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Pd-catalyzed bidentate auxiliary assisted remote C(sp^3)–H functionalization

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Pd-catalyzed C–H functionalisation affords effective synthetic tools to construct C–C and C–X bonds. Despite the challenges, the distal functionalization of C(sp^3)–H bonds has witnessed significant developments and the use of bidentate auxiliaries has garnished this area by providing an opportunity to control reactivity as well as selectivity beyond proximal sites. This article covers the recent developments on the Pd-catalyzed bidentate auxiliary-assisted distal C(sp^3)–H functionalization and is categorized based on the nature of functionalizations.

1. Introduction

Transition-metal-catalyzed functionalization of C–H bonds has revolutionized the state of art in modern trends of retrosynthetic disconnections with amenable late-stage diversification of complex molecules.[1] The applicative potential of ubiquitous C–H bond as an ideal functional core is supported by representative paradigms over the years.[2] By obviating the need to pre-functionalize the starting materials, it has offered a greener strategy to synthetic chemists. The demand for the selective functionalization of inert C–H bonds is still a challenging task. Over the last decade, the functionalization of C(sp^2)–H bonds has witnessed extensive progress[3] while that of C(sp^3)–H is still underdeveloped, particularly the distal functionalization. Owing to the lower acidity of C(sp^3)–H bonds, absence of π-bonds to coordinate with the metal of choice, a low-lying σ* orbital and the flexible nature of alkyl groups, the selective functionalization of such inert C–H bonds offers a challenging goal. To this end, early organometallic findings have revealed that a five-membered metallacycle is preferably favoured over a larger one (Scheme 1A)[4] as spurred by the initial seminal studies on proximal C–H functionalization concisely demonstrated by Murai, Sanford, Daugulis, Yu and others (Scheme 1B).[5] Carrying out functionalization at distal positions demands intermediary

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of larger metallacycles (six-membered or more), which have thermodynamic stability constraints than the five-membered metallacycles (Scheme 2A). This intrinsic preference for proximal cyclometallation (β-C(sp^3)–H) than distal one (γ/δ-C(sp^3)–H) also offers a challenge for activation of distal sp^3 C–H bonds. To address the proclivity in the functionalization of C–H distal bonds, the efforts put in by the researchers to employ newer catalysts, ligands and the use of tailored directing groups (DGs) have emerged as an efficient synthetic strategy to promote both the selectivity and reactivity beyond proximity. Within the realm of the directed C–H bond functionalization, achieving high positional selectivity demands coordination of the metal followed by the cleavage of C–H bond. In order to have impressive and substantial results, the required impetus entails the combination of transition-metal-catalyst and a tethered DG.

Palladium regarded as the ''champion catalytic metal'', offers selectivity primarily either by C–H activation to generate a palladacycle or/and functionalization of the resulting palladacycle. Pertinently, the viability of the Pd-catalysed regioselective functionalization is chiefly ruled by the thermodynamics of the metallacycle.[6] Among DGs, bidentate ones are an important tool in accessing remote C–H activation.[7] The tunable coordinating ability, ease of metal chelation coupled with reversible coordination offers preferential use of bidentate DGs over monodentate ones (Scheme 2B). Followed by the pioneering use of 8-aminoquinoline amide and picolinamide as bidentate auxiliaries by Daugulis in 2005,[8] a number of others *viz*;

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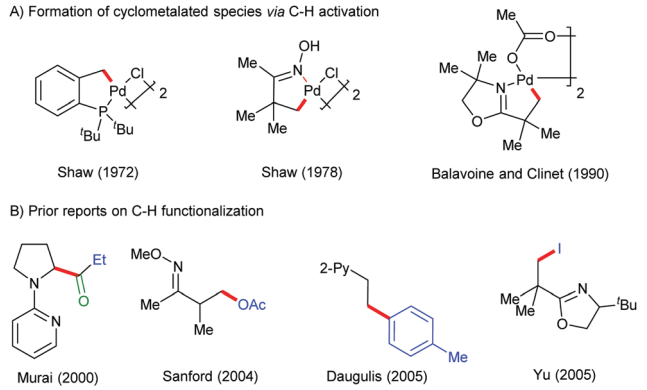
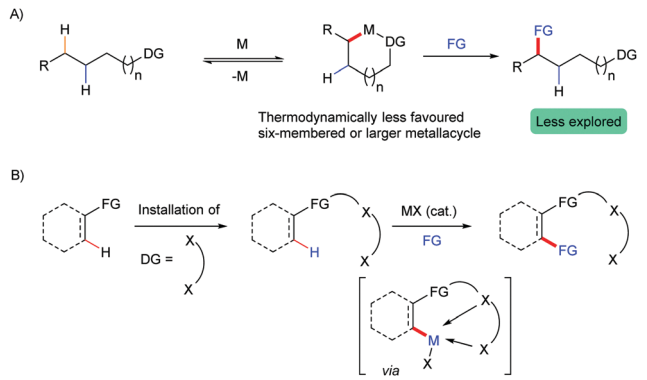


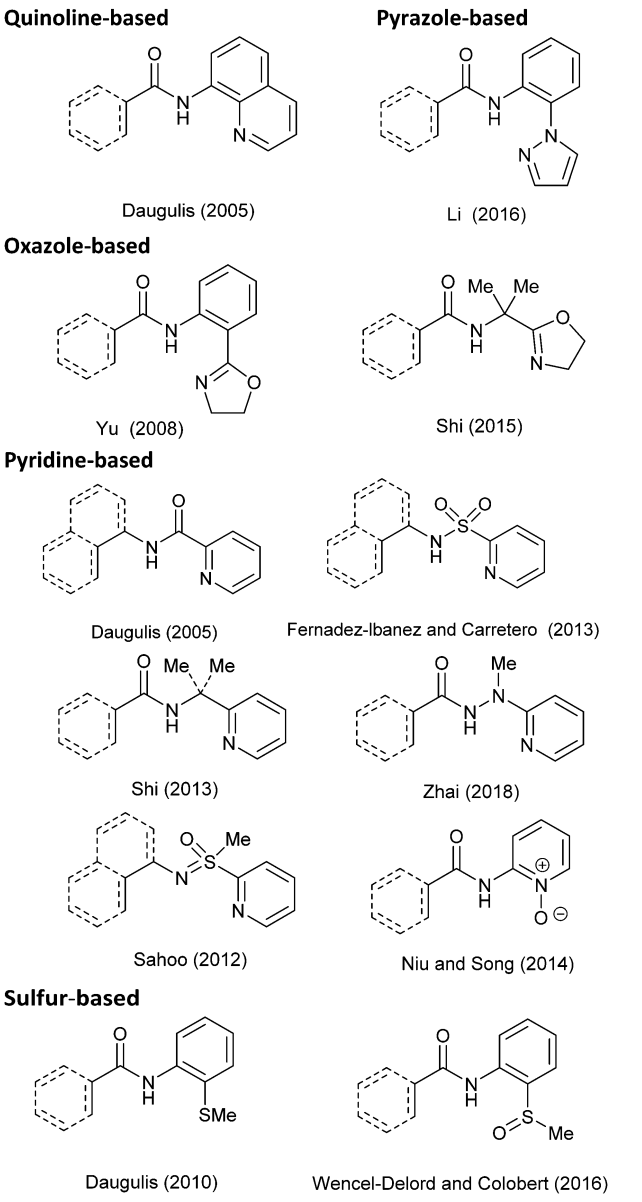
Scheme 1 Proximal C–H functionalization.



