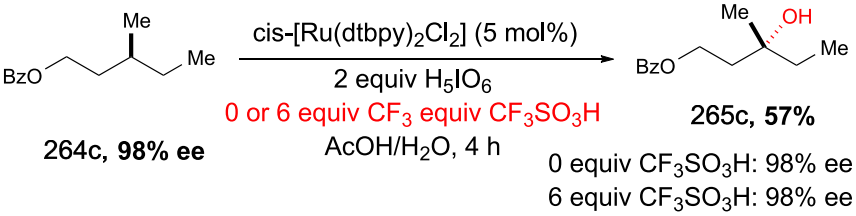
(Scheme 189).[123] In this work, *N*-bromosuccinimide (NBS) was employed as the brominating reagent, and catalytic amounts of Cu^{II}/phenanthroline complexes were utilized as catalysts. A variety of substituted aliphatic amides were efficiently transformed into corresponding γ-brominated products in good yields.

C–H azidation

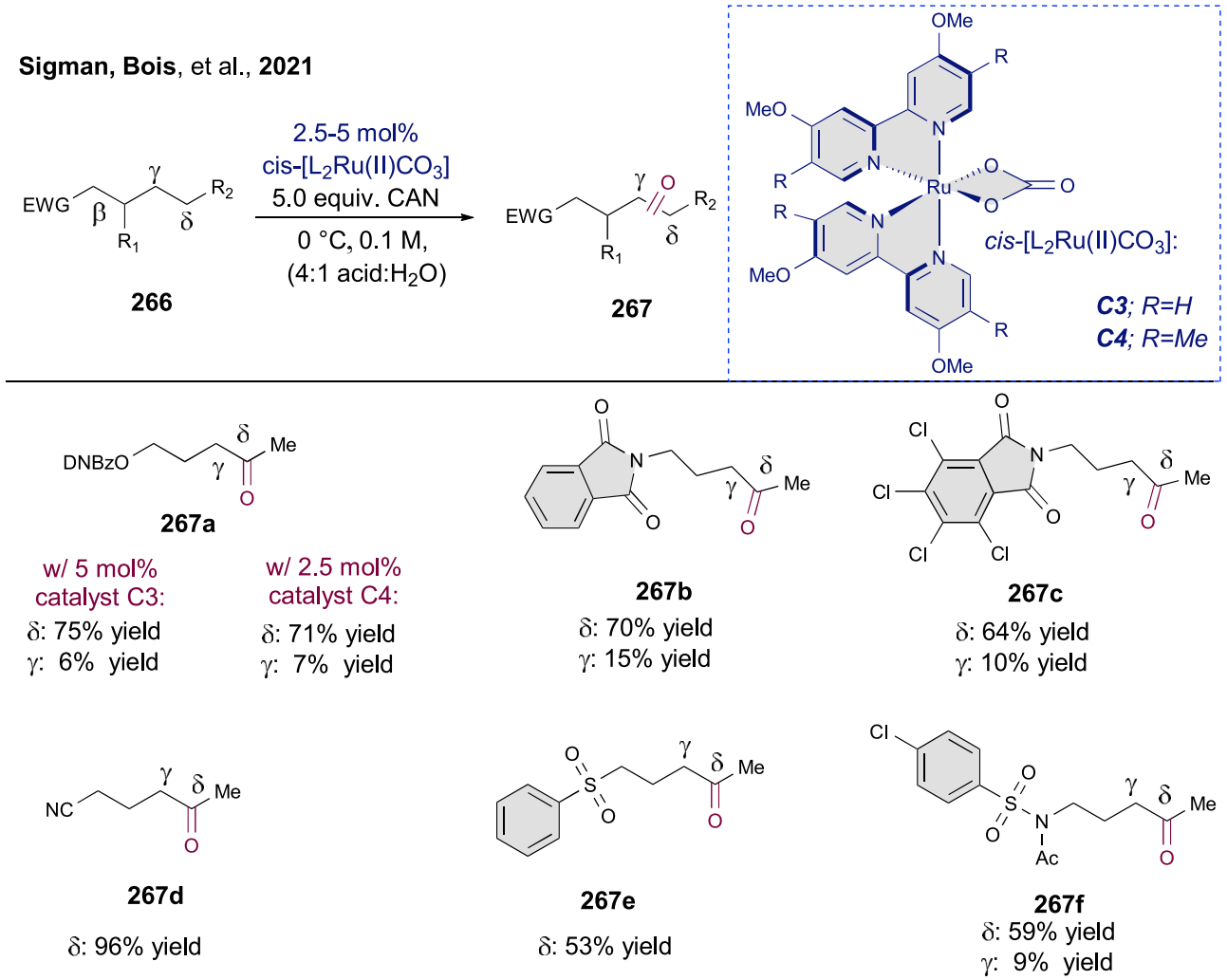
Additionally, Zhu and co-workers reported an Fe(III)-catalyzed distal γ-C(sp^3)–H bond azidation reaction of structurally diverse ketoxime esters (Scheme 190).[124] In the reaction, $TMSN_3$ was employed not only as a nitrogen source but also as a reductant to reduce $Fe(acac)_3$ and generate the active Fe(II) species *in situ*. A plausible mechanism was proposed (Scheme 191); upon reduction, the Fe(II) species undergoes a single electron transfer (SET) with the ketoxime ester **283** to form the iminyl radical **283A**. Subsequently, protonation of **283A** with HOAc generates the more electrophilic radical cation **283B**, which then undergoes 1,5-HAT to produce the translocated carbon radical **283C**. Upon Fe-mediated redox azido transfer, the carbon radical **283C** generates the azido iminium intermediate **283D** and restores the Fe(II) catalyst. Finally, hydrolysis of **283D** affords γ-azido ketones **284**.

