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Review

Palladium-Catalyzed C(sp^3)–H Bond Functionalization of Aliphatic Amines

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SUMMARY

Methods that enable the practical and selective functionalization of traditionally unreactive aliphatic C-H bonds have synthetic applications in fields ranging from drug discovery to advanced materials. One of the major challenges is the development of strategically important reactions on aliphatic molecules containing synthetically useful functional groups. Aliphatic amines are central to the function of many biologically active molecules as evidenced by their prevalence in a large number of pharmaceutical agents. Over the past decade, chemists have found ways to tailor the electronic and steric properties of directing functionalities and ligands to enable palladium-catalyzed C-H activation of aliphatic amine derivatives. Many of these methods have been successfully applied to the synthesis of pharmaceuticals and complex natural products. This review provides an overview of these methods and describes recent contributions, as well as the remaining challenges in this emerging field.

The Bigger Picture

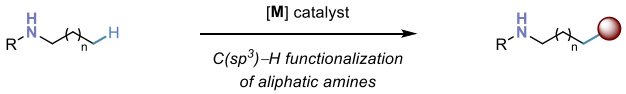
The preparation and functionalization of complex aliphatic amines remains an important challenge to synthetic and medicinal chemists, given that their structural and functional properties are fundamental to biological activity. With the development of C–H functionalization, Pd-catalyzed methods for aliphatic amines has emerged as a powerful approach for the synthesis of complex variants of these molecules. Central to many of the designs is the facilitating role of tailored amine groups, which steer the C–H bond cleavage during cyclometallation. This review discusses three major strategies of using directing functionalities that enable the selective C–H functionalization of aliphatic amines, including amine-derived directing group strategy, transient directing group strategy, and native amine directed strategy. We believe that these methods will inspire new applications of aliphatic amine C–H functionalization in the synthesis of nitrogen-containing pharmaceuticals and natural products.

INTRODUCTION

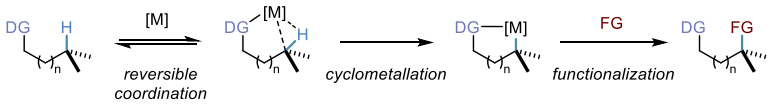
The synthesis and functionalization of amines is fundamental to a variety of chemical applications, such as the preparation of alkaloid natural products, pharmaceuticals, biologically active molecules, and functional materials.[1] For this reason, synthetic chemists continue to be interested in the construction and functionalization of these important molecules. Traditionally, the established methods for aliphatic amine synthesis include carbonyl reductive amination[2] and alkylation[3] via nucleophilic displacement of a leaving group by the amine nitrogen. While these conventional aliphatic amine syntheses rely on the inherent reactivity of functional groups, the incorporation of transition metal catalysis provides novel strategies to construct carbon–nitrogen bonds, including C–N cross-coupling reactions,[4-6] alkene hydroamination,[7,8] and C–H insertion of nitrenes.[9,10] Although these methods have further expanded the toolkit of available transformations, the need for functional amines continues to fuel research into the development of general catalytic reactions for the synthesis of nitrogen-containing molecules.

Over the past decade, metal-catalyzed functionalization of C(sp^3)–H bonds has emerged as a powerful strategy for the synthesis and diversification of aliphatic amines (Scheme 1).[11-15] Compared to classical synthetic methods, in which reactants are typically pre-functionalized prior to a coupling step, C–H functionalization directly converts simple hydrocarbon moieties

via an organometallic intermediate to functionalized products.[16,17] In this manner, C–H functionalization offers both a more streamlined and atom efficient approach to chemical synthesis. Although conceptually appealing, mild and selective cleavage of C–H bonds, particularly unactivated C(sp^3)–H bonds, is a fundamental challenge owing to their inert and ubiquitous nature.[18-20] Control of site selectivity is crucial for a synthetically useful process, with the approach that has attracted most interest being the use of directing groups (DG, Scheme 2) – a Lewis basic motif present in the substrate that readily coordinates to a metal centre. The directing group positions the metal at the site of activation and promotes intramolecular conversion of a proximal C–H bond to a C–M bond resulting in cyclometallation.[21,22] The metallacycle intermediate may then undergo further functionalization to give the derivatized product. The directing group promotes C–H functionalization both in terms of kinetics of the C–H bond cleavage, by increasing the local effective concentration of the metal complex, as well as thermodynamics, by stabilizing the intermediate metallacycle by chelation.[23,24] Among the many transition metal catalysts able to promote C–H functionalization, palladium salts have been demonstrated to be remarkably versatile for the functionalization of aliphatic amine derivatives. Both primary, as well as more hindered secondary C(sp^3)–H bonds, are readily cleaved by complexes of palladium. Furthermore, the intermediate palladacycles have the potential to be transformed to a diverse range of functionalized products, either in an inter- or intramolecular fashion.[25,26]

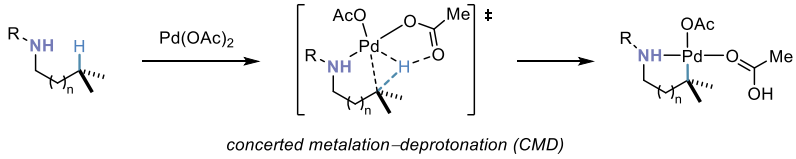


Scheme 1. Transition-Metal-Catalyzed C(sp^3)–H Functionalization of Aliphatic Amines

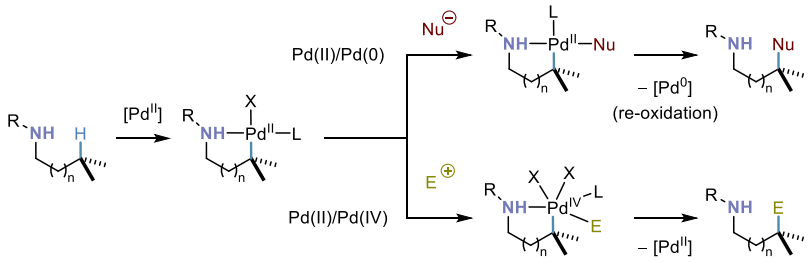


Scheme 2. Directed C–H Activation: Coordination, Cyclometallation and Functionalization

There are two main catalytic manifolds for Pd-catalyzed C–H functionalization: Pd(II)/Pd(0) catalysis and Pd(II)/Pd(IV) catalysis.[25-27] In both cases, reactions proceed via initial redox-neutral Pd(II)-mediated C–H bond cleavage, giving rise to a [Pd(II)–R] intermediate capable of undergoing different functionalization pathways. For C(sp^3)–H bonds, cleavage occurs via a concerted six-membered transition state with simultaneous metalation and proton transfer, known as concerted metalation–deprotonation (CMD, Scheme 3). Bound carboxylate ligands typically act as an internal base in this process.[28,29] After CMD, Pd(II)/Pd(0) catalysis involves attack by nucleophiles (e.g. organoboronic acids or esters) or insertion of CO or alkenes, followed by reductive elimination to Pd(0) and subsequent re-oxidation to catalytically active Pd(II) (Scheme 4). Conversely, electrophilic coupling partners (e.g. organohalides or hypervalent iodine reagents) undergo oxidative processes via Pd(II)/Pd(IV) pathways. Coordinatively saturated and highly electrophilic Pd(IV) species are noted as having distinct reactivity compared with Pd(II) species, providing access to alternative reductive elimination pathways, in particular, C–heteroatom bond formation.[30]



Scheme 3. Mechanism of the Concerted Metalation–Deprotonation Pathway

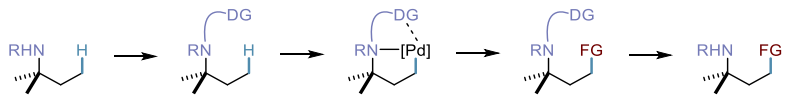


Scheme 4. Catalytic Manifolds for Pd-Catalyzed C–H Functionalization of Aliphatic Amines

This review summarizes the three main methods for promoting Pd-catalyzed C–H functionalization of aliphatic amines: (i) amine-derived directing group strategy, (ii) transient directing group strategy, and (iii) native amine-directed strategy. We also adopt mechanistic manifolds as discussed above in classifying Pd(II)/Pd(IV) catalysis and Pd(II)/Pd(0) catalysis. The intention of this review article is to give an overview on this emerging field and inspire the use and continuing development of this novel tool for the synthesis of functionally diverse aliphatic amines.

AMINE-DERIVED DIRECTING GROUP STRATEGY

The amine-derived directing group strategy – the most explored approach to C–H functionalization – involves the installation of directing groups (DGs) onto the substrate in a separate step prior to functionalization, in which coordinating and/or electron-withdrawing functionality are tethered to the amine nitrogen to promote cyclometallation (Scheme 5). Following directed C–H functionalization, the DG is removed, furnishing the free-(NH) amine product. Although, the installation and removal of the DG adds two (or more) steps to the synthetic sequence, carefully designed DGs provide a variety of beneficial features for amine functionalization. For example, the masking of amine functionality with a DG confers improved stability to the substrate, and hence tolerance to a wider range of reaction conditions. Furthermore, DGs provide a dominant, well-defined interaction with the metal centre, making the catalytic transformation more robust in nature. Finally, the DG may be tuned through modification of sterics and electronics, providing opportunities to influence the efficiency and selectivity of the reaction. Most commonly, directing group strategies have centred around the use of strongly coordinating, chelating auxiliaries to guide catalyst–substrate interactions,[31-33] though weakly coordinating auxiliaries have also been successfully used in the presence of additional ligands.[27]