Scheme 2 Bidentate DG-assisted (remote) C–H functionalization.

oxazolyl, pyridinyl, pyrazolyl, pyridine-*N*-oxide and sulfur-based auxiliaries have been employed successively (Table 1).[9] Chatani, Ge and others carried out chelation-guided β-C–H arylation/alkylation employing various metal salts.[10] Groups such as Chen,[11] Carratero[12] and Yu[13] hold contributions towards remote γ-C–H functionalization. This article covers the precedents and the mechanistic aspects in Pd-catalysed bidentate auxiliary assisted distal C(sp^3)–H functionalization. The activation of proximal C(sp^3)–H bonds (α and β) will not be discussed here since the same is well documented.[14]

Table 1 Representative examples of bidentate directing auxiliaries

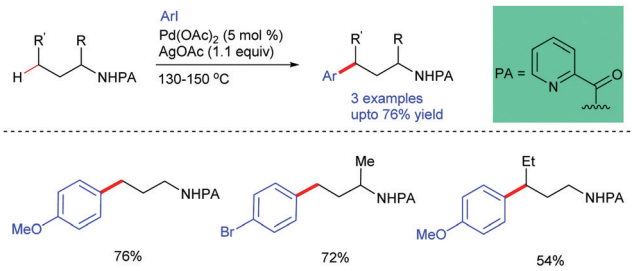


2. C–C bond formation

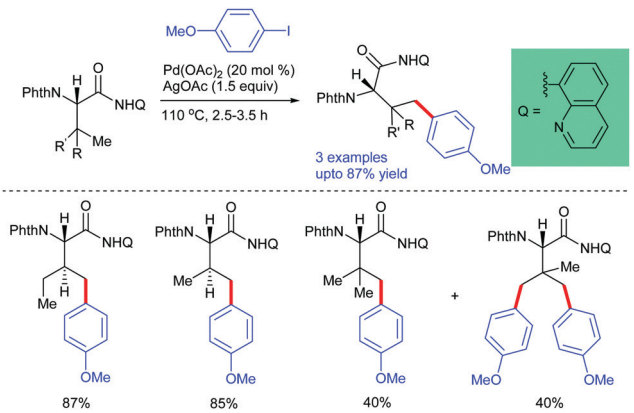
Transition-metal-catalyzed C–C bond formation is of paramount importance owing to its significance in the key steps to architect complex scaffolds from relatively less functionalized starting materials and it has traditionally attracted the attention of the synthetic community over the years.[15] In the realm of the C–C bond formation, site-selective distal C–H functionalization has heralded a new avenue for the synthesis of a plethora of compounds, which are difficult to realize *via* traditional synthetic methodologies.

2.1 Arylation

The presence of multiple chemically equivalent C–H bonds offered a challenge to have regio- and chemoselectivities in the distal C–H functionalization. To overcome, transition-metal-catalyzed DG-assisted C–H functionalization has emerged as a reliable synthetic approach although few functional groups bearing nitrogen, sulphur and oxygen atoms, having excellent compatibility for coordination with a metal centre, can activate an unactivated C–H bond through the proximity effect. Over the years, the DG-assisted distal C–H functionalization has allured the synthetic community despite possessing its own limitations such as poor atom economy owing to inevitable installation and removal of the DG. The first reasonable distal C–H functionalization was demonstrated by the Daugulis group in 2005.[8a] A Pd-catalyzed γ-C–H arylation of alkyl amines was disclosed utilizing picolinamide as a bidentate auxiliary (Scheme 3). Though substrate scope has been limited to three examples, the remote functionalization precedent marks an



Scheme 3 γ-C–H Arylation of aliphatic amines.

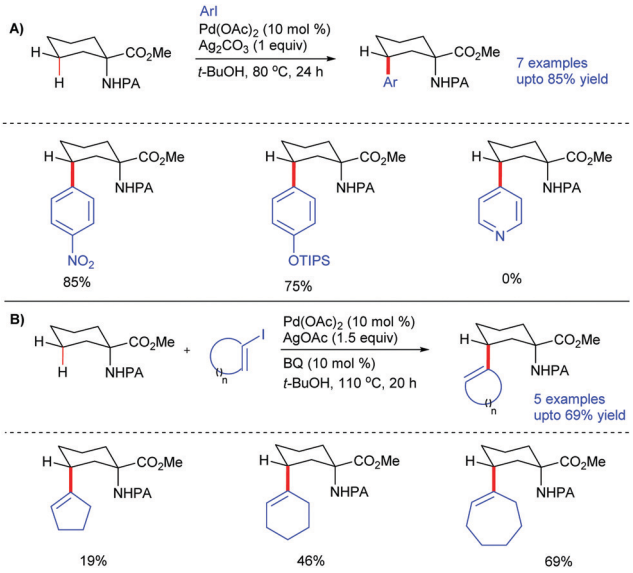


Scheme 4 γ-C–H arylation of α-amino acid derivatives.

important breakthrough. Primary C–H bonds react faster compared to the secondary ones, leading to selective monoarylation of methyl groups.

Soon after, Corey and co-workers in 2006 demonstrated an intriguing finding towards the γ-C–H activation of amino acid derivatives (Scheme 4).[16] In the presence of $Pd(OAc)_2$, the transformation was successfully carried out by utilizing the bidentate 8-aminoquinoline amide. *N*-phthaloyl (Phth) protected L-isoleucine and L-valine furnished mono arylated products, whereas L-*tert*-leucine gave a mixture of mono and diarylated products. This operationally simple approach stood out as a vital alternative for accessing remote arylated amino acids, which are otherwise difficult to achieve.

Inspired by these initial breakthroughs, Chen and co-workers carried out an efficient picolinamide auxiliary assisted remote γ-C–H arylation as well as alkenylation of aliphatic amines, particularly cyclohexylamino acid derivatives, utilizing aryl and cyclic vinyl iodides as aryl and alkenylating agents, respectively (Scheme 5).[17] The reaction tolerated diverse electron-rich and deficient aryl iodides towards monoarylation compared to the bisarylation due to the arising steric factors (Scheme 5A). However, 4-iodopyridine showed no reaction, which might be attributed to the complex formation with the catalyst. In the case of alkenylation, the overall yield depends on the ring size of the cyclic vinyl iodides and the yield of the alkenylated product enhances with the increase of the ring size (Scheme 5B). The authors carried out the formal synthesis of natural antibacterial agent (+)-obafluorin and were successful to remove the bidentate auxiliary quite easily.

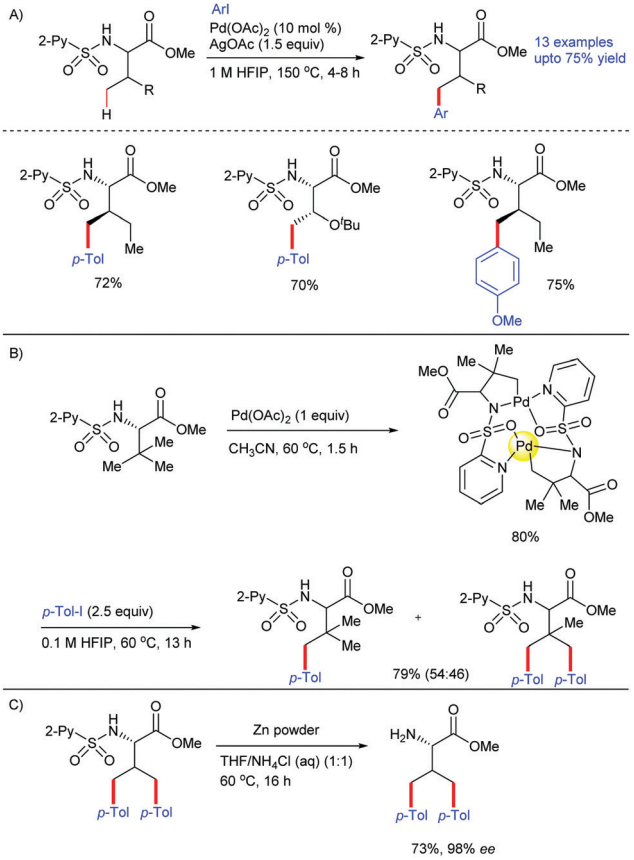


Scheme 5 γ-C–H arylation and alkenylation of aliphatic amines.