C–H alkenylation

The radical-mediated 1,*n*-HAT has also been proven effective as an attractive synthetic strategy to selectively functionalize γ-C–H bonds of alcohols. In 2019, Gevorgyan and co-workers developed a radical relay Heck reaction at unactivated γ-C(sp^3)–H sites of alcohols via 1,6-HAT (Scheme 192).[125] The incorporation of xantphos with the Pd catalyst under blue LEDs provided an effective catalytic system. The reaction does not require the use of exogenous photosensitizers or external oxidants. Instead, his protocol utilizes a novel, easily installable and readily removable

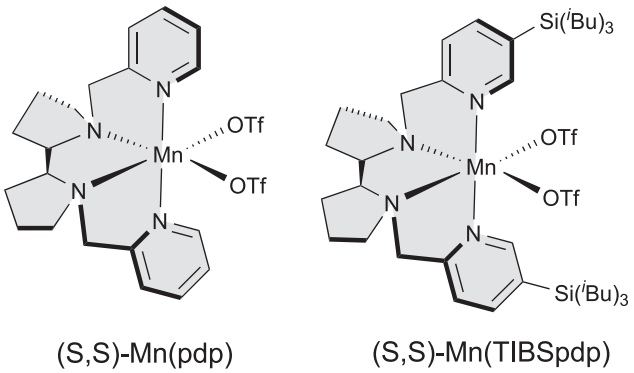


Scheme 178. Enantiospecific hydroxylation of tertiary C–H substrates

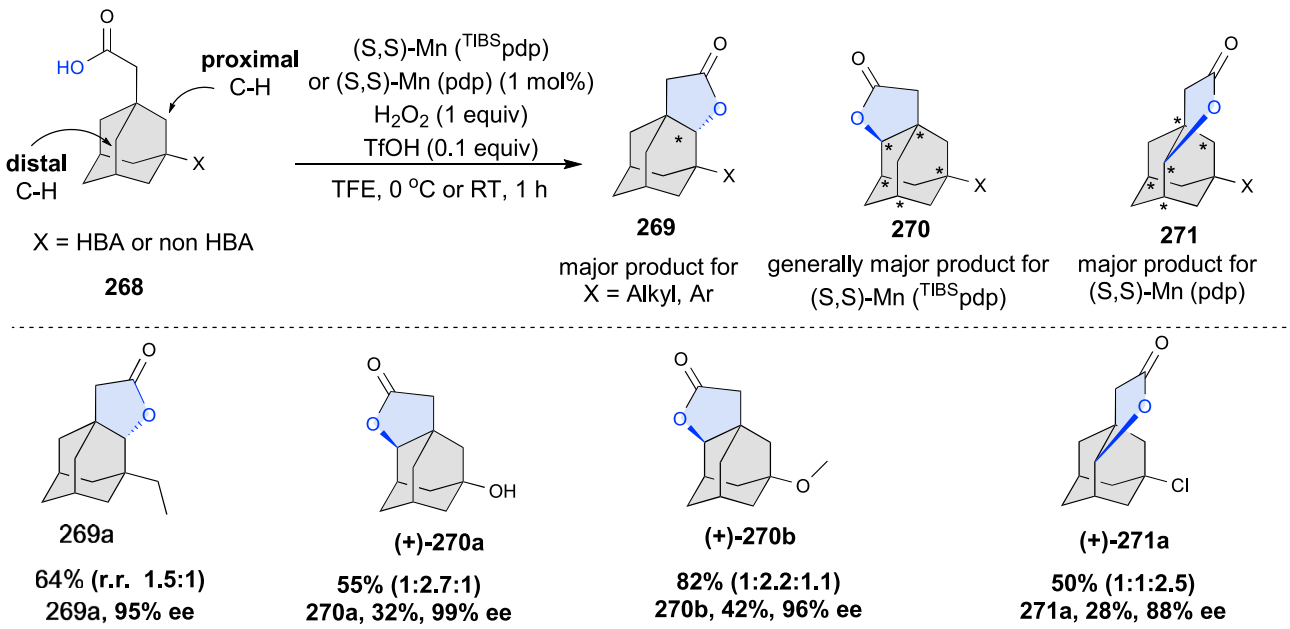


Scheme 179. The site-selective oxidation of remote aliphatic C–H bond by bis(bipyridine)Ru catalyst

silicon-based auxiliary that enables I-atom/radical translocation events at the γ-position selectively. Various substituted alkenes were efficiently transformed into their corresponding γ-Heck products in good yields. It is worth mentioning that