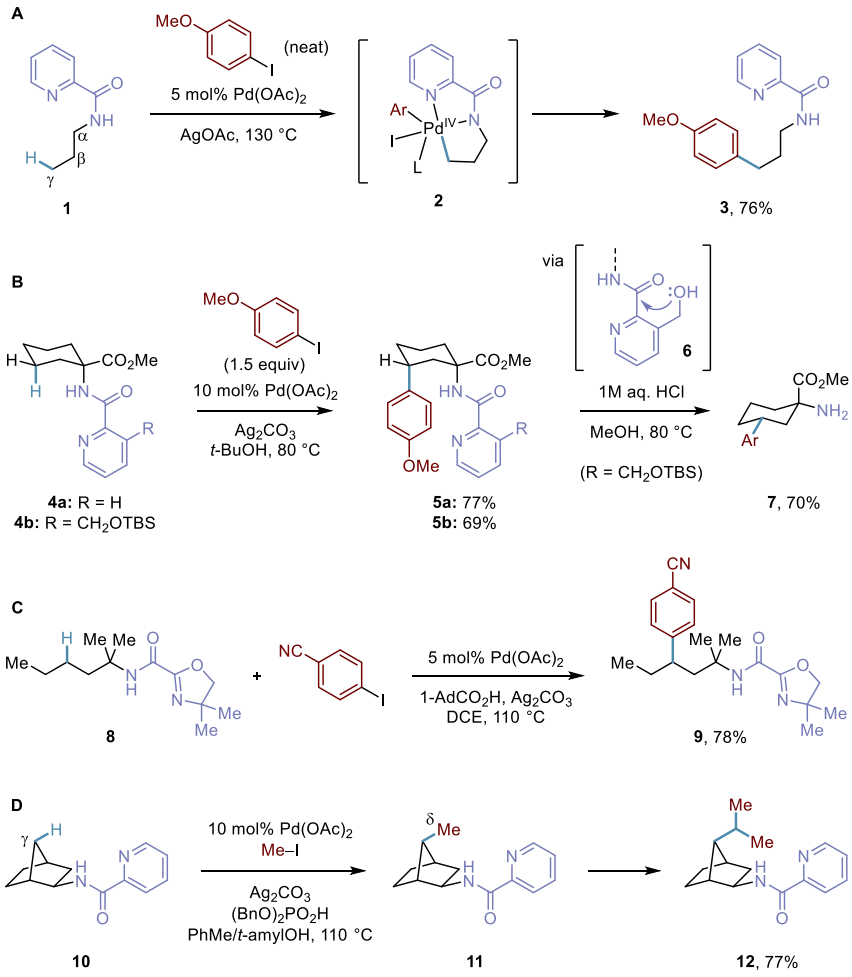


Scheme 5. Amine-Derived Directing Group Strategy for Site-Selective C–H Functionalization

Pd(II)/Pd(IV) Catalysis

Seminal work, by Daugulis in 2005, reported the first example of an amine-derived directing group strategy for Pd-catalyzed C(sp^3)–H functionalization (Scheme 6A).[34] The picolinamide directing group – a monoanionic, bidentate auxiliary – promoted exclusive γ-C–H arylation of alkyl amine derivatives (**1**), demonstrating the remarkable site selectivity that could be achieved via directed C–H activation. Aryl iodides were used as arylating agents, with a Ag(I) salt acting as halide scavenger. In addition to directing the metal to the site of activation, the strongly donating auxiliary stabilizes the high valent Pd(IV) intermediate (**2**) formed upon oxidative addition of the aryl iodide, thus also promoting the functionalization step. Notably, selective mono-functionalization was observed (**3**), despite excess aryl iodide and high temperature being used (neat conditions, 130 ºC). In 2011, Chen applied the picolinamide directing group to the functionalization of cyclic amino esters (**4**, Scheme 6B).[35] Milder, more practical arylation conditions (1.5 equiv aryl iodide, 80 ºC) were developed for a methylene γ-C–H functionalization. γ-C(sp^3)–H alkenylation was also reported using cyclic alkenyl iodides. However, the difficulty encountered in removing the picolinamide directing group (**5a**) prompted the authors to design a more readily cleaved auxiliary. This was achieved by installing a silyl-protected *ortho*-hydroxymethylene group onto the picolinamide (**5b**), which

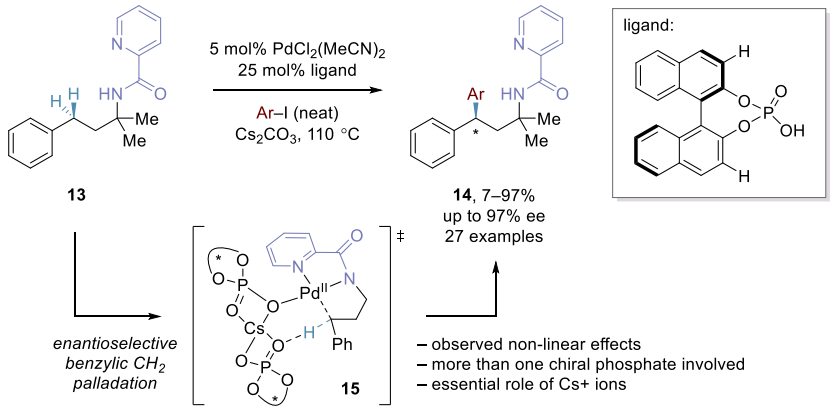
under mild acidic conditions underwent intramolecular acyl transfer (**6**) to furnish the free amino ester derivative (**7**). Later, γ-methylene C–H arylation was extended by Shi to more challenging acyclic amines (**8**) using an oxazoline-carboxylate auxiliary, allowing access to branched alkyl arylation products (**9**, Scheme 6C).[36] Other than C–H arylation, Chen developed a picolinamide-directed γ-C(sp^3)–H alkylation using primary alkyl iodides (Scheme 6D).[37] The methodology was generally selective for mono-alkylation of γ-methyl groups, though, interestingly, efficient threefold methylation was observed in the case of norbornene-derived substrate (**10**) (first γ-C–H alkylation to **11**, then δ-C–H alkylation twice), giving isopropyl-substituted product (**12**). Ag_2CO_3 and $(BnO)_2PO_2H$ were crucial as additives in the reaction, in which the Ag(I) salt was proposed to facilitate oxidative addition of the alkyl iodide to the metal centre via an S_N2-type process, with the phosphoric acid acting as a phase-transfer catalyst to gradually solubilize Ag(I) ions.



Scheme 6. Picolinamide- and Oxazoline-Carboxylate-Directed C(sp^3)–H Functionalization: C–C Bond Formation

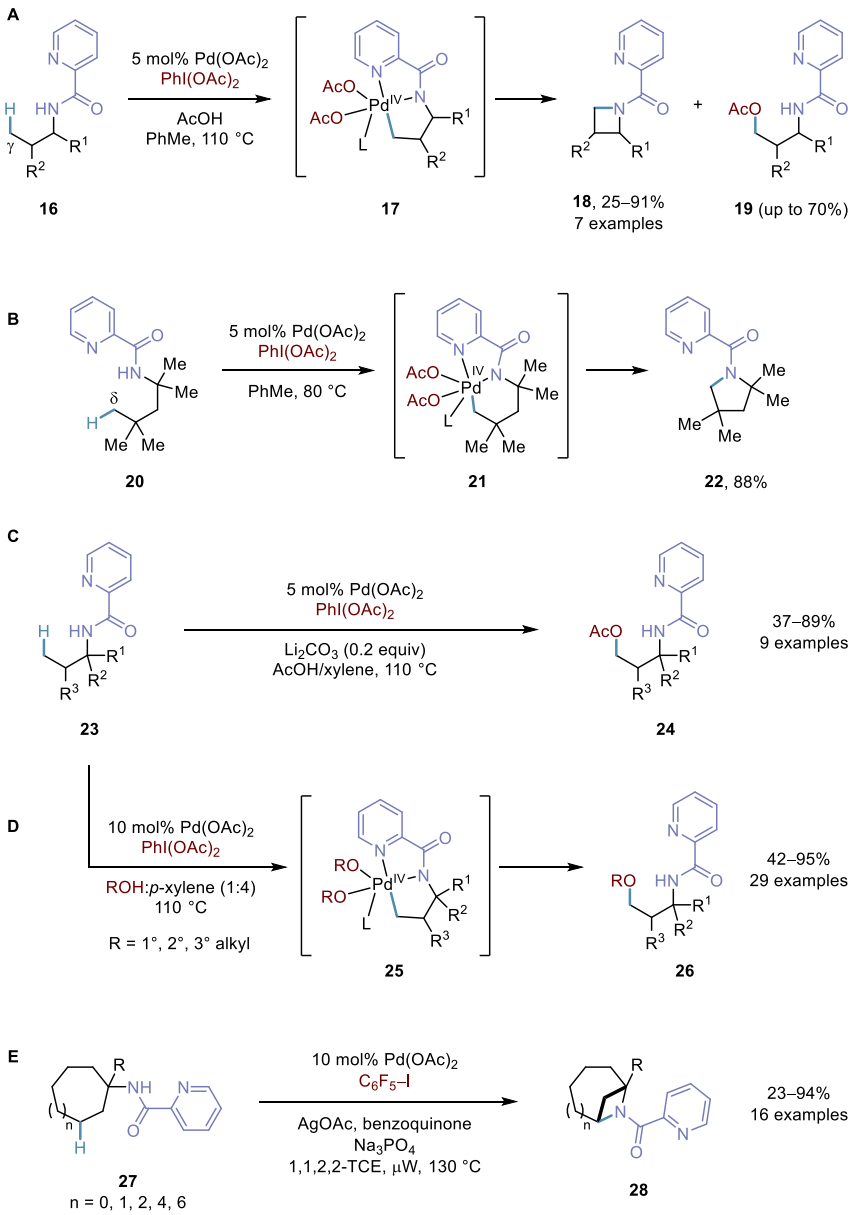
Enantioselective transformations involving picolinamide-directed C–H functionalization remain rare, though a notable first example was reported by Chen in 2016.[38] Enantioselective benzylic methylene C–H arylation of γ-aryl alkyl amines (**13**) using aryl iodides and an unsubstituted chiral BINOL-derived phosphoric acid ligand afforded γ-diarylated derivatives (**14**, up to 97% ee, Scheme 7). Substitution on the BINOL scaffold gave lower enantioselectivity, while Cs_2CO_3 and solventless conditions were found to be essential for obtaining high ee's. The observation of non-linear effects when varying the enantiopurity of the ligand indicated that more than one ligand was likely involved in the enantio-determining step. Considering the important role of Cs^+ in the reaction, the authors proposed a model for

enantioselectivity involving a cesium diphosphate salt (or higher order cluster), in which one phosphate is bound to Pd while the second assists in the C–H bond cleavage (**15**).