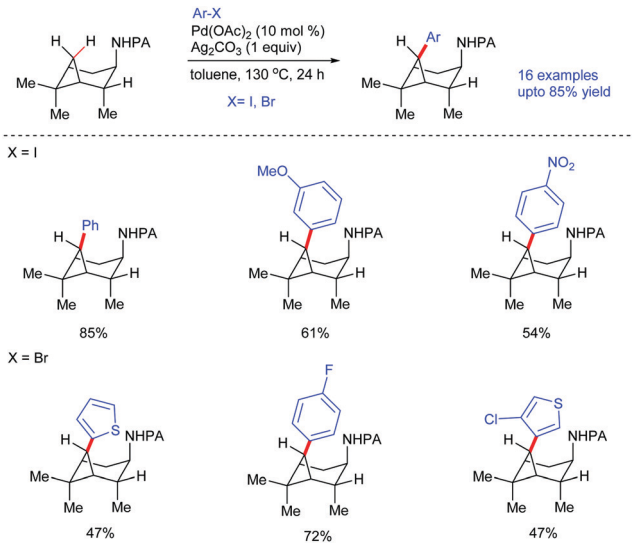
In 2013, the Carretero group reported a seminal Pd-catalyzed γ-C–H arylation of amino acid derivatives utilizing *N*-(2-pyridyl) sulfonyl as a bidentate auxiliary and aryl iodide as the arylating agent (Scheme 6A).[12] The reaction delivered the monoarylated product with excellent diasteroselectivity (dr ≥ 20 : 1). Pertinently, the authors extended the protocol for the unprecedented remote C–H monoarylation of dipeptides. To show the utility of *N*-(2-pyridyl)sulfonyl auxiliary, a bimetallic Pd(II)-complex was synthesized, which reacted swiftly to provide a 1 : 1 mixture of mono and bis-arylated products (Scheme 6B). The removal of the chelating group was easily accomplished by Zn powder in a 1 : 1 THF/NH_4Cl (aq) at 60 °C (Scheme 6C).

3-Pinanamines are privileged structural scaffolds that witness a widespread presence in medicinal chemistry. The core structure exhibits numerous bioactivities such as anti-influenza, antibacterial and antifungal properties.[18] Consequently, the direct functionalization of 3-pinanamine core offers the space for a plethora of functionalized molecules that can be of biological as well as pharmaceutical interests. In this line, the Wang group disclosed a Pd-catalyzed γ-C–H arylation of 3-pinanamines using aryl halides as an arylating agent (Scheme 7).[19] Although electron-rich and poor aryl iodides and bromides have been found to be compatible, *N*-heteroaryl halides such as 2-bromopyridine, 4-bromopyrimidine and 4-iodo-1*H*-imidazole produced inferior results.

Recently, a Pd-catalyzed γ-C–H arylation of carboxylic acids was introduced by the Maiti group utilizing 8-aminoquinoline amide DG with excellent monoselectivity (Scheme 8A).[20] Aryl iodides showed outstanding compatibility to deliver the products in high yields. Intriguingly, γ-cyclization was observed in the case of mesitoic acid amide *via* an intramolecular cyclization. Interestingly, *N*-protected amino acids such as L-valine and L-isoleucine, despite bearing β-hydrogen, underwent γ-arylation in moderate to good yields. The bidentate auxiliary was removed using TsOH/MeOH under heating to yield the free ester (Scheme 8B).

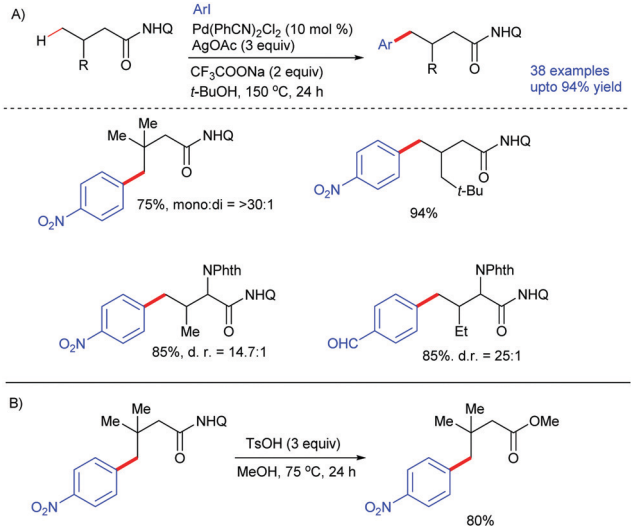


Scheme 6 γ-C–H arylation of amino acid derivatives.



Scheme 7 γ-C–H arylation of 3-pinanamines.

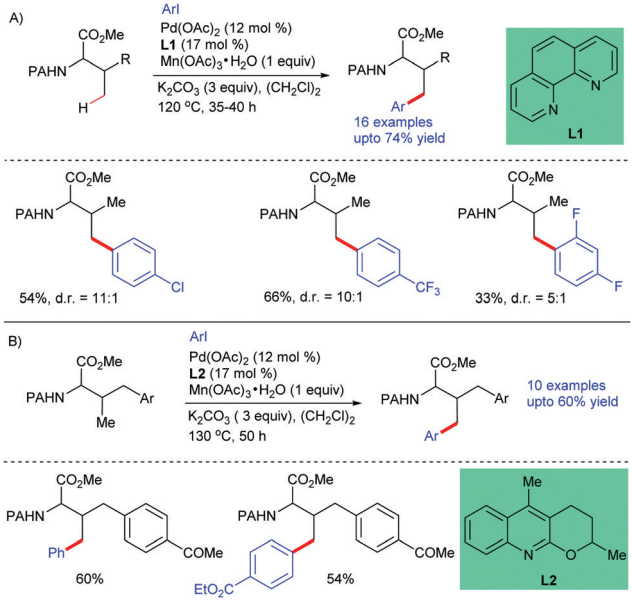
Peptide-based drugs possess characteristic absorption, distribution, metabolism, excretion and toxicity (ADMET). Many efforts have been thus made towards the functionalization of amino acids. Although β-C–H functionalization[21] of amino acids has been developed owing to the formation of a favourable five-membered metallacycle; the remote C–H functionalization is



Scheme 8 γ-C–H arylation of aliphatic amides.