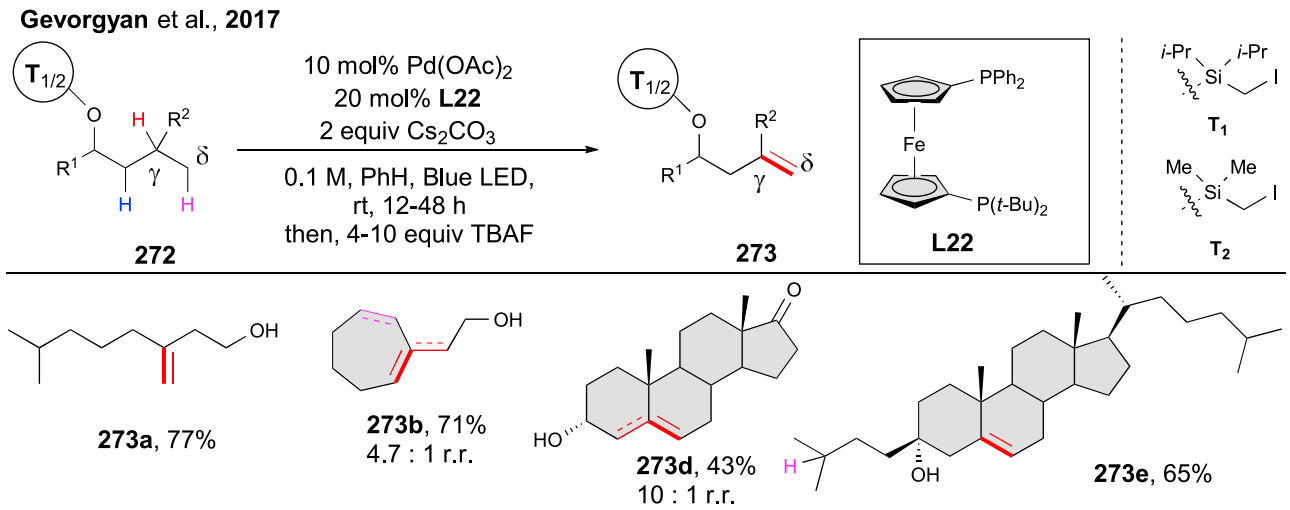


Scheme 180. The structures of catalysts (S,S)-Mn(TIBSpdp) and (S,S)-Mn(pdp)

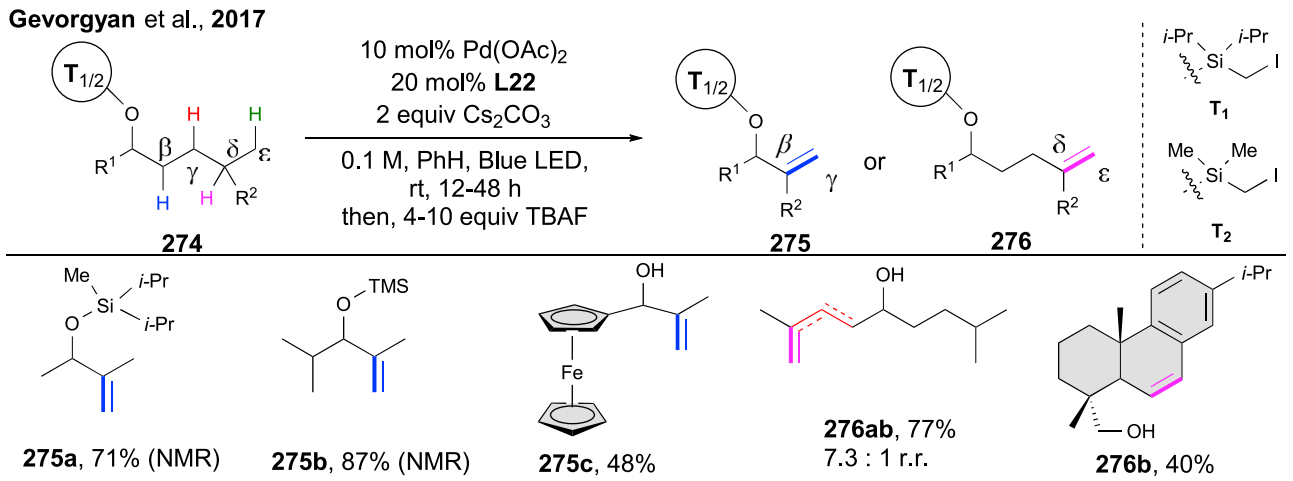


Scheme 181. Enantioselective γ-C(sp^3)–H oxidation of free carboxylic acids

substrates containing competitive tertiary C–H bonds were compatible, and γ-functionalized alkenols were still obtained as the sole regioisomers due to the higher preference of the Si-auxiliary for 1,6-HAT. A plausible mechanism is depicted in Scheme 193; upon irradiation with visible light, the Pd(0) complex is excited into the active Pd(0)* species, which undergoes single electron transfer (SET) with alkyl iodide **285** to produce the hybrid Pd-radical species **285A**. Subsequently, **285A** triggers a 1,6-HAT to afford the radical species **285C**, which reversibly forms the I-atom transfer intermediate **285B**. Then, either intermediate **285B** or **285C** couples with alkene to produce the Pd-radical species **285D**, which upon β-H elimination yields the radical relay Heck product 286 and regenerates the Pd(0) catalyst.



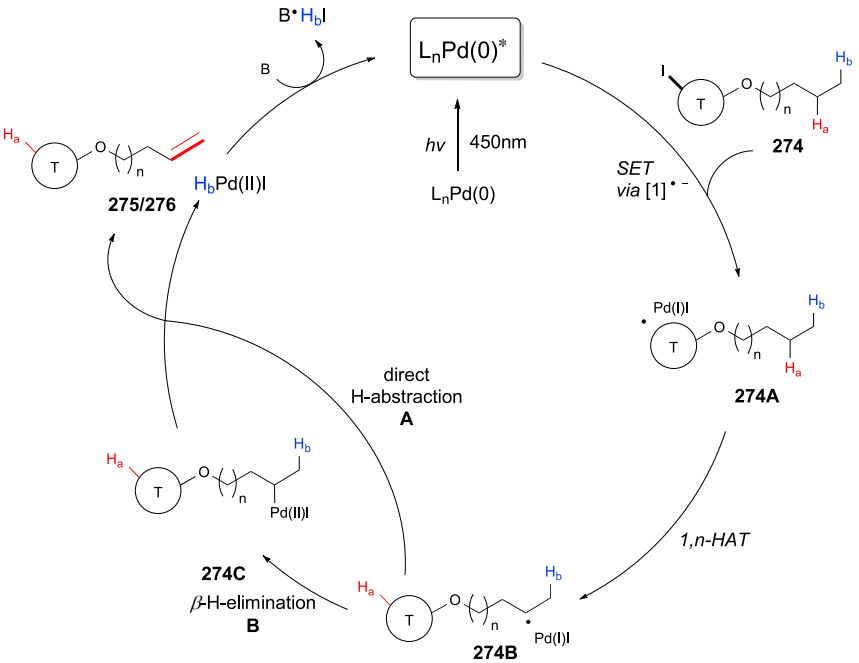
Scheme 182. The auxiliary-enabled visible-light-induced Pd-catalyzed remote γ-/δ-desaturation of alcohols