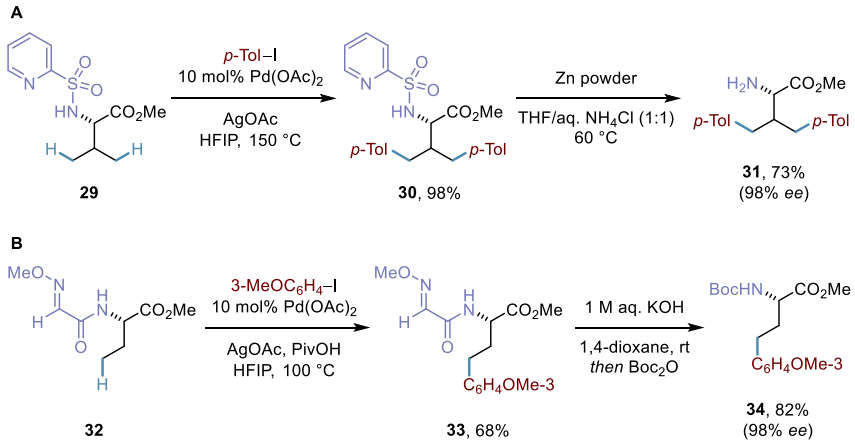
Scheme 7. Picolinamide-directed Enantioselective Benzylic Methylene C–H Arylation

A variety of C–heteroatom bond formations have also been achieved using the picolinamide directing group. In 2012, Chen described the transformation of alkylamine derivatives (**16**) to azetidine (**18**) and pyrrolidine derivatives via intramolecular γ- and δ-methyl C–H amination, respectively (Scheme 8A).[39] The synthesis of pyrrolidines (**22**), using appropriately substituted substrates (**20**), was simultaneously reported by Daugulis (Scheme 8B).[40] Employing $PhI(OAc)_2$ and catalytic $Pd(OAc)_2$, Chen and Daugulis demonstrated the unique ability of hypervalent iodine and high valent Pd(IV) intermediates (**17**, **21**) to promote intramolecular C–N bond formation. However, it is noteworthy the by-product arising from intermolecular C–O acetoxylation (**19**) was observed for less highly branched substrates, indicating the significant challenge involved in controlling competing reductive elimination pathways from Pd(IV) intermediates. Chen later developed conditions for selective γ-C–O acetoxylation (**23** to **24**) using $PhI(OAc)_2$ in the presence of substoichiometric Li_2CO_3, in which alkali metal salts were observed to suppress competing C–N reductive elimination (Scheme 8C).[41] Meanwhile, using $PhI(OAc)_2$ and a mixed ROH:*p*-xylene solvent system, Chen reported a picolinamide-directed γ-C(sp^3)–H alkoxylation (Scheme 8D).[42] The high valent Pd(IV) intermediate could be intercepted by 1°, 2° and 3° alcohols (**25**) to afford a diverse range of alkyl ether products (**26**). More recently, Liu and Wu employed the picolinamide auxiliary (**27**) for the synthesis of structurally complex azabicycles (**28**, Scheme 8E).[43] Perfluorinated iodobenzene, C_6F_5I, was used as the oxidant to efficiently promote intramolecular C–N amination.



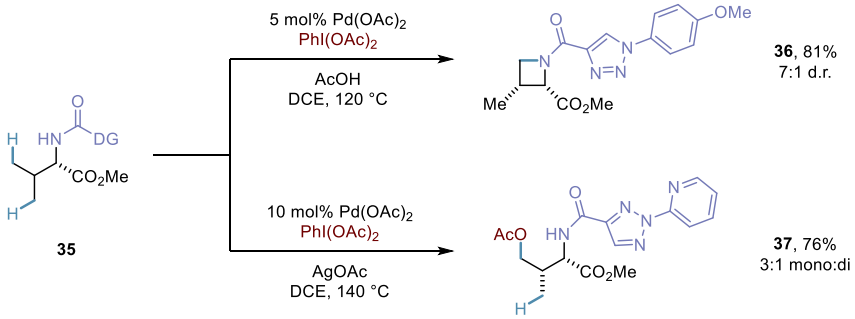
Scheme 8. Picolinamide-Directed C(sp^3)–H Functionalization: C–Heteroatom Bond Formation

The picolinamide directing group represented a significant advance in directed C–H functionalization of amine derivatives. Nevertheless, Chen's work highlighted the critical importance of having straightforward and mild procedures to install and remove the directing group, resulting in the design of an acyl transfer strategy that was promoted by dilute acid. In 2013, two further examples of cleavable bidentate directing groups were reported: Carretero's *N*-(2-pyridyl)sulphonamide DG[44] (**29**) and Ma's 2-methoxyiminoacetyl DG (**32**, Scheme 9).[45] In each case, Pd-catalyzed γ-C–H arylation was demonstrated (**30**, **33**). Following this, the *N*-(2-pyridyl)sulphonamide group was cleaved by treatment with Zn powder in THF/aq. NH_4Cl at 60 °C to afford the aminoester (**31**). Conversely, the 2-methoxyiminoacetyl group was hydrolysed using 1 M aq. KOH in dioxane at room temperature, with subsequent Boc-protection giving protected amino acids (**34**). Later examples of directing groups removed under mild hydrolytic conditions include the 5-methylisoxazole-3-carboxamide (MICA)[46] and benzothiazole-2-sulfonyl (Bts) groups.[47]



Scheme 9. Early Examples of Amine-derived Directing Groups Cleaved Under Mild Conditions

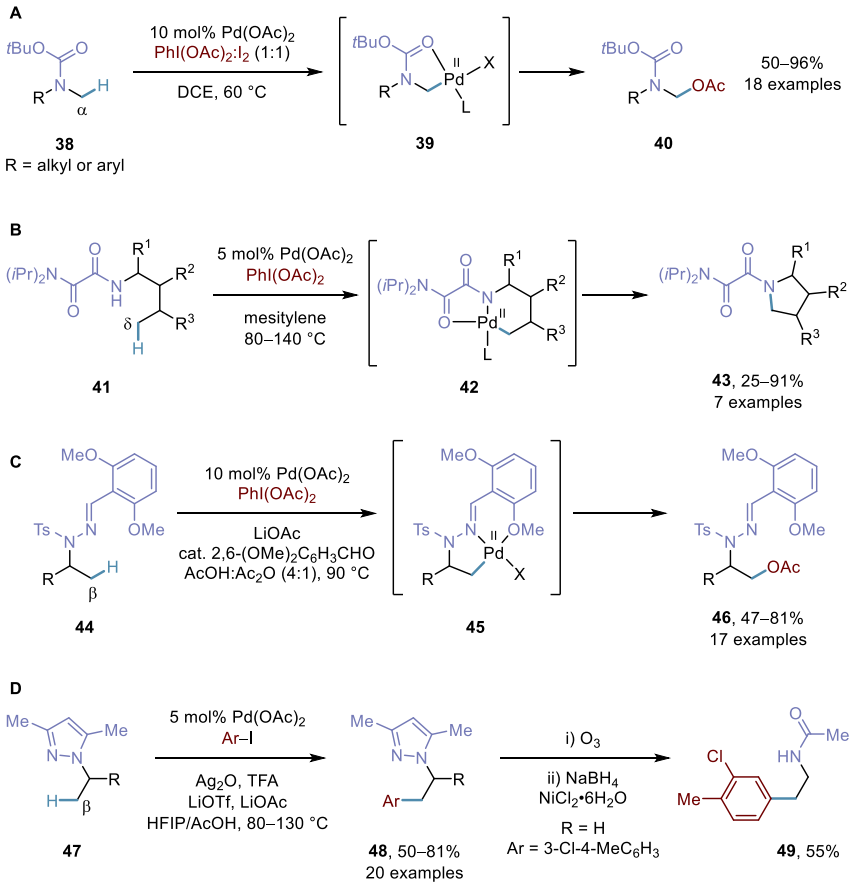
In addition to modifying the chemical properties of the DG (e.g. hydrolytic stability), newly designed DGs have also enabled tuning of substrate reactivity, for example in the selectivity of reductive elimination from metallacyclic intermediates. In 2013, Shi demonstrated that 1,2,3-triazole DGs could favour either intramolecular C–N amination or intermolecular C–O acetoxylation depending on the denticity of the directing group in the substrate (**35**, Scheme 10).[48] Using $PhI(OAc)_2$, a bidentate triazole DG was observed to promote C–N bond formation, giving azetidine products (**36**). On the other hand, a tridentate triazole DG was observed to favour C–O acetoxylation (**37**). Although the origin of the selectivity is unclear, the authors speculate that the in-plane meridional binding mode of the tridentate DG disrupts the geometry of anionic ligands around the metal centre, causing a switch in selectivity of reductive elimination.



Scheme 10. Directing Group-Controlled Reductive Elimination from High-Valent Pd

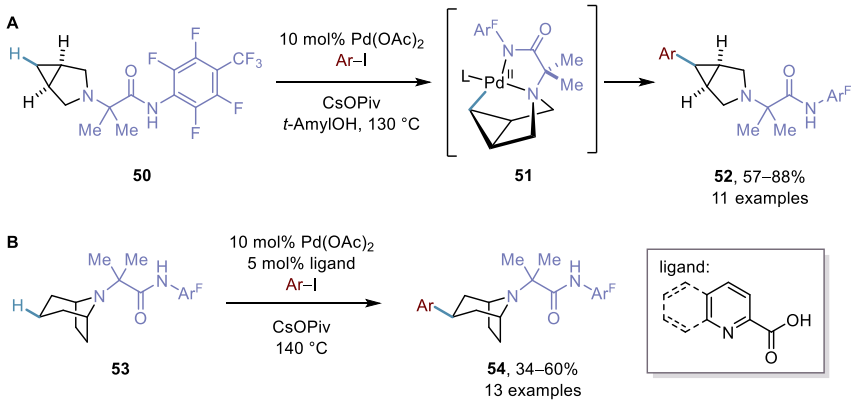
While the vast majority of methods discussed so far have led to γ-C–H functionalization via the kinetically favoured five-membered palladacycle with coordination to the metal through the amine-derived nitrogen, several directing group strategies have been developed that enable activation at positions other than the γ-position of amines. An early example, by Yu in 2006, reported a Boc-directed α-methyl acetoxylation of *N*-methylamines and anilines (**38**, Scheme 11A).[49] The combination of $PhI(OAc)_2$ and I_2 formed the required oxidant, IOAc, in situ, giving α-functionalized products (**40**) in excellent yields via putative intermediate (**39**). In 2014, Yao and Zhao reported intramolecular δ C–H amination of oxalyl amide-protected amines (**41**) to pyrrolidine derivatives (**43**) via six-membered palladacycle intermediates (**42**, Scheme 11B).[50] Using $PhI(OAc)_2$, good yields of cyclized products were obtained. Notably, the unbranched *n*-butylamine derivative (**41**, $R^1 = R^2 = R^3 = H$) gave 25% yield of the pyrrolidine product. Later, the oxalyl amide group was shown to also be capable of promoting γ-C(sp^3)–H functionalization via five-membered palladacycles, including γ-arylation[51,52] and γ-acetoxylation.[53] In 2016, Dong reported a β-methyl C–H acetoxylation of hydrazone derivatives (**44**, Scheme 11C), employing an *exo* directing group strategy in which the π bond of the hydrazone is exocyclic in the intermediate metallacycle (**45**).[54] The directing group could be cleaved from the functionalized products (**46**) in a sequential one-pot process by addition of

zinc directly to the reaction mixture, furnishing tosyl-protected amines. In 2017, Daugulis discovered a simple pyrazole directing group could also activate the β position of aliphatic substrates (**47**) (Scheme 11D).[55] C–H arylation with aryl iodides (**48**) followed by ozonolysis gave pharmaceutically relevant β-phenethylamine products (**49**).