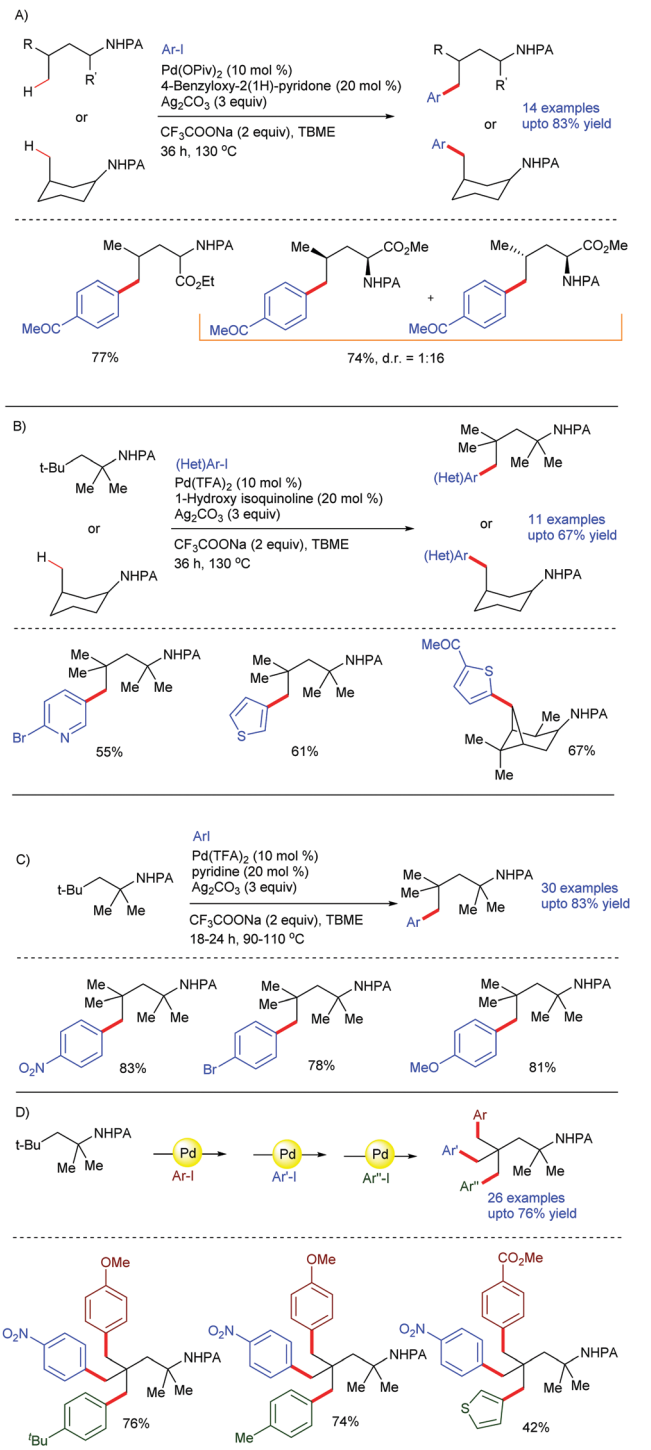
still underdeveloped. In 2018, Jana and co-workers disclosed a ligand enabled Pd-catalyzed mono- as well as unsymmetrical diarylation of γ-C–H of protected amino acids under a silver-free condition (Scheme 9).[22] Using 1,10-phenanthroline **L1**, the reaction of a diverse electron-rich and poor aryl iodides have been accomplished. Electron-poor aryl iodides such as 4-chloro, 4-trifluoromethyl and 2,4-difluoro-substituted aryl iodides afforded monoarylation products (Scheme 9A). The reaction using **L2** produced the diarylated products with excellent diastereoselectivity (>20 : 1) (Scheme 9B). The reaction with aryl bromides and aryl chloride provided inferior results.

Although the bidentate auxiliary-assisted γ-C–H arylation of amines, carboxylic and amino acids have witnessed considerable progress, yet the more distant C–H bond *viz.* a δ-C–H



Scheme 9 γ-C–H arylation/diarylation of N-protected amino acids.

functionalization has been overlooked, owing to the prerequisite of six-membered or higher metallacycle, which is difficult to form due to unfavorable thermodynamic constraints. In 2019, Maiti and co-workers disclosed path-breaking findings for δ-C–H arylation of amines and amino acids with the fine-tuning of ligand to mitigate the thermodynamic barrier under a Pd-catalysis (Scheme 10).[23] Various amines, heteroaryl iodides as well as amino acids such as L-leucine derivatives are compatible to deliver the monoarylated products (Scheme 10A–B). In the case of 2,4,4-trimethylpentane-2-amines, pyridine stood out as the ligand of choice (Scheme 10C). Further, triarylation has been achieved by tweaking the reaction temperature from 90 °C to 130 °C (Scheme 10D).

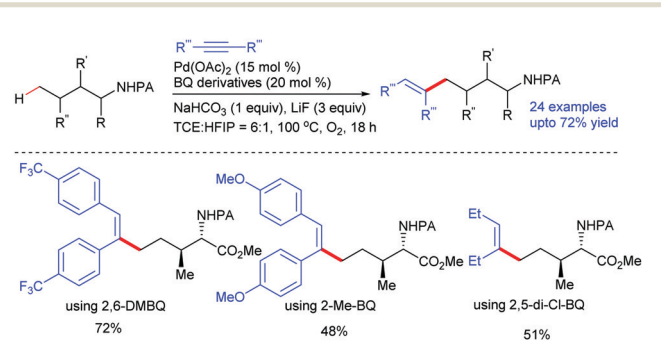


Scheme 10 δ-C–H arylation of amines and protected amino acids.

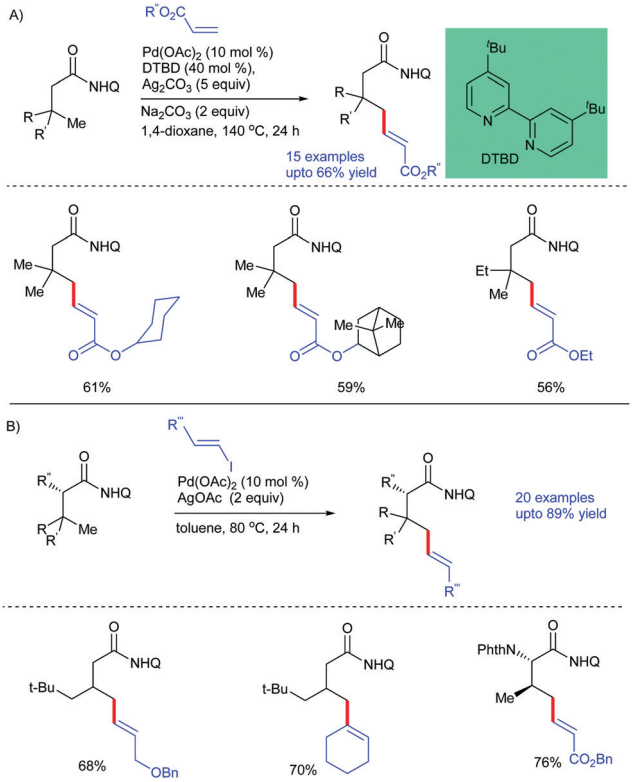
2.2 Alkenylation

Since the inception of DGs, site-selective C(sp^2)–H alkenylation has witnessed significant advances.[24] However, C(sp^3)–H alkenylation is still scarce. In 2014, Wang and co-workers successfully achieved C–H alkenylation of 8-methylquinolines with alkynes.[25a] Later, You[25b] and Maiti[25c] groups independently described a Ni-catalyzed β-C–H alkenylation utilizing 8-aminoquinoline amide DG at high temperature with moderate *E*/*Z* selectivity. Subsequently, a picolinamide directed δ-C–H alkenylation of aliphatic amines with internal alkynes under Pd-catalysis was introduced by the Shi group (Scheme 11).[26] This unprecedented δ-selectivity in the presence of γ-C–H bonds was governed *via* the formation of a six-membered palladacycle. The scope has been examined with various electronically substituted aryl as well as aliphatic internal alkynes, providing the δ-alkenylated derivatives in moderate to good yields.