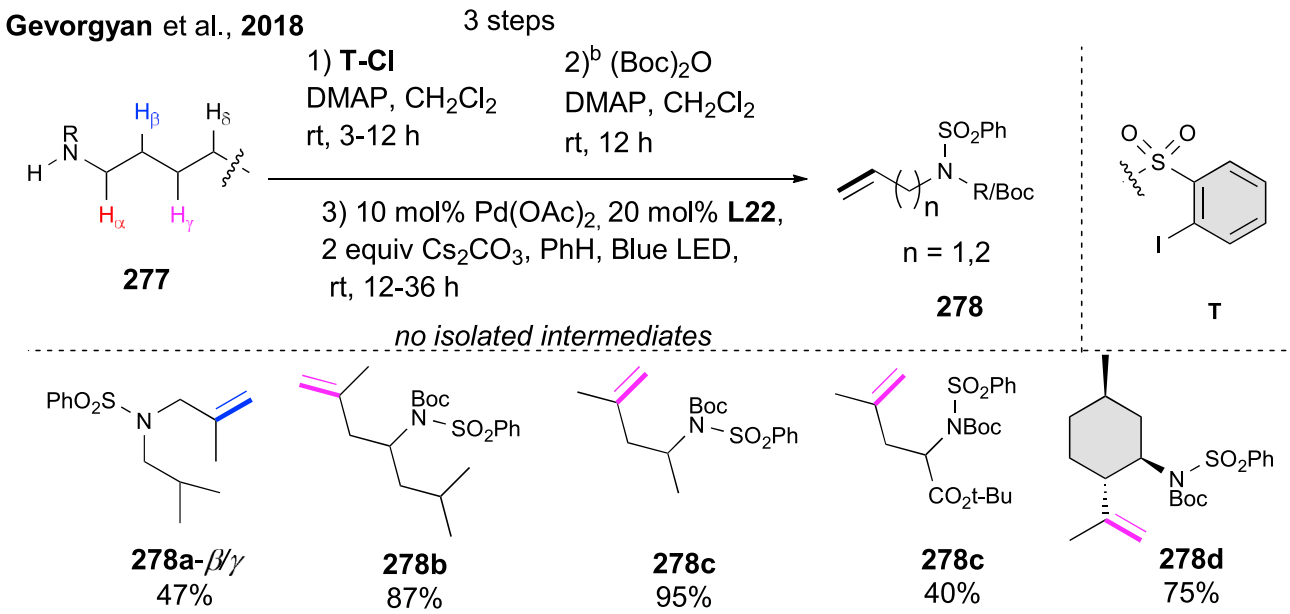
Scheme 183. The auxiliary-enabled visible-light-induced Pd-catalyzed remote β-/γ-, and δ-/ε-desaturation of alcohols

C–H alkylation

Concurrently, the Studer group reported intermolecular γ-C(sp^3)–H alkylation of ketones by using an α-aminoxy acid auxiliary via 1,5-HAT photoredox catalysis (Scheme 194).[126] The starting material oxime ethers were readily prepared by the condensation of the corresponding ketones with α-aminoxy acid. The Ir-based photocatalyst (Ir(III)(dFCF_3ppy)$_2$(dtbbpy)PF_6 **PC1**) was found to be optimal in this reaction system. CsF was identified as an effective base, whereas other potassium and sodium salts such as K_2CO_3, KOAc, NaOAc, and Na_2HPO_4 provided inferior results. Various 2-arylacrylates and oxime ethers exhibited good reactivity and the corresponding γ-C(sp^3)–H functionalized ketones were obtained in good to excellent yields. A plausible mechanism is depicted in Scheme 195; first, upon irradiation

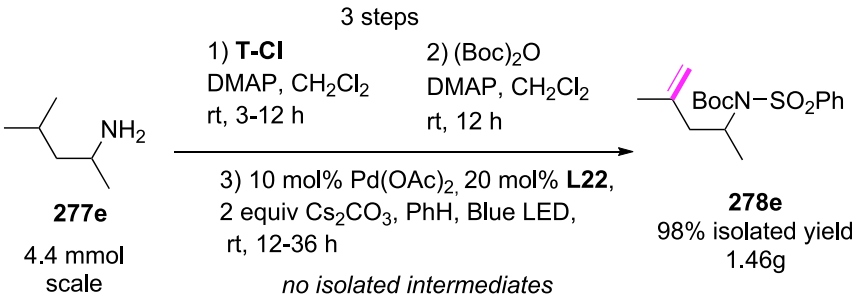


Scheme 184. The proposed mechanism of visible-light-induced Pd-catalyzed remote desaturation of aliphatic alcohols