Scheme 11. Directing Group Strategies for C–H Functionalization at Positions Other Than the γ Position

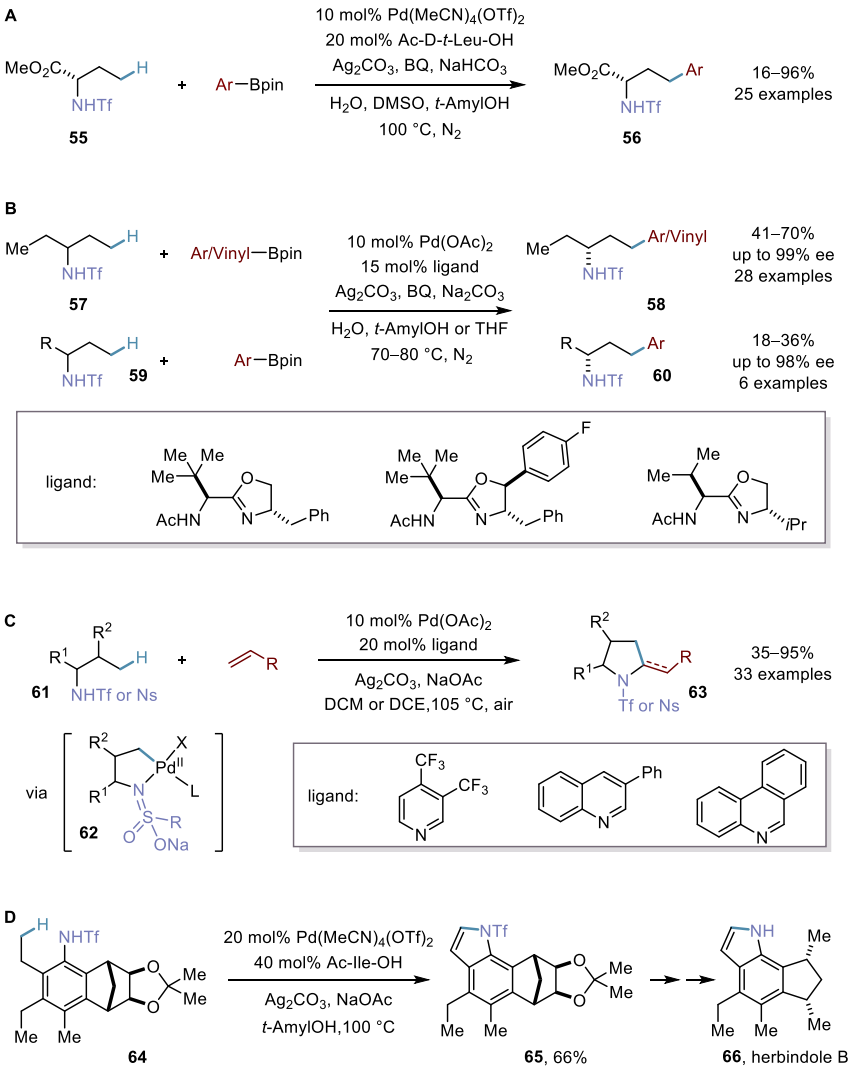
In 2016, Sanford demonstrated the possibility of transannular C–H functionalization, reporting a γ-arylation of cyclic aliphatic amines containing a fluoroamide directing group (**50**, Scheme 12A).[56] Functionalization with both aryl and heteroaryl iodide coupling partners proceeded in good yields to arylated products (**52**) via bridged palladacycle intermediates (**51**), with several pharmaceutical drugs (e.g. varenicline) being arylated in remote positions. Recently, Sanford reported a second-generation catalyst system for transannular C–H arylation (Scheme 12B).[57] Addition of a pyridine or quinoline carboxylate ligand gave benefits in terms of yield, rate and scope over ligandless conditions. Mechanistic studies indicated that the ligand increases turnover by recovering the active catalyst from off-cycle intermediates. Biologically relevant tropane derivatives (**53**), as well as 7-azanorbornane and homotropane cores, could be functionalized in a transannular fashion (**54**) for the first time under the improved conditions.



Scheme 12. Transannular C–H Arylation of Alicyclic Amine Derivatives

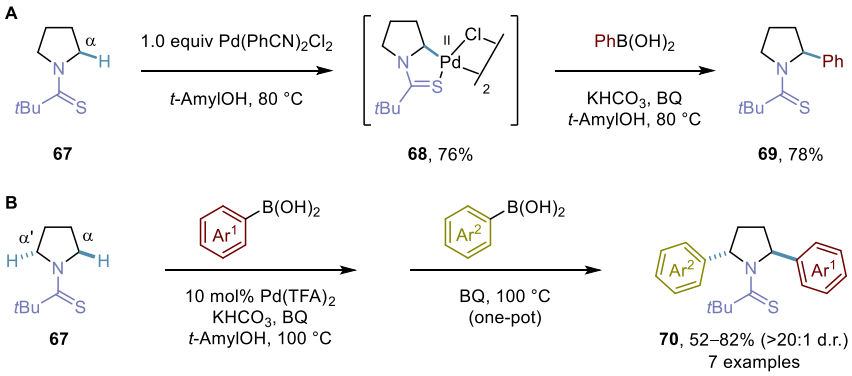
Pd(II)/Pd(0) Catalysis

The Pd(II)/Pd(0) catalytic manifold has also been well explored for amine-derived directing group strategies. Most commonly, transmetallating boron reagents along with a suitable terminal oxidant have been employed to enable C–C bond formation. Using Pd(II)/Pd(0) catalysis, Yu and co-workers found that sulfonamide-protected amines could effectively promote C–H functionalization with the assistance of mono-*N*-protected amino acid ligands. In 2014, Yu first reported the functionalization of γ-methyl C–H bonds of *N*-triflyl-protected amines (**55**) with aryl boronate esters, giving arylated sulfonamide derivatives (**56**, Scheme 13A).[58] *N*-acetyl-protected amino acid ligands were found to be essential for reactivity, and in fact, no reaction was observed in their absence. DFT studies indicated the carbonyl of the *N*-acetyl group of the ligand acts as the internal base in the CMD step of the mechanism.[59,60] Subsequently, Yu developed an enantioselective variant of the ligand-enabled arylation reaction for *N*-triflyl-protected cyclopropylmethylamines, using *N*-Boc protected valine as a chiral ligand and aryl iodides as arylating agents.[61] Recently, Yu developed a more broadly scoping enantioselective γ-C(sp^3)–H arylation and vinylation of *N*-triflyl-protected amines (**57**, **59**), using chiral *N*-acetyl-protected aminomethyl oxazoline ligands with boron reagents to enable highly enantioselective desymmetrization and kinetic resolution to chiral derivatives (**58**, **60**, Scheme 13B).[62] In 2015, a Pd(II)-catalyzed olefination of γ-C(sp^3)–H bonds of Tf- and Ns-protected aliphatic amines (**61**) was demonstrated by the same group, involving 1,2-migratory insertion of the olefin into the intermediate palladacycle (**62**). Subsequent aza-Wacker oxidative cyclization or conjugate addition of the olefinated intermediates afforded functionalized pyrrolidines (**63**, Scheme 13C). Three pyridine- and quinoline-based ligands were developed to match different classes of protected aliphatic amines, tuning the reactivity of the metal centre to enable efficient catalytic C(sp^3)–H olefination for a wide range of substrates.[63] In 2016, Tf-protected 2-ethylanilines (**64**) were shown to undergo intramolecular C(sp^3)–H amination/oxidative indole formation (**65**), which found application in the syntheses of alkaloids *cis*-trikentrin A and herbindole B (**66**, Scheme 13D).[64]



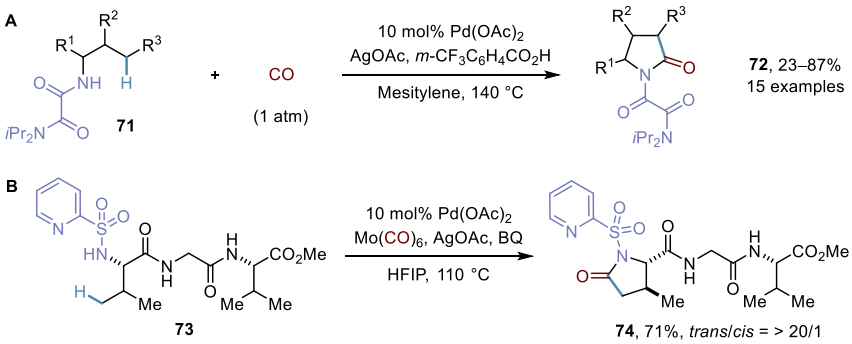
Scheme 13. Sulfonamide-Directed C(sp^3)−H Functionalization of Aliphatic Amines

Additionally, moving to a different type of directing group, Yu reported the functionalization of α-methylene C–H bonds in thioamide-protected pyrrolidines (**67**).[65] Their initial efforts found that treatment of thioamide (**67**) with stoichiometric $Pd(PhCN)_2Cl_2$ produced the key intermediate palladacycle (**68**), which could undergo efficient arylation with phenylboronic acids in the presence of a mild base and stoichiometric benzoquinone (BQ) to give the α-arylated product (**69**, Scheme 14A). Upon further development, this α-methylene C–H arylation was rendered catalytic by using 10 mol% $Pd(TFA)_2$ catalyst and 1.1 equiv BQ. Mono-selective arylation was achieved using aryl and heteroaryl boronic acids. Consequently, a one-pot procedure for a diastereoselective sequential diarylation was developed, forming trans α,α'-diarylated products (**67** to **70**, Scheme 14B). An enantioselective version of the reaction was later reported using a chiral BINOL-derived phosphoric acid ligand.[66]