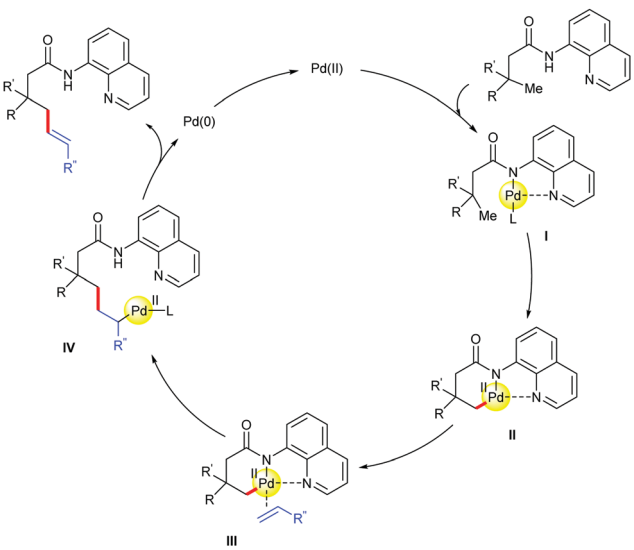
In 2017, Maiti and co-workers described a Pd-catalyzed alkenylation of γ-C–H bonds of carboxamides with substituted acrylates and vinyl iodides (Scheme 12).[27] In a series of *N,O*- and *N,N*-bidentate DGs screened, the combination of 8-aminoquinoline amide and 4,4′-di-*tert*-butyl-2,2′-bipyridine (DTBD) produced superior results. Diverse olefins and carboxamides reacted to give the alkenylated products in good yields and selectivities, comprising bulky bioactive molecules such as ergosterol and vitamin E units. Spurred by these initial findings, they extended the strategy for γ-olefination with vinyl iodides. Further, amino acid-based carboxamides such as Phth protected L-valine, L-*tert*-leucine and L-isoleucine derivatives have been tolerated to furnish the mono-olefinated γ-vinyl acid derivatives. The reaction involves the 8-aminoquinoline amide-directed C–H activation, leading to the formation of a six-membered palladacycle **I**. Coordination with olefin provides **II**, which upon migratory insertion and β-hydride elimination delivers the product (Scheme 13).



Scheme 11 δ-C–H alkenylation of aliphatic amines with alkynes.



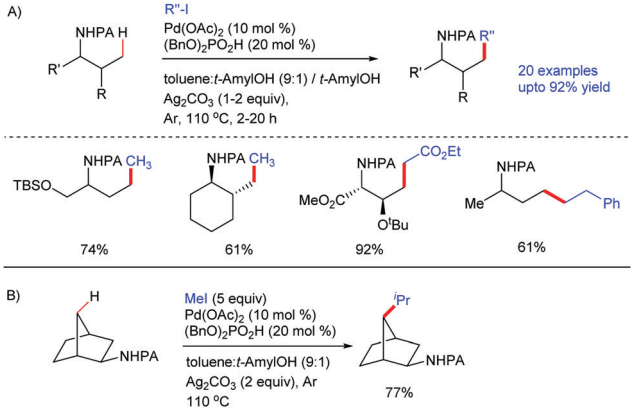
Scheme 12 γ-C–H alkenylation with acrylates and vinyl iodides.



Scheme 13 Catalytic cycle for γ-C–H alkenylation.

2.3 Alkylation

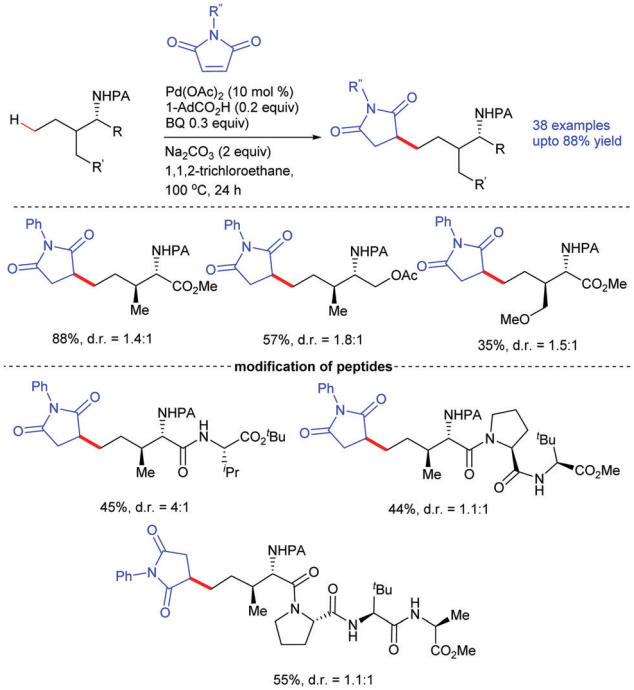
Transition-metal-catalyzed site-selective alkylation of C–H bond has been found to be a strenuous task although the progression in this space through the cross-coupling of alkyl halides can lead to a large array of readily available and economical starting feedstock.[28] In this regard, a seminal γ-C–H alkylation was described by Chen and co-workers exploiting picolinamide as a



Scheme 14 γ-C–H alkylation of aliphatic amines.

bidentate auxiliary and alkyl iodides as an alkylating agent under Pd-catalysis (Scheme 14A).[29] Pertinently, dibenzyl phosphate and Ag_2CO_3 played a key role as promoters. A plethora of alkyl amines and alkyl iodides underwent a reaction in good yields. In addition, the demonstration of sequential C–H methylation highlighted the synthetic utility of the protocol (Scheme 14B).

The use of maleimide as an alkylating agent for chemo- and regioselective C–H functionalization has been explored due to its post-synthetic applications.[30] Shi and co-workers displayed a Pd(II)-catalyzed δ-selective distal C–H alkylation of picolinamide protected amino acids and peptides using maleimides as an alkylating agent *via* a six-membered palladacycle in competition with γ-methyl C–H bonds (Scheme 15).[31] A wide variety of diversely functionalized *N*-aryl and -alkyl maleimides along



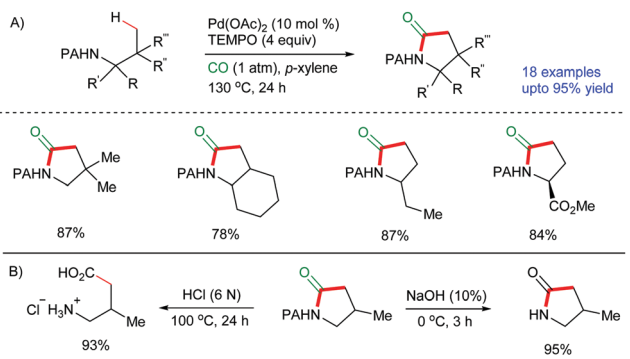
Scheme 15 γ-C–H Alkylation with maleimides.

with γ-arylated, γ-alkoxylated, γ-alkylated isoleucine and isoleucinol were compatible, giving the δ-alkylated products in moderate to good yields. A library of substituted di-, tri- and tetrapeptides bearing L-*tert*-leucine, L-valine, L-proline, L-isoleucine and cyclohexylglycine counterparts reacted exclusively at the δ-positions. The synthetic utility was shown by the removal of DG and further functionalization of the products. Although both γ- and δ-C–H activation was found to be reversible, mechanistic studies rationalized the origin of δ-selectivity using the Curtin–Hammett principle.