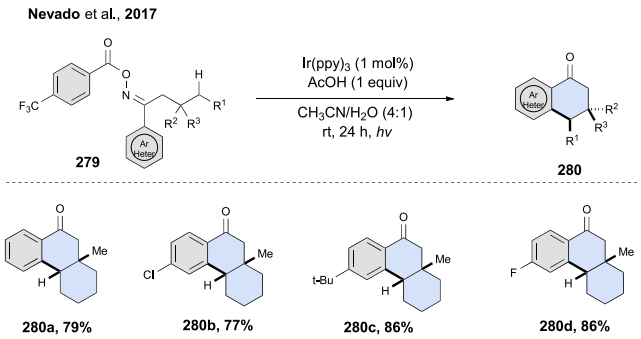


Scheme 185. The auxiliary-enabled visible-light-induced Pd-catalyzed remote β-γ and γ-δ desaturation of amines

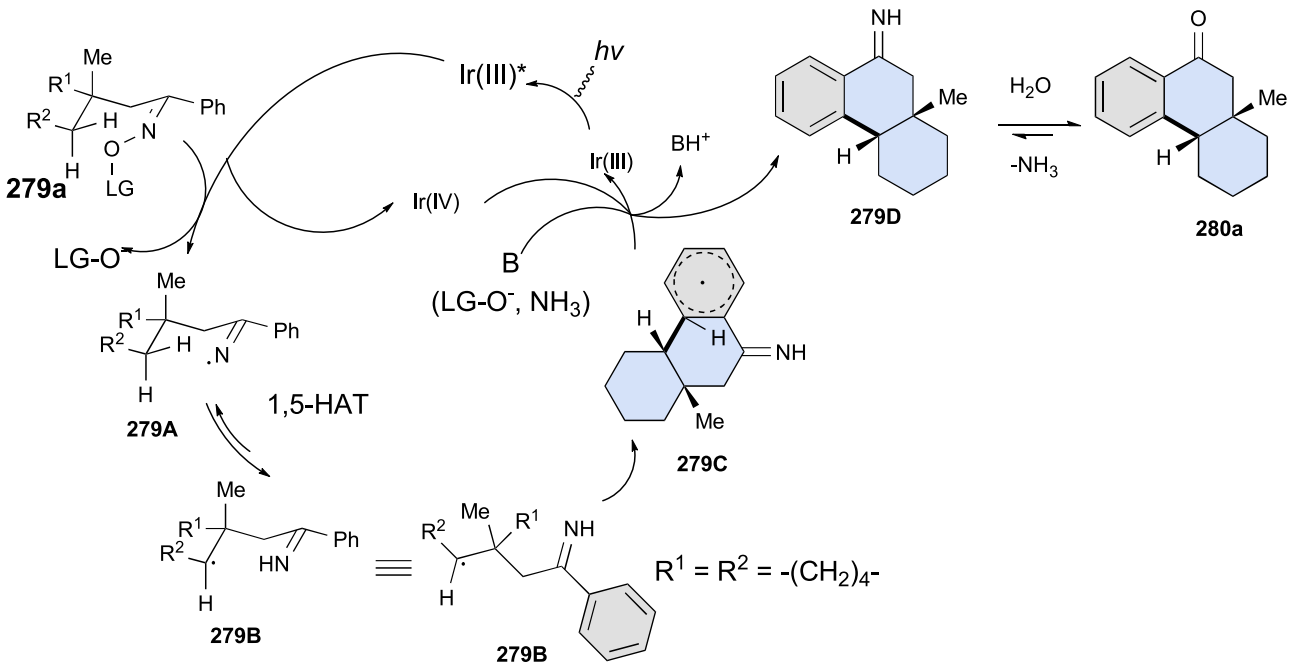
with visible light, Ir(III)(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$ is excited to an *Ir(III)(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$ complex, which is reduced by carboxylate **287A** via single electron transfer (SET) to produce the carboxyl radical **287B** and Ir(II)(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$. Subsequently, the iminyl radical **287C** is generated through the fragmentation



Scheme 186. A gram-scale desaturation of amine 277e into homoallylic amine 278e by the auxiliary-enabled visible-light-induced Pd-catalyzed



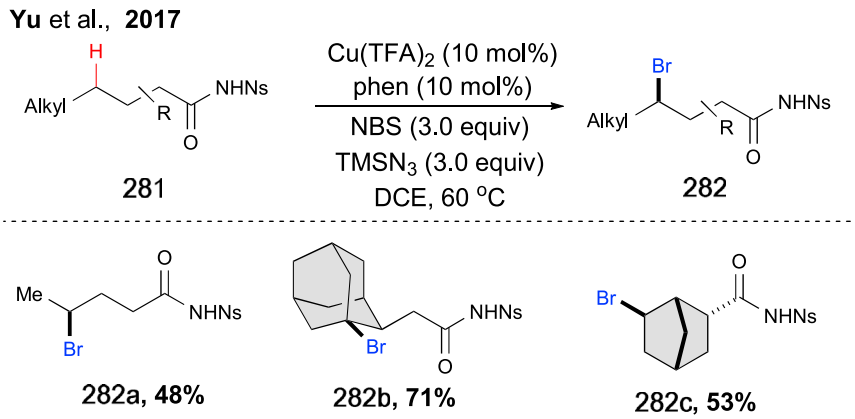
Scheme 187. Visible-light-mediated γ-C(sp^3)–H functionalization of ketones through a 1,5-HAT