Scheme 14. Thioamide-Directed Methylene C−H Functionalization of Pyrrolidines

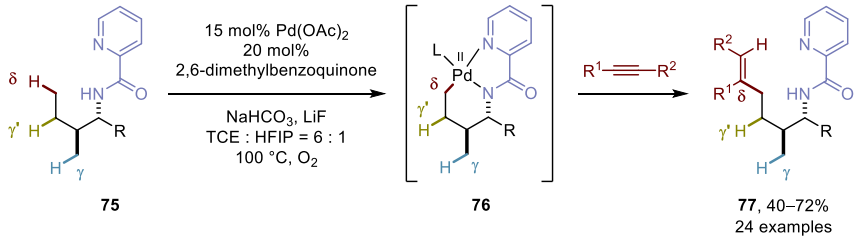
Pd-catalyzed carbonylation of C(sp^3)−H bonds has been another well explored functionalization that exploits Pd(II)/Pd(0) catalysis. Two bidentate directing groups have been reported that enable carbonylative cyclization of aliphatic amines producing γ-lactam derivatives. Using gaseous CO (1 atm), Zhao developed a Pd-catalyzed regioselective γ-carbonylation of oxalyl amide-protected aliphatic amines (**71**, Scheme 15A).[67] Both γ-methyl and cyclopropyl methylene C–H bonds could be activated, providing the corresponding γ-lactams (**72**) in moderate to excellent yields. Meanwhile, using $Mo(CO)_6$ as the source of CO, γ-C(sp^3)−H carbonylation of *N*-(2-pyridyl)sulfonyl (*N*-SO_2Py)-protected amines (**73**) was reported by Carretero (Scheme 15B).[68] Notably, the reaction was applied to complex di- and tripeptide substrates, enabling late-stage diversification to γ-lactams (**74**).



Scheme 15. Pd(II)-Catalyzed γ-C(sp^3)−H Carbonylation

Pd(II)/Pd(II) Catalysis

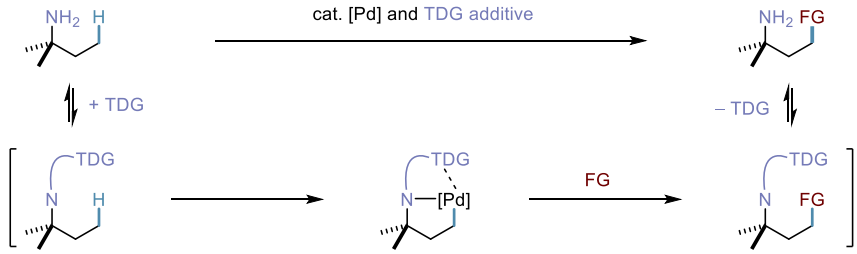
Although much less common, C–H functionalization using redox neutral Pd(II)/Pd(II) catalysis is also known. In 2016, Shi demonstrated a site-selective alkynylation of δ-C(sp^3)−H bonds in picolinamide-protected aliphatic amines (**75**, Scheme 16).[69] Notably, after the insertion of the alkyne into the intermediate six-membered palladacycle (**76**), the final product (**77**) is obtained by protonation with AcOH or HFIP rather than reductive elimination, releasing the Pd(II) catalyst and leading to an overall redox neutral process. Deuteration experiments disclosed that the cleavage of kinetically favored γ-C−H bonds is reversible under the standard conditions. Furthermore, no deuterium incorporation at the δ-position was observed in the presence of alkyne, suggesting that either δ-C−H activation is irreversible or that migratory insertion of the alkyne is significantly faster than the reverse reaction. In 2018, a computational study revealed a dimeric mechanism involving two Pd centres with bridging acetates.[70] In contrast to the monomeric mechanism, in which migratory insertion is selectivity determining, δ-C(sp^3)–H bond activation was found to be energetically favoured by the $Pd_2(OAc)_4$ dimer over other sites of activation, being attributed to reduced ring strain in the larger ring transition state.



Scheme 16. Alkenylation of δ-C(sp^3)–H Bonds with Alkynes via a Six-Membered Palladacycle

TRANSIENT DIRECTING GROUP STRATEGY

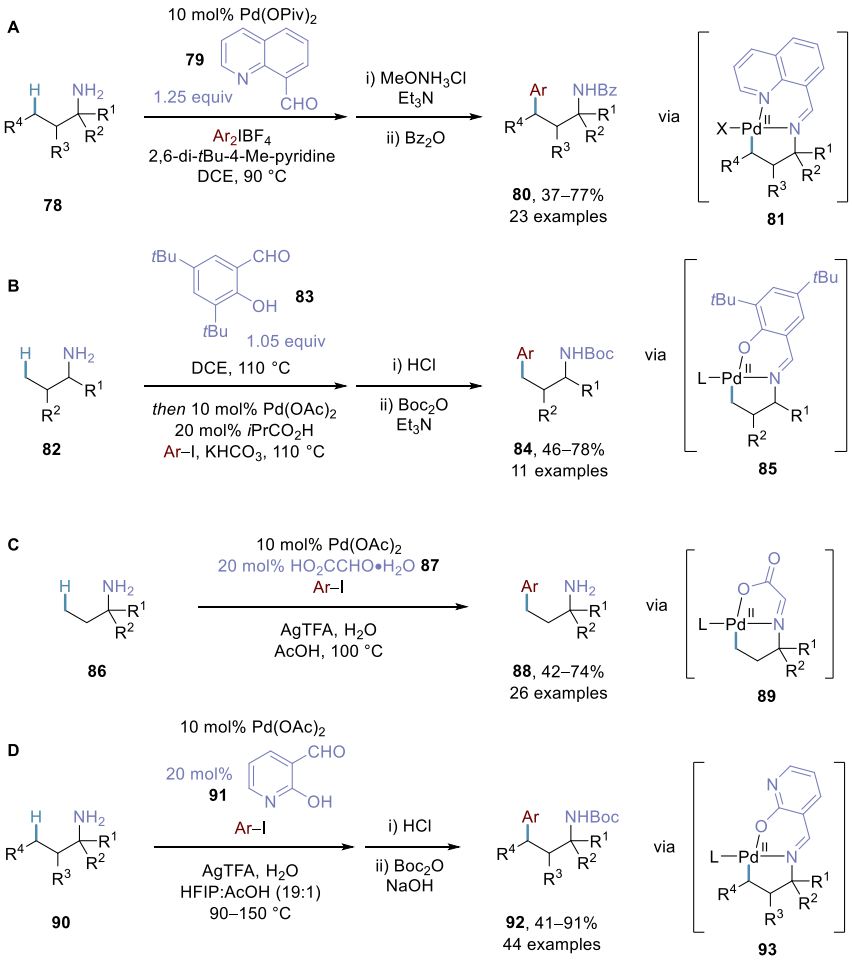
A recent advance in the field of Pd-catalyzed C–H functionalization has been the development of in situ-formed transient directing groups (TDGs), whereby directing group installation, C–H bond cleavage/functionalization and directing group removal occur sequentially in one pot (Scheme 17).[71,72] As a result, TDG strategies encompass the benefits of traditional DG strategies, while simultaneously overcoming the drawback of having additional steps for DG installation and removal. Current methods have predominantly exploited reversible imine formation between primary amine substrates and DG-containing aldehydes (either in catalytic or stoichiometric quantities) to generate active intermediates capable of promoting cyclometallation.



Scheme 17. Transient Directing Group Strategy for Site-Selective C–H Activation

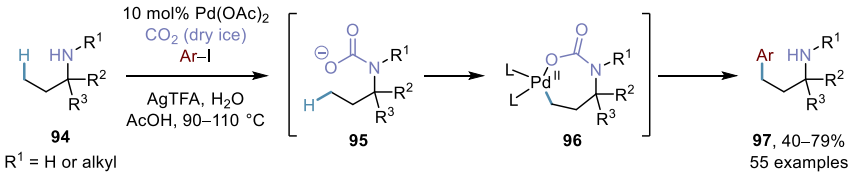
Pd(II)/Pd(IV) Catalysis

To date, all reported methods have employed high valent Pd(II)/Pd(IV) catalysis. In 2016, Dong reported the use of quinoline-8-carboxaldehyde (**79**) as a stoichiometric additive for γ-methyl and methylene C–H arylation of unprotected primary amines (**78**, Scheme 18A).[73] The in situ-formed imine contained a bidentate *exo*-directing group, forming a 5-membered palladacycle (**81**) which was functionalized using diaryl iodonium salts to γ-arylated products (**80**). The conditions were also effective for δ-methyl C–H arylation of aniline-derived substrates. Shortly after, Murakami developed an analogous C–H arylation reaction using a readily available salicylaldehyde (**83**) in stoichiometric quantities, forming phenoxy-imines capable of directing C–H activation (**85**, Scheme 18B).[74] A bulky *ortho*-substituent on the aldehyde arene was essential in disfavouring coordination of two equivalents of the imine to Pd and thus formation of an unreactive diimine complex. In 2016, Ge[75] and Yu[76] independently reported the use of TDGs in catalytic quantities, exploiting the rapid reversibility of imine formation. Ge's method utilized catalytic glyoxylic acid (**87**) with aryl iodides and AgTFA to promote γ-methyl C–H arylation of primary amines bearing fully-substituted α-(NH_2) centres (**86**, Scheme 18C). Conversely, Yu employed catalytic 2-hydroxynicotinaldehyde (**91**) as a TDG in which both γ-methyl and γ-methylene C–H arylation could be achieved (Scheme 18D). The scope of the reaction was demonstrated for a diverse range of alkyl amine substrates (**90**) and (hetero)aryl iodide coupling partners. Notably, upon scale-up (2 mmol), the Pd catalyst and directing group loadings could be lowered to 2 and 4 mol% respectively.