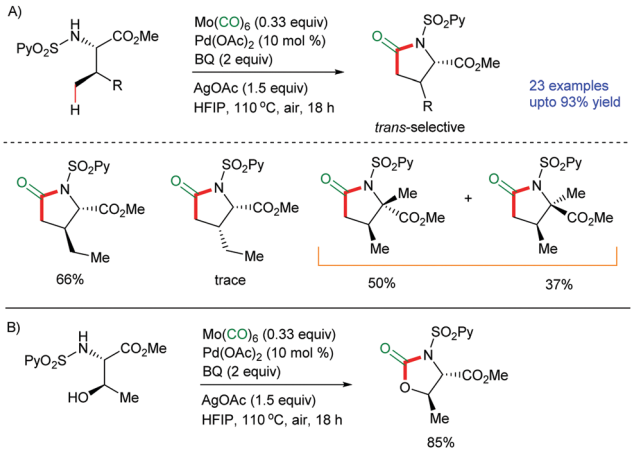
2.4 Carbonylation

Transition-metal-catalyzed carbonylation using CO gas has allured industry and academia due to the cost-effectiveness and easy availability; despite the unavoidable toxicity associated with it. After the initial discovery by the Fujiwara group in 1980 for the carbonylative activation of arene under Pd-catalysis,[32a] Yu,[32b] Gaunt[32c] and Chatani[10a] groups reported carbonylation of C–H bonds. In 2015, Wang and co-workers displayed a Pd-catalyzed carbonylative annulation of alkylamines to construct a plethora of γ-lactams and amino acids, utilizing TEMPO as oxidant and CO as C1 feedstock under elevated temperature (Scheme 16A).[33] To demonstrate the synthetic utility, the authors converted protected pyrrolidone to a γ-amino acid or γ-lactam depending on the acidic or basic environment (Scheme 16B).

The Carretero group accomplished a DG-assisted Pd-catalyzed γ-selective carbonylative cyclization of amine derivatives *via* C–H activation using $Mo(CO)_6$ as a carbonyl surrogate. The bidentate auxiliary, (2-pyridyl)sulfonyl attached amino group of amino acid derivative could undergo cyclometallation to generate Pd-intermediate, which follows C–H activation to furnish functionalized γ-lactams (Scheme 17).[34] The use of $Mo(CO)_6$ as an air-stable carbonyl source rectifies the problem of handling toxic CO gas and prevents the deactivation of Pd(II)-species. The primary sp^3 C–H bonds were more reactive with high *trans*-selectivity to produce the target γ-lactams. The substrate containing the free carboxyl group underwent a reaction with excellent yield. However, threonine derivative having a free –OH group at β-position failed to undergo C–H carbonylation and led to the formation of cyclic carbamate as a major product (Scheme 17B). The strategy worked well for both the methyl and methylene γ-C–H bonds.



Scheme 16 γ-C–H carbonylation of protected amines.



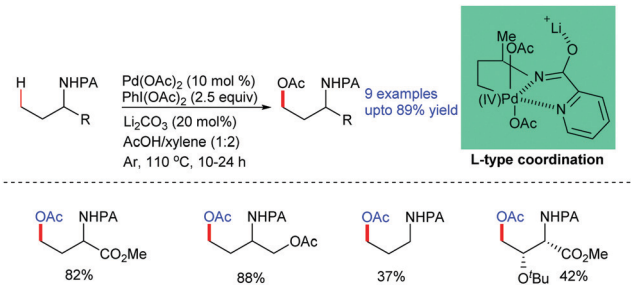
Scheme 17 Carbonylative cyclization of amino acids using $Mo(CO)_6$ as CO source.

3. C–Heteroatom bond formation

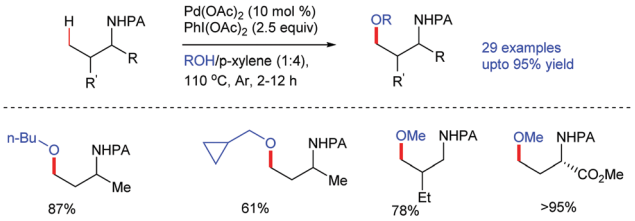
C–heteroatom bond-forming reactions constitute the mainstay of modern-day synthetic practices due to their importance in the synthesis of natural products and pharmaceuticals.[35] In this regard, transition-metal-catalyzed C–H activation protocols have proven to be a valuable tool for the construction of C–heteroatom bonds. However, preferential installation of heteroatoms at a distal position with respect to the functional group remains elusive.

3.1 C–O bond formation

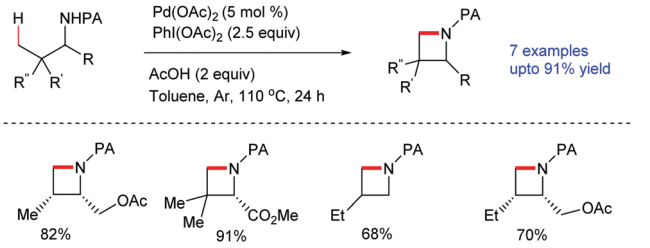
In 2014, Chen and co-workers carried out a Pd-catalyzed remote acetoxylation of the unactivated γ-C–H bond of alkyl amines with picolinamide using $PhI(OAc)_2$ as the oxidant (Scheme 18).[36] The authors addressed a probable competition between C–N and C–O reductive elimination, leading to the cyclized azetidine and acetoxylated products. However, they successfully tackled the issue using the substoichiometric amount of Li_2CO_3 as an additive, as it favors C–O reductive elimination over the C–N one. Further, using a mixture of AcOH and xylene improved the yield of γ-acetoxylated products. This strategy was found amenable with diverse functionalities at the α-positions. However, in the case of unsubstituted and β-substituted substrates, the yields are moderate and the formation of the cyclized product occurred. The authors hypothesized L-type coordination of the



Scheme 18 Oxidative C–H acetoxylation.



Scheme 19 γ-C–H Alkoxylation with alcohols.



Scheme 21 γ-Selective C–H activation for the synthesis of azetidine.

deprotonated amide group of picolinamide in correlation to the interaction of Li^+ with *O*-imidate that can facilitate the favorable C–O acetoxylation.

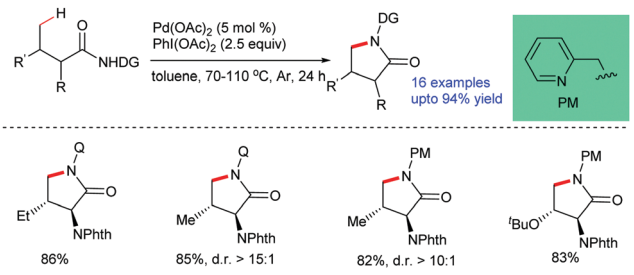
Regioselective construction of ether moieties has emerged as a promising tool owing to the omnipresence of these structural scaffolds in a plethora of bioactive natural products and pharmaceuticals.[37] In this vein, Chen and co-workers documented a concise method to access functionalized alkyl ethers through γ-C–H activation of aliphatic amines using picolinamide DG in the presence of Pd-catalyst (Scheme 19).[38] This intermolecular C–H alkoxylation utilized a broad range of 1° alcohols with an excess of $PhI(OAc)_2$ as the oxidant under an inert atmosphere. A library of 2° and 3° alcohols was found amenable with a prolonged reaction time. Additionally, the protocol is well tolerated with a wide variety of amines, delivering the alkoxylated products in moderate to good yields. The substrates without α-substituents at the γ-position were readily alkoxylated in competition with 2° γ-C–H bonds and no δ-alkoxylated alkyl ethers were formed. The reaction proceeds through a five-membered palladacycle and removal of the DG showcased the synthetic utility of the methodology for further transformations.