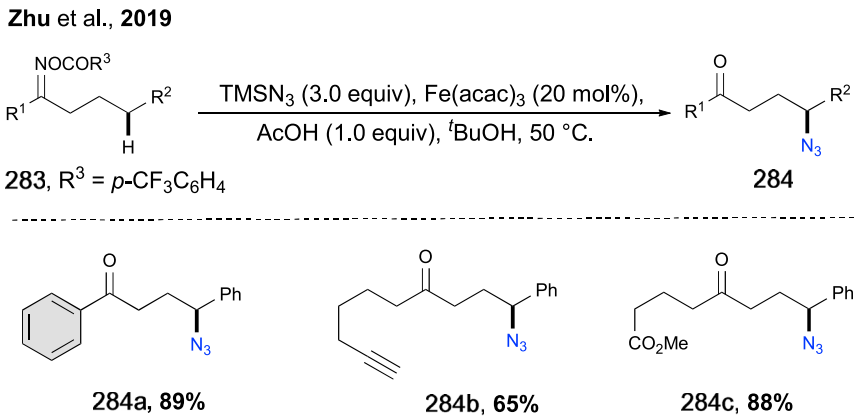
Scheme 188. Proposed reaction mechanism for visible-light-mediated γ-C(sp^3)–H functionalization of ketones

of the carboxyl radical **287B** via the loss of CO_2 and acetaldehyde. The iminyl radical **287C** undergoes a 1,5-HAT forming the carbon-centered radical **287D**, which then reacts via intermolecular conjugate addition to provide the adduct radical **287E**. Upon which, the intermediate **287E** is reduced by Ir(II)(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$ to generate **287F** and reproduce the photocatalyst Ir(III)(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$. Finally, **287F** is protonated and hydrolyzed to produce the γ-functionalized ketones **288**.

In 2019, Roizen and co-workers discovered sulfamate-ester-derived nitrogen-centered-radical-mediated 1,6-HAT processes to achieve γ-alkylation of alcohols (Scheme 196).[127] In the presence of light, a photocatalyst, and K_2CO_3 in MeCN, the directed Giese reaction effectively provided the desired products in good yields.



Scheme 189. Bromination of γ-methylene C(sp^3)–H bonds of aliphatic amides

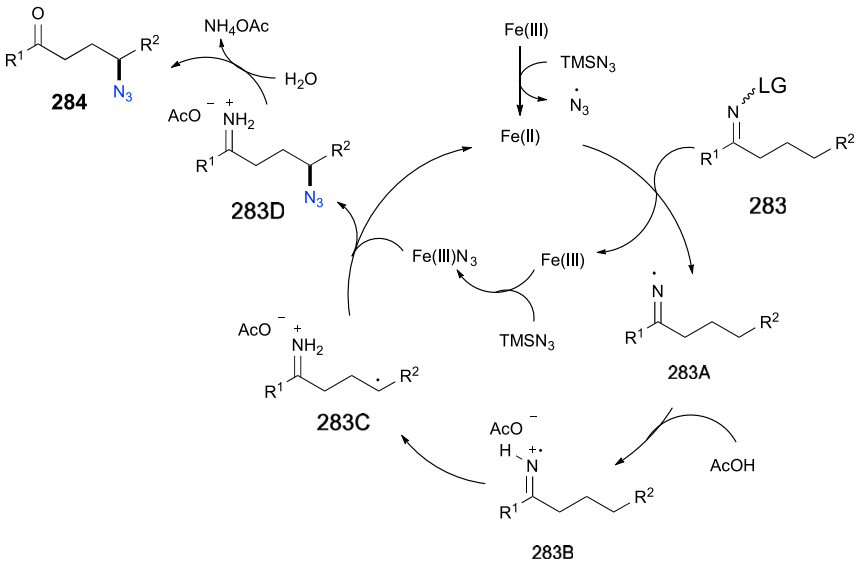


Scheme 190. The Fe(III)-catalyzed distal γ-C(sp^3)–H azidation of ketones

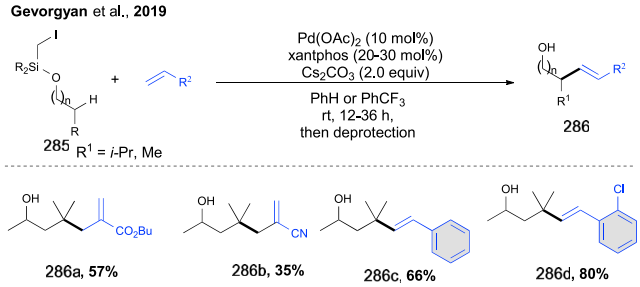
Visible-light-mediated γ-C(sp^3)–H functionalizations via 1,*n*-HAT have developed rapidly. This approach provides an attractive catalytic option with high selectivity and has shown effectiveness in the synthesis of complex molecules. However, the number of available photocatalysts capable of promoting these chemical transformations has been quite limited. Most available photocatalysts are Ru and Ir complexes, as well as organic dyes. More efforts are needed to find new effective photocatalysts for this field. In addition, the scope of these reactions is limited in terms of substrate activation, and they sometimes require the use of too many additives, thus more work is needed to improve the practicality of the overall protocol.