Scheme 18. Transient Directing Group Strategies for the Functionalization of Unprotected Amines

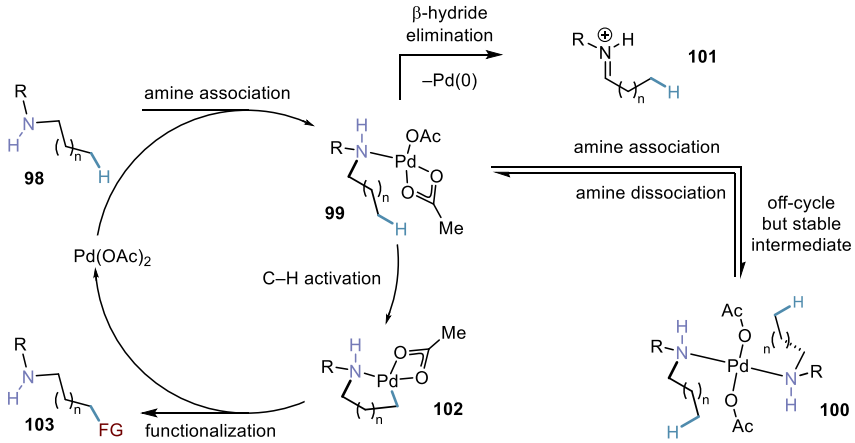
Recently, Young reported a carbon dioxide-mediated C(sp^3)–H arylation of amines (Scheme 19).[77] Young's methodology is distinct from the imine-based TDG strategies, instead relying on the formation of a transient carbamate intermediate (**95**) to direct the Pd catalyst. By employing conditions similar to Ge, and using CO_2 in the form of dry ice, unprotected aliphatic amines (**94**) were functionalized at the γ position in moderate to good yields to arylated derivatives (**97**). The authors propose a mechanism proceeding via a putative seven-membered palladacycle (**96**). In addition to primary amines, it is notable that secondary amines – incompatible substrates for imine formation – also underwent efficient C–H arylation when higher loadings of CO_2 were used.



Scheme 19. CO_2-Mediated C(sp^3)–H Arylation of Unprotected Primary and Secondary Amines

NATIVE AMINE-DIRECTED STRATEGY

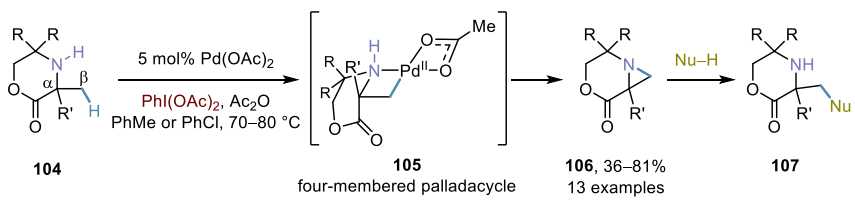
The use of native amine functionality to promote C–H functionalization is conceptually the most straightforward approach, in which the innate coordinating ability of the amine nitrogen is directly exploited in substrate-catalyst interactions. Native amine-directed transformations typically take place in a single step and without the addition of exogenous directing groups. As a result, a native amine-directed strategy provides the opportunity for optimal atom efficiency, as well as a complementary approach for developing transformations that are not readily amenable to TDGs, for example intramolecular processes. However, until recently, strategies to functionalize unprotected aliphatic amines had remained underexplored, principally due to the unique set of challenges posed by amines for Pd-catalyzed C–H functionalization (Scheme 20).[78] Firstly, amines are known to strongly coordinate to Pd(II), forming stable and unreactive bis(amine) complexes (**100**).[21] C–H bond cleavage via CMD requires a vacant site of coordination, and therefore cannot proceed from this intermediate. Secondly, once coordinated, aliphatic amines may undergo β-hydride elimination, leading to oxidative degradation of the substrate (**101**) and reduction of the Pd catalyst. Nevertheless, through careful reaction design, several approaches have been discovered which overcome these challenges, establishing native amine-directed C(sp^3)–H functionalization as a versatile and emerging area in chemical synthesis.



Scheme 20. Native Amine-Directed Strategy for C–H Functionalization, and the Associated Challenges

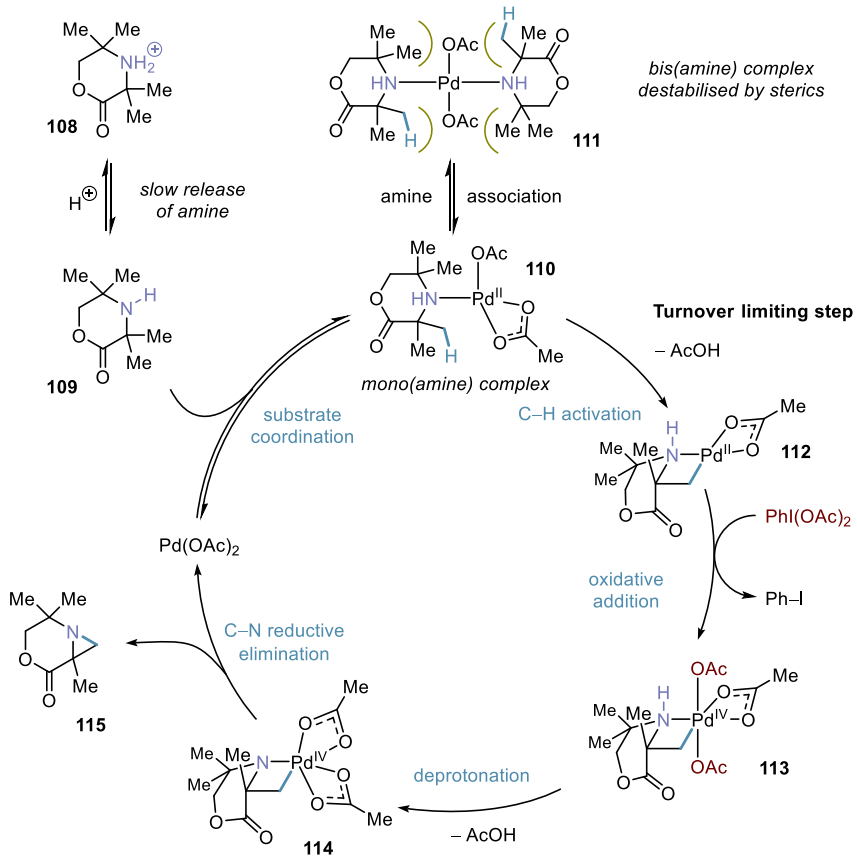
Pd(II)/Pd(IV) Catalysis

In 2014, Gaunt reported the first example of Pd-catalyzed C–H functionalization of unprotected aliphatic amines (Scheme 21).[79] Sterically hindered secondary amines (**104**) bearing fully substituted centres α to the amine nitrogen were used, precluding formation of the bis(amine) complex and β-hydride elimination. Significantly, the hindered substrates underwent non-classical four-membered cyclopalladation via β-C(sp^3)–H activation (**105**), which upon oxidation with $PhI(OAc)_2$, afforded the strained aziridine product (**106**). The reaction tolerated a variety of functional groups including aryl, protected alcohol, protected amine, halide and ester groups. Sequential nucleophilic ring-opening of the aziridines provided access to densely functionalized amino acid derivatives (**107**). Crucially, this previously unknown bond disconnection was an early indication of a general C(sp^3)–H functionalization platform for the diversification of saturated *N*-heterocycles – a class of small molecule that predominantly features in pharmaceutical drugs.

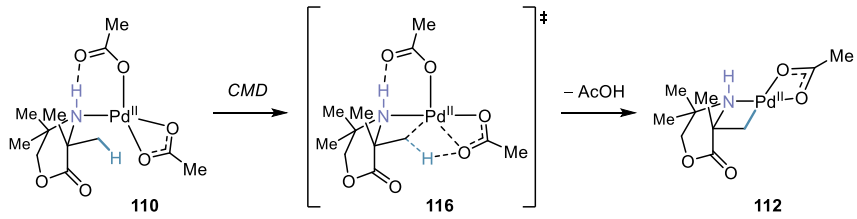


Scheme 21. Pd-Catalyzed β-Methyl C–H Amination to Aziridines

In 2015, a mechanistic study for the Pd-catalyzed aziridine formation was reported, in which a detailed catalytic cycle was proposed based on kinetic and DFT analysis (Scheme 22).[80] During the investigation, it was observed that addition of acetic acid led to a significant increase in the reaction rate, indicating slow release of free amine into the cycle was favourable in further curtailing formation of the bis(amine) complex (**111**). C–H bond cleavage in the mono(amine) complex (**110**) was found to be the turnover-limiting step. Notably, computational studies demonstrated the importance of a hydrogen bonding interaction between a bound acetate and the N–H of the substrate in ideally positioning the β-C–H bond prior to CMD (**116** Scheme 23). After formation of the palladacycle (**112**), a low energy pathway was calculated for oxidation to Pd(IV) intermediate (**113**), followed by deprotonation to amido complex (**114**) and C–N reductive elimination to give the aziridine product (**115**).



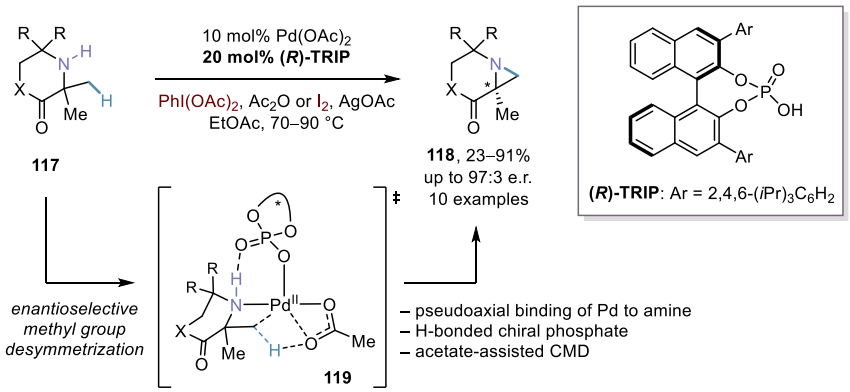
Scheme 22. Catalytic Cycle of Pd-Catalyzed β-Methyl C–H Aziridination



Scheme 23. DFT Calculation of the CMD Pathway

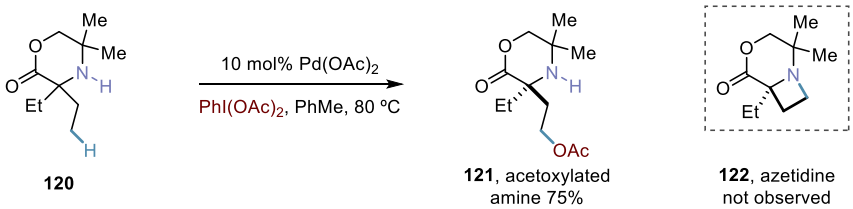
Later, in 2017, an enantioselective variant of the aziridine formation was reported by Gaunt, employing hindered amines bearing β-*gem*-dimethyl substituents (**117**) and chiral BINOL-derived phosphoric acid ligand, (*R*)-TRIP (Scheme 24).[81] The reaction was the first enantioselective desymmetrization of prochiral methyl groups using Pd(II)/Pd(IV) catalysis.