3.2 C–N bond formation

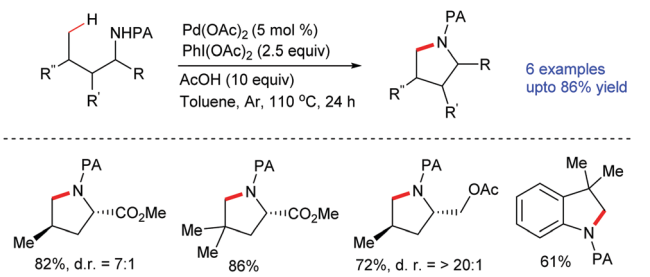
Pyrrolidinones are privileged structural units that are ubiquitous in myriads of natural products, functional materials and pharmaceuticals.[39] To this end, a Pd-catalyzed *N*,*N*-bidentate DG-assisted concise methodology for the efficient construction of pyrrolidinone derivatives was described by Chen and co-workers *via* the remote intramolecular γ-C–H amination (Scheme 20).[40] The reaction successfully exemplified 8-aminoquinoline amide and 2-pyridylmethyl amine (PM) derived directing auxiliaries for γ-lactamization utilizing $PhI(OAc)_2$-mediated cyclization of amino acid residues. The scope was examined with a wide variety of α,β-substituted butanamides, and the amination occurs selectively at the 1° C–H bonds, delivering lactams in good yields. The utility of the protocol was further illustrated by intramolecular amination of γ-aryl butanamides at the 2° benzylic C–H bonds that enabled the formation of γ-arylated pyrrolidinones with three contiguous stereogenic centers in good yields. The reaction proceeds through a Pd(II)/Pd(IV) catalytic pathway *via* the involvement of a six-membered palladacycle and the removal of the DG demonstrated the synthetic efficacy of the protocol.

Chen's group described the synthesis of four and five-membered N-heterocycles *via* intramolecular Pd-catalyzed picolinamide directed distal C–H activation.[41] Azetidines were successfully formed *via* the γ-selective intramolecular C–H amination using $Pd(OAc)_2$ in the presence of $PhI(OAc)_2$ under an inert atmosphere (Scheme 21). The substrates having α- and β-substituents were furnished in high yields, while substrates without β-substituent produced inferior results. The reaction proceeds *via* a five-membered palladacyle and the torsional strain forced by β-substituent plays a key role in providing high selectivity in intramolecular γ-C–H amination. The reaction has been extended to δ-selective C–H amination to construct pyrrolidines from substrates having both a primary δ-C–H bond and a sterically hindered γ-C–H bond (Scheme 22). Excess of AcOH and the presence of γ-substituent were crucial for constructing the pyrrolidines in greater yield.

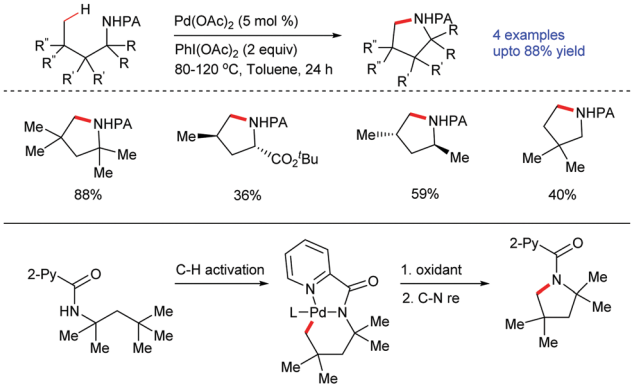
Daugulis and co-workers carried out functionalization of methyl groups adjacent to the quaternary center (Scheme 23).[42] They envisaged that C–H activation at δ-positions is possible *via* oxidation of the intermediate palladacycle into a high-valent species followed by C–N reductive elimination to afford pyrrolidine derivatives. For the δ-C–H activation, picolinamide was employed and the deuterium exchange experiment revealed



Scheme 20 Synthesis of pyrrolidinones *via* γ-C–H amination.



Scheme 22 δ-Selective C–H amination for the synthesis of a five-member heterocycle.

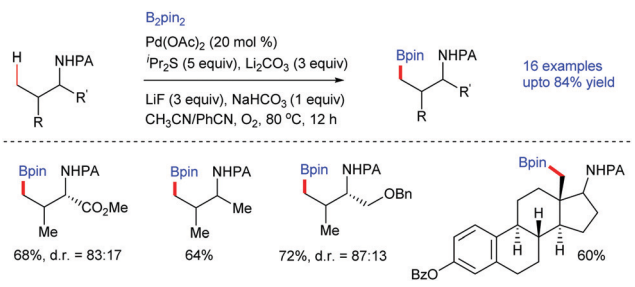


Scheme 23 Intramolecular δ-C–H amination.

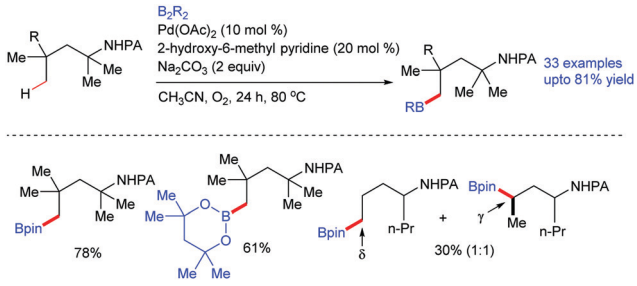
that no bonds other than the terminal methyl groups were deuterated (33%). For the formation of cyclized pyrrolidine products, $PhI(OAc)_2$ was employed in toluene to convert Pd(II) to a higher oxidation state. Reductive elimination later affords the cyclized product and regenerates the Pd(II)-catalyst. The C–H/N–H cyclization of picolinamides having *tert*-octylamine, L-leucine, 4-methyl-2-aminopentane and benzylic C–H bonds afforded the products in moderate to good yields.

3.3 C–B bond formation

Boronic acids and their esters are an important class of compounds in synthetic chemistry due to their ubiquity in material and medicinal chemistry.[43] The synthesis of alkyl boronic acids and their esters have attained significant attention in recent years owing to impressive protease inhibiting activity.[44] Thus, the development of sustainable and atom economical protocols for their synthesis is highly desirable. In 2014, the Shi group reported a Pd-catalyzed DG-assisted remote C–H borylation of unactivated primary C–H bonds using B_2pin_2 as borylation source (Scheme 24).[45] The oxidative C–H bond functionalization *via* the C–B bond formation of amino acids, amino alcohols and amines has been achieved in good yields with high diastreoselctivity using picolinamide DG under atmospheric oxygen. The C–H bond activation proceeds *via* twin five-membered fused palladacycles. Picolinyl tethered amino acid derivatives gave good yields of the γ-selective borylated products. The unreactive C–H bond of the angular methyl group in picolinyl installed steroid derivatives could be successfully borylated.



Scheme 24 Oxidative γ-C–H borylation.

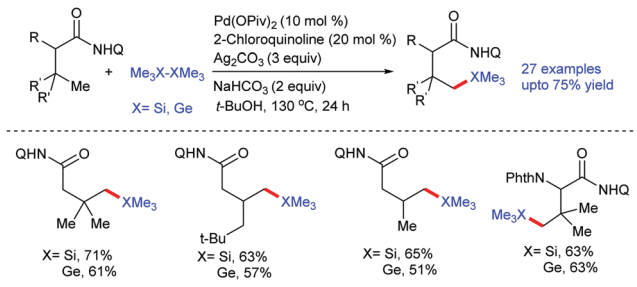


Scheme 25 δ-C–H oxidative borylation of aliphatic amines.