CONCLUSIONS AND FUTURE DIRECTIONS

The development of transition-metal-catalyzed site-selective γ- and δ-C(sp^3)–H functionalization processes detailed in this review mainly includes the following reactions: γ-C(sp^3)–H acetylation, alkenylation, alkoxylation, alkyation, amination, arylation, bromination, carbonylation, cyclization, diazenylation, germanylation, heteroarylation,



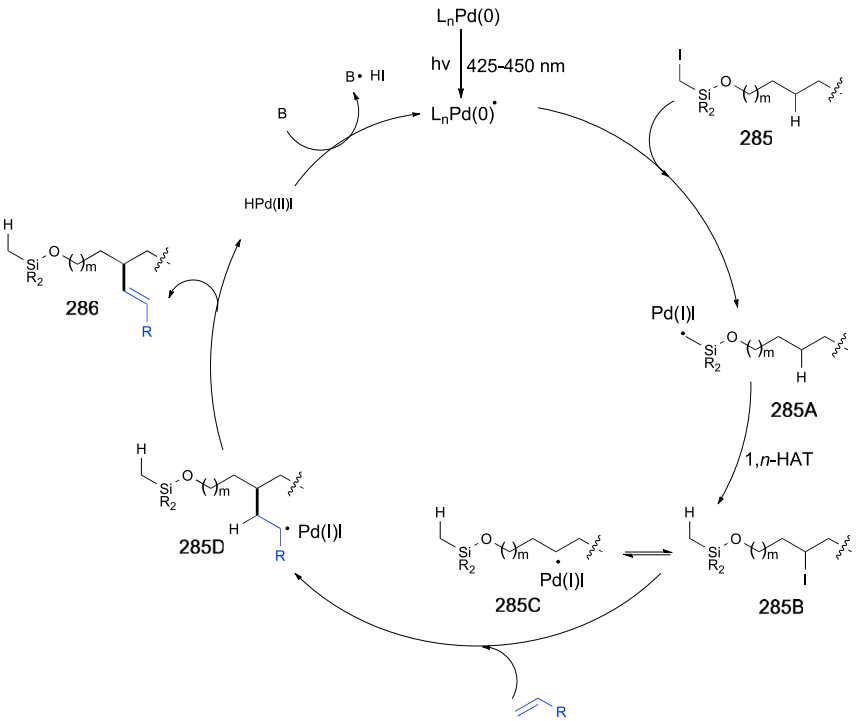
Scheme 191. Plausible mechanism for the Fe(III)-catalyzed γ-C(sp^3)–H bond azidation reaction of ketones



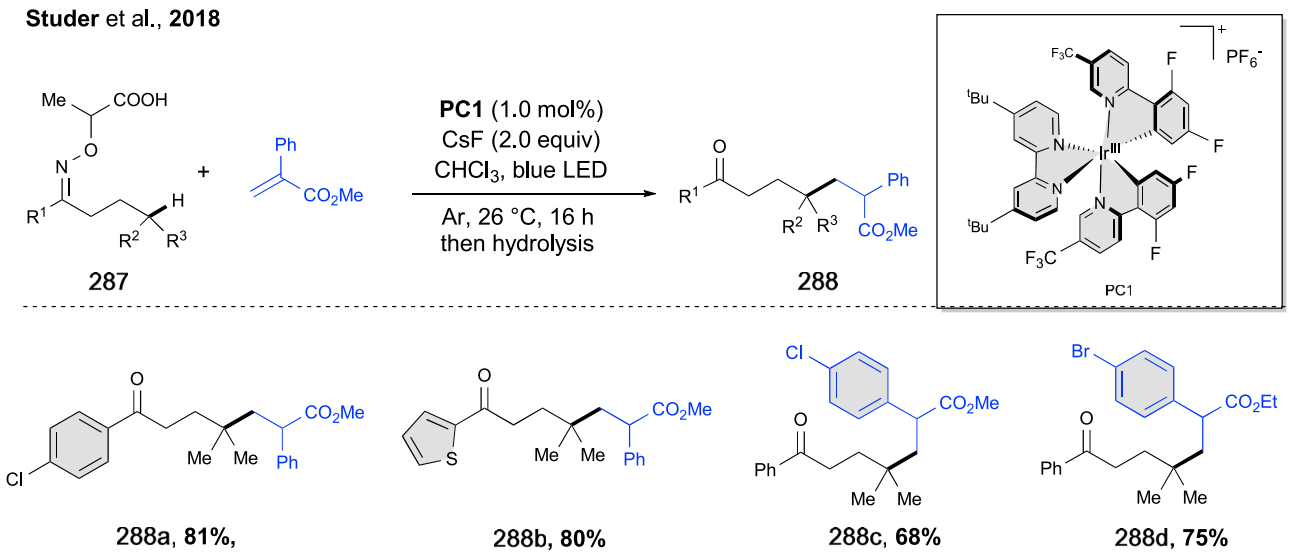
Scheme 192. Heck reaction at unactivated γ-C(sp^3)–H sites of alcohols

hydroxylation, lactamization, lactonization, oxygenation, silylation, trifluoromethylation, enantioselective arylation, and fluorination and δ-C(sp^3)–H silylation, oxidation, cyclization, arylation, alkenylation, alkylation, and borylation of simple aliphatic substrates via insertion, oxidation, non-covalent interaction, and HAT strategies directed by auxiliary groups, TDGs, and native functional groups. Additionally, the mechanisms of these reactions were detailed, and examples of natural products and drug molecules constructed according to these protocols were discussed.