The enantioenriched aziridines (**118**) could be further transformed to stereo-defined heterocyclic building blocks by nucleophilic ring opening. Recent computational studies[82] indicate that enantioselectivity originates from a species such as (**119**): with the Pd bound in a pseudoaxial position on the amine, one molecule of (*R*)-TRIP ligand hydrogen bonds to the amine(NH) to set up a chiral environment within which acetate-assisted C–H bond cleavage takes place.

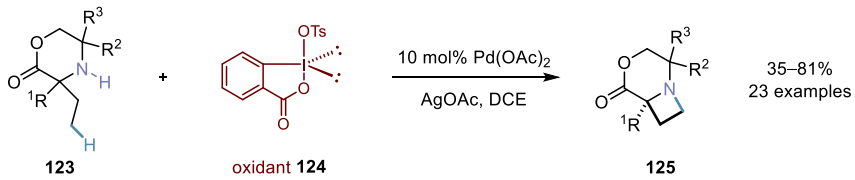


Scheme 24. Pd-Catalyzed Enantioselective C–H Aziridination

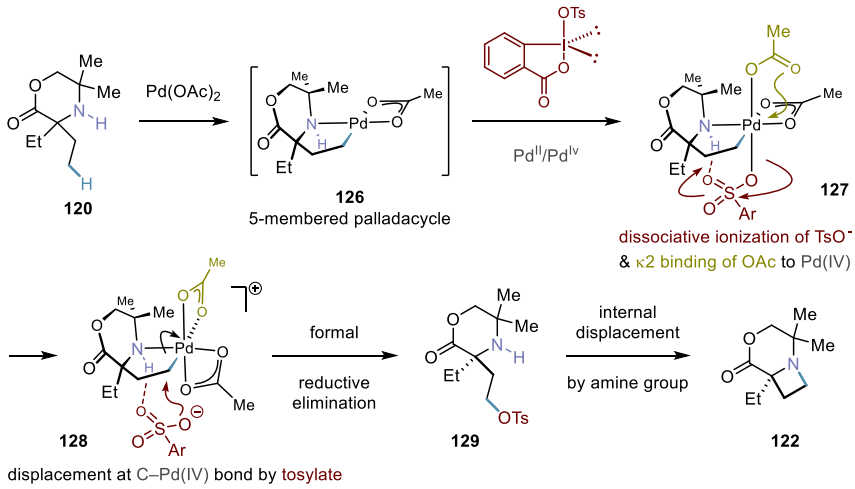
Based on the Pd-catalyzed aziridine formation, the related homologated amine (**120**) was proposed to undergo γ-C–H amination to form the corresponding azetidine (**122**). However, the reaction produced only the γ-C–H acetoxylation product (**121**), with no sign of azetidine product when treated under identical conditions to those of the aziridine-forming process ($PhI(OAc)_2$, PhMe, 80 °C; Scheme 25).[79] Notably, competitive C–H acetoxylation was frequently observed as a side product in the related auxiliary-directed azetidine-forming reactions.[39] Thus, obtaining selectivity for C–N reductive elimination from aminoalkyl palladium(IV) species to form aliphatic cyclic amine products remained a challenge. In 2018, Gaunt and co-workers successfully demonstrated a Pd-catalyzed γ-C–H amination of cyclic secondary aliphatic amines (**123**) to substituted azetidines (**125**, Scheme 26).[83] The approach taken aimed not to target direct C–N reductive elimination, but rather exploit the relative facility of C–O reductive elimination to generate an activated intermediate containing a leaving group that would rapidly cyclize. In this regard, a tosylated benziodoxole oxidant (**124**) was found to be an effective agent for C–H tosylation, promoting exclusive selectivity to azetidines after cyclization. Computational studies supported a pathway involving oxidation of the intermediate five-membered palladacycle (**126**) to octahedral Pd(IV) complex (**127**), followed by dissociative ionization of tosylate and anchimeric κ2 carboxylate binding to form cationic Pd(IV) complex (**128**). Nucleophilic attack of the displaced tosylate at the carbon bearing the Pd(IV) group forms the C–OTs bond (**129**), which in turn is attacked by the proximal amino group to form the azetidine (Scheme 27). The process is tolerant of a variety of functional groups including structural features derived from chiral α-amino alcohols, enabling the diastereoselective synthesis of enantiopure azetidines.



Scheme 25. Pd-Catalyzed γ-C–H Acetoxylation

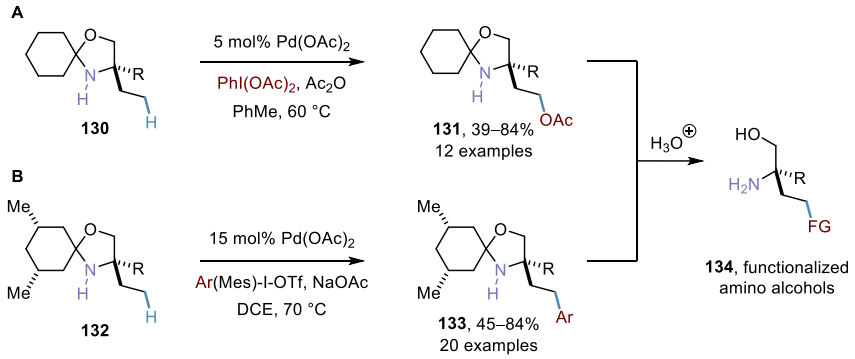


Scheme 26. Pd-Catalyzed γ-C–H Amination to Form Azetidine



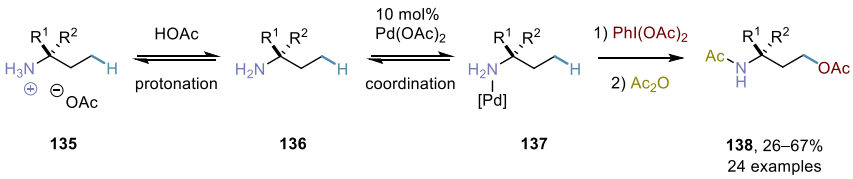
Scheme 27. Selective Reductive Elimination at Alkyl Palladium(IV) by Dissociative Ligand Ionization

The sterically-driven approach to C–H functionalization was further explored by Gaunt using a 'steric tethering' strategy, whereby a labile moiety that increases sterics is temporarily attached to the amine to enable Pd-catalyzed C–H functionalization. In this manner, *N*,*O*-ketal substrates (**130**, **132**) were used as sterically hindered derivatives of 1,2-amino alcohols, with C–H functionalization being promoted by Pd(II)/Pd(IV) catalysis.[84] A selective γ-methyl acetoxylation was developed using $PhI(OAc)_2$, giving access to a range of protected amino diol products (**131**) (Scheme 28A). Conversely, slight modification of the *N*,*O*-ketal motif and use of diaryliodonium salts enabled the formation of the corresponding arylated products (**133**) (Scheme 28B). Crucially, the functionalized *N*,*O*-ketals could be sequentially cleaved under mild acidic conditions to afford remotely functionalized amino alcohols (**134**).



Scheme 28. Pd-Catalyzed Acetoxylation and Arylation of Amino Alcohols using a Steric Tethering Approach

Besides the C–H functionalization of secondary aliphatic amines, a single example of C(sp^3)–H acetoxylation of primary amines (**136**) was reported by Shi in 2017 (Scheme 29).[85] Amine protonation was utilized to moderate the binding capability of the unprotected substrate (**135–137**), enabling acetoxylation in good selectivity to γ-amino alcohol derivatives (**138**).

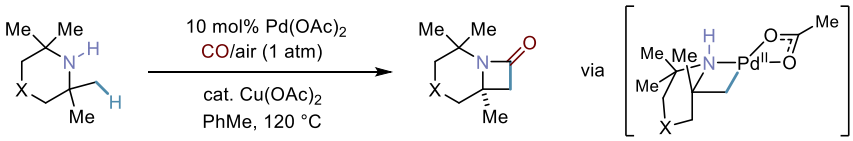


135 **136** **137** **138**, 26–67%, 24 examples

Scheme 29. Pd-Catalyzed Acetoxylation of Aliphatic Primary Amines

Pd(II)/Pd(0) Catalysis

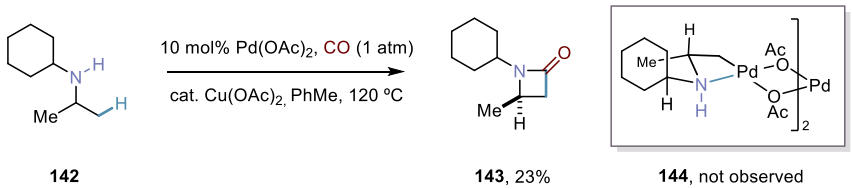
In addition to developing C–H amination of hindered cyclic amines using Pd(II)/Pd(IV) catalysis, Gaunt and co-workers also explored the reactivity of these amine molecules under the complementary Pd(II)/Pd(0) manifold. Replacing $PhI(OAc)_2$ with carbon monoxide and a suitable terminal oxidant ($Cu(OAc)_2$), conditions for C–H carbonylation were developed. Hindered tetramethylpiperidine (TMP) substrates (**139**) were demonstrated to undergo β-C–H carbonylation in good yields, providing β-lactam products (**140**, Scheme 30).[79] Mechanistically, the amine-directed C–H activation leads to the formation of the four-membered cyclopalladation complex (**141**), which undergoes coordination of CO, 1,1-migratory insertion, and reductive elimination to generate the β-lactam.