Recently, Maiti's group showed the distal δ-selective C–H oxidative borylation of aliphatic amines with borane reagents using picolinamide-assisted C–H activation in the presence of $Pd(OAc)_2$/2-hydroxy-6-methyl pyridine at 80 °C under oxygen atmosphere (Scheme 25).[46] The reactions proceed *via* a six-membered palladacycle. The reaction of picolinyl installed *tert*-octylamines with various borylating sources produced good yields of the δ-selective product. The competition between the secondary γ-C–H and primary δ-C–H bonds offered the formation of a 1 : 1 mixture of γ- and δ-borylated products. The reaction was amenable to electronically varied substituted aliphatic amines, however, simple substrates such as butan-1-amine and pentan-2-amine failed to undergo borylation due to the instability of cyclopalladium species.

3.4 Chalcogenatation

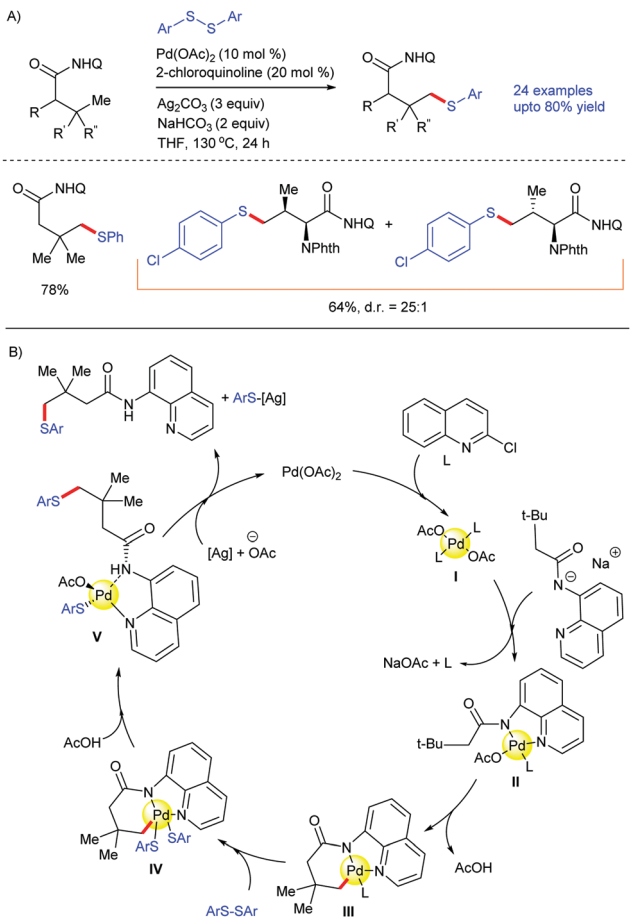
Aliphatic C–Si bond formation is a fascinating research area for synthetic chemists due to their synthetic utility as well as the inimitable physical and chemical properties of organosilicon compounds.[47] The introduction of intermolecular silylation of the β-C–H bond of the Phth-protected amino acids is independently described by groups *viz*; Kanai,[48a] Zhang[48b] and Shi.[48c] Later, the Maiti group showed a regioselective remote Pd-catalyzed C–H functionalization of aliphatic carboxylic and amino acid derivatives to form the carbon–heteroatom bond, C–X (X = Si and Ge) using 8-aminoquinoline amide DG (Scheme 26).[49] The bidentate chelation-assisted protocol was found proficient for the distal C–H functionalization, furnishing the γ-silylated or γ-germanylated products with high diasteroselectivity. The strategy was further extended using hexamethyldisilane and hexamethyldigermane as Si- and Ge-source, respectively. The C–H activation proceeded *via* the formation of a six-membered



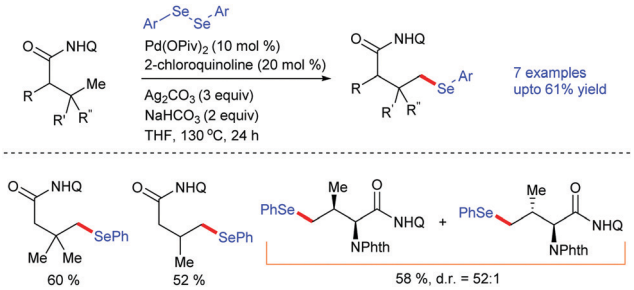
Scheme 26 γ-C–H silylation and germanylation.

palladacycle, which was subjected as a catalyst to fabricate the desired product in good yield.

Following the regioselective silylation and germanylation, the authors accomplished a Pd-catalyzed chalcogenation of α-amino as well as simple carboxylic acids using 8-aminoquinoline amide in presence of 2-chloroquinoline ligand (Scheme 27).[50] A library of aryl disulphides underwent a reaction in high yields, irrespective of the electronic properties, whereas alkyl disulphide gave a moderate yield. The reaction employing TEMPO showed no effects, which suggests that the reaction may not involve a radical intermediate. $Pd(OAc)_2$ first binds with 2-chloroquinoline to the precatalyst **I**, which undergoes directed palladation with the bidentate auxiliary to deliver the complex **II** (Scheme 27B). The γ-selective C–H activation leads to the formation of a six-membered palladacyle **III** *via* concerted metalation–deprotonation (CMD). The oxidative addition with disulphide, results in the formation of **IV** which subsequently undergoes reductive elimination followed by ligand exchange with Ag-species to furnish the γ-thioarylated product along with the regeneration of Pd-catalyst. As the reactivity of selenium has been found to be similar with respect to sulphur, the scope of the γ-selective C–H selenoarylation was further examined with the aid of diselenides (Scheme 28).



Scheme 27 γ-C–H thioarylation of acetamide and amino acid derivatives.



Scheme 28 γ-C–H selenoarylation of acetamide and amino acid derivatives.

The selenoarylated products formed with high diastereoselectivities albeit lower yield was observed compared to thioarylation.

Conclusion and outlook

The site-selective functionalization of remote C–H bonds offers a challenge in organic synthesis as reaching out to a remote position requires the formation of a larger metallacycle, which has thermodynamic constraints. Further, the fluxional alkyl chains render regioselectivity. The generation of close proximity between metal and the distal C–H bond demands handlings either a substrate of choice or the DG. Despite the difficulties encountered, remote functionalization has been achieved by employing bidentate DGs. Nevertheless, in order to explore the tremendous potential of distal C–H functionalization, a systematic study is obligatory. Though the Pd-catalysed directed arylation, oxygenation, alkylation, amination, borylation and carbonylation of γ-C–H bonds have been reported, yet, the distal δ-C–H functionalization through a six-membered palladacycle is scarce. The use of a native functional group to provide distal coordination and activation is of prime importance. Modified DGs and the stabilization of higher membered metallacycles in order to achieve remote functionalization beyond γ-sites *viz*: ε, η, θ, ι is one of the undeveloped areas to explore. Non-directed C–H functionalization, reducing catalyst loading, and use of inexpensive oxidants are important prospects for further developments. Moreover, the Pd-catalyzed distal functionalization is limited mostly to C–C, C–N, or C–O bond formation. The strategy can be extended to other C–heteroatom bonds. Employing specific ligands to tune the reaction and have remote C–H functionalization of biologically relevant scaffolds. Nevertheless, we hope that the synthetic strategies covered in this article will be helpful in understanding the chelation-guided remote functionalization of inert C–H bonds.

Conflicts of interest

There are no conflicts to declare.

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