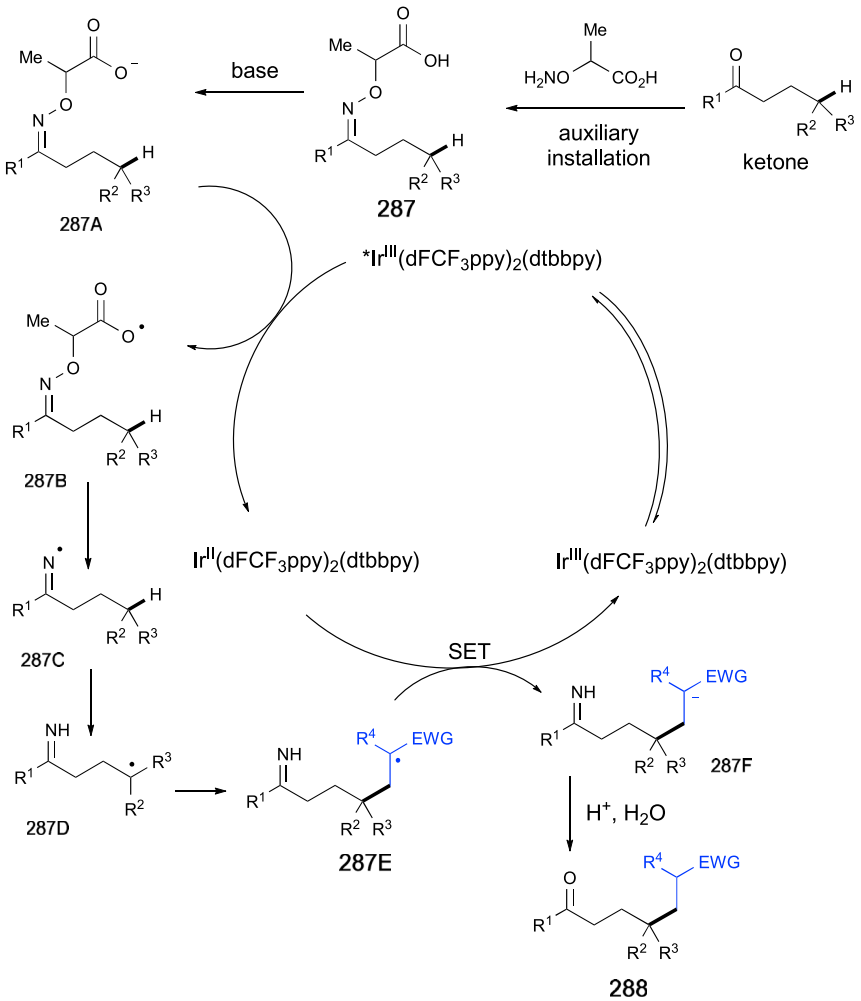
As discussed, transition-metal-catalyzed site-selective γ- and δ-C(sp^3)–H functionalization research has achieved noticeable progress in the past years; however, these strategies still require significant development to improve the practicality and versatility of these remote transformations. First, site-selective γ- and δ-C(sp^3)–H functionalization of the majority of aliphatic substrates is still difficult to achieve via a TDG or non-directing-group strategy.



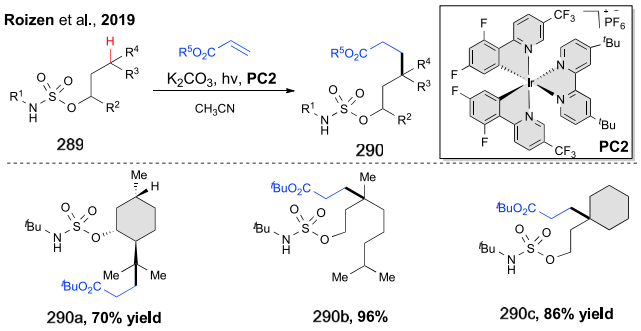
Scheme 193. Proposed mechanism for the Heck reaction at unactivated γ-C(sp^3)–H sites of alcohols



Scheme 194. The intermolecular γ-C(sp^3)–H alkylation of ketones using an α-aminoxy acid auxiliary



Scheme 195. Suggested mechanism for the intermolecular γ-C(sp^3)–H alkylation of ketones



Scheme 196. The γ-C(sp^3)–H alkylation of alcohols by sulfamate-ester-derived nitrogen-centered-radical-mediated 1,6-HAT processes

Secondly, γ- and δ-C(sp^3)–H functionalization reaction scope in aliphatic substrates such as aldehydes, ketones, thiols, secondary amines, and tertiary amines is narrow. Thirdly, enantioselective γ- and δ-C(sp^3)–H functionalization of aliphatic substrates is still in its infancy. Fourthly, precious transition metals, such as Pd, are still the most widely used catalysts, and these reactions often require catalyst loadings of ∼10 mol % to be practical and effective. Fifth, harsh reaction conditions, such as high temperatures, long reaction times, and the use of stoichiometric amounts of metal salts are usually required. To overcome these shortcomings and offer broadly applicable synthetic methods, the development of novel strategies involving the use of a TDG, an external ligand, or an ancillary ligand to achieve γ- and δ-C(sp^3)–H functionalization of unprotected aliphatic substrates is still needed. The external ligand strategy has particularly proved effective in recent studies and is predicted to help resolve many of the aforementioned challenges. Furthermore, the development of inexpensive and effective catalysts and the exploration of new technologies for recycling precious metal catalysts could significantly enhance the cost efficiency of these processes. Additionally, it will be necessary to develop environmentally friendly solutions, such as using oxygen as an oxidant and developing electrocatalytic and/or photocatalytic remote C(sp^3)–H activation strategies. Further advances in remote C(sp^3)–H functionalization require developing efficient catalytic enantioselective functionalization methodologies. Finally, the development of novel catalytic systems to achieve these remote transformations under mild conditions still needs further investigation. Finally, it is important to utilize these techniques in the synthesis of structurally complex relevant molecules, enabling faster access to drug candidates and biomolecules.

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AUTHOR CONTRIBUTIONS

H.G. proposed the topic of the review. B.L. investigated the literature and prepared the manuscript. M.E. and H.G. helped to revise the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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