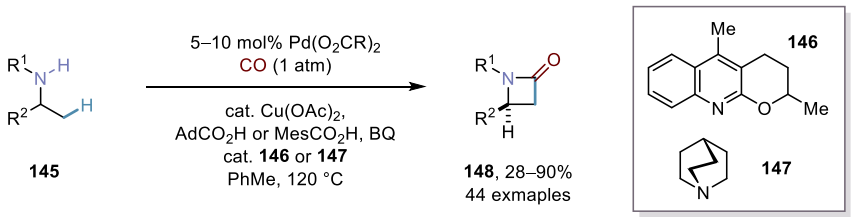
139 **140**, 55–87%, 7 examples **141**

Scheme 30. Pd-Catalyzed β-C–H Carbonylation of Hindered TMP Substrates

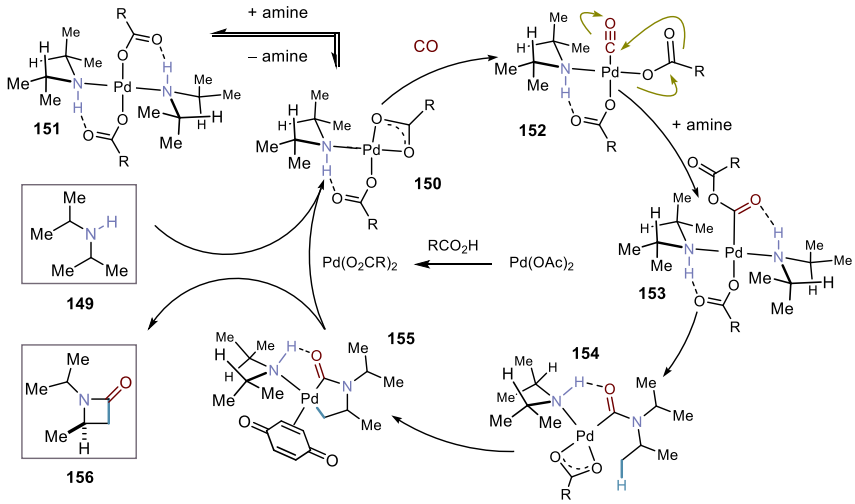
While hindered amines were found to undergo efficient Pd-catalyzed C–H carbonylation, less substituted amines (e.g. **142**) – functional molecules more commonly encountered as synthetic intermediates or in medicinal compounds – gave comparatively low yields (**143**, 23% yield; Scheme 31), mainly resulting in oxidative degradation and *N*-acetylated amine product.[78] Furthermore, the corresponding four-membered palladacycle (**144**) could not be observed. Consequently, mechanistic investigations involving reaction parameter re-optimization and computational calculation were undertaken, leading to the successful development of a general β-C–H carbonylation methodology (Scheme 32). Key modifications to the reaction conditions included use of a bulky carboxylic acid additive (1-adamantane carboxylic acid or 2,4,6-trimethylbenzoic acid), a benzoquinone (BQ), and catalytic quantities of either Li-quinoline (**146**) or quinuclidine (**147**). The new conditions enabled C–H carbonylation of a broad range of aliphatic secondary amines (**145**) to β-lactam derivatives (**148**).[78] Significantly, the mechanism is thought to proceed via a non-classical C–H activation mechanism, in which insertion of CO occurs prior to C–H bond cleavage (Scheme 33). First, entry into the catalytic cycle involves ligand exchange on $Pd(OAc)_2$ for a sterically hindered carboxylate followed by amine association to form the mono(amine)-Pd(II) complex (**150**), which is in equilibrium with the off-cycle bis(amine)-Pd(II) complex (**151**). CO binding forms (**152**), wherein attack of CO by the bound carboxylate and binding of a second amine equivalent forms Pd-anhydride complex (**153**). Subsequent attack of the amine at the internal carbonyl of (**153**), favoured by the bulky anhydride terminus derived from the acid additive, irreversibly generates carbamoyl-Pd species (**154**). A key hydrogen bonding interaction between the carbonyl of the carbamoyl moiety and a second ligated amine sets up a facile and reversible $C(sp^3)$–H activation, which takes place through a CMD pathway to form a five-membered cyclopalladation intermediate (**155**). Finally, BQ-assisted reductive elimination occurs, giving β-lactam (**156**) and a Pd(0) species. Oxidation of Pd(0) with $Cu(OAc)_2$ regenerates the active Pd(II) species, whereby Li-quinoline and quinuclidine additives are thought to stabilize the Pd(0) species before oxidation by preventing deactivating aggregation.



Scheme 31. C–H Carbonylation of Less Substituted Aliphatic Amines

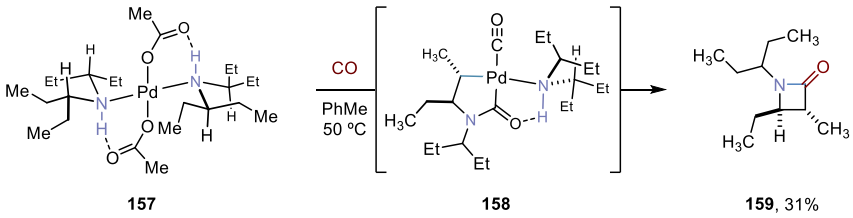


Scheme 32. General Pd-Catalyzed β-C–H Carbonylation of Aliphatic Amines

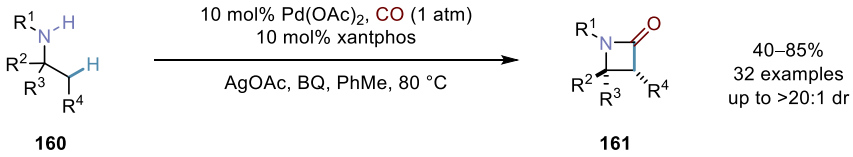


Scheme 33. Catalytic Cycle of β-C–H Carbonylation of Aliphatic Amines

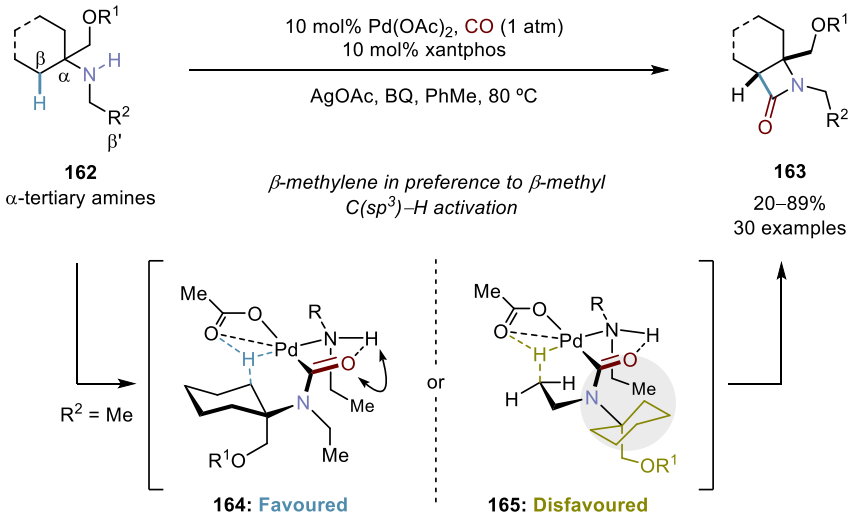
The C–H carbonylation of less substituted amines was also found to extend to β-methylene functionalization. Under stoichiometric conditions, bis-amine Pd(II) complex (**157**), derived from a secondary amine containing no β-methyl groups, was found to react with CO to form *trans*-disubstituted β-lactams (**159**, Scheme 34). In accordance with the β-methyl carbonylation, the reaction is proposed to involve the putative carbamoyl–Pd(II) complex (**158**). Following this, a Pd-catalyzed β-methylene carbonylation of secondary aliphatic amines (**160**) was realized (Scheme 35).[86] The use of bis(phosphine) ligand xantphos was found to be crucial in securing good yields for the catalytic transformation, giving rise to a diverse range of β-lactam products (**161**). Xantphos is proposed to increase turnover number by stabilizing Pd(0) at the end of the catalytic cycle. Notably, under the catalytic Pd(II)/xantphos conditions, α-tertiary amines (**162**) displaying both a β-methyl C–H bond and β-methylene C–H bond could undergo exclusive carbonylation at the traditionally less reactive and more hindered methylene position (**163**, 67%, R^2 = Me, Scheme 36).[87] This remarkable β-methylene selectivity is attributed to the hydrogen bonding interaction in the carbamoyl-Pd(II) intermediate (**164**, **165**), between the carbamoyl carbonyl and a ligated amine, which locks their relative conformation. The large α-tertiary substituent creates a steric clash upon β-methyl activation and hence β-methylene activation is favoured. A range of highly functionalized β-lactam building blocks were obtained in good yields, which could be further derivatized to access novel heterocyclic scaffolds.



Scheme 34. Carbamoyl–Pd(II) Complex Enabled β-Methylene C–H Activation

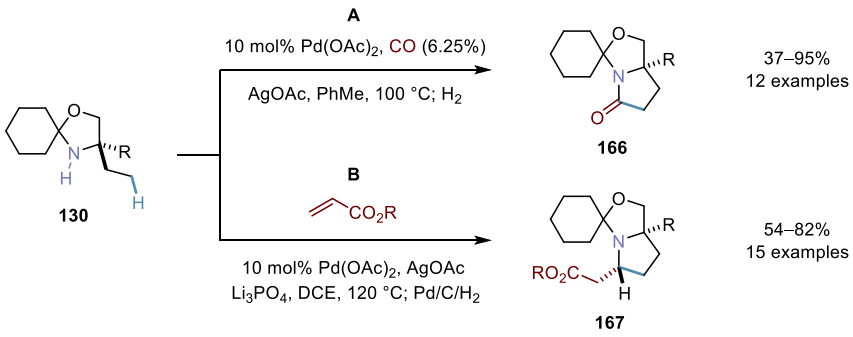


Scheme 35. Pd-Catalyzed β-Methylene C–H Carbonylation of Aliphatic Amines



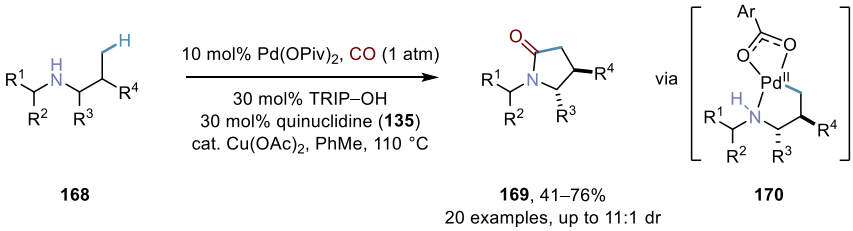
Scheme 36. Pd-Catalyzed Highly Selective Carbonylation of β-Methylene C–H bonds

Whereas less substituted amines are typically functionalized at the β-position in the presence of CO to give four-membered ring products, the sterically-driven approach using Pd(II)/Pd(0) catalysis was further explored by Gaunt to enable formation of five-membered ring products. Using the steric tethering approach with *N*,*O*-ketal substrates (**130**), in the presence of CO (6.25% CO in air) and AgOAc, Pd-catalyzed C–H carbonylation took place smoothly leading to one carbon homologation and concomitant cyclization to form γ-lactams (**166**) – a nitrogen-containing heterocyclic motif common to many natural products (Scheme 37A).[84] Additionally, treatment of the *N*,*O*-ketal substrates with acrylates generated pyrrolidine products (**167**), formed from a C–H alkenylation reaction followed by intramolecular aza-Michael addition (Scheme 37B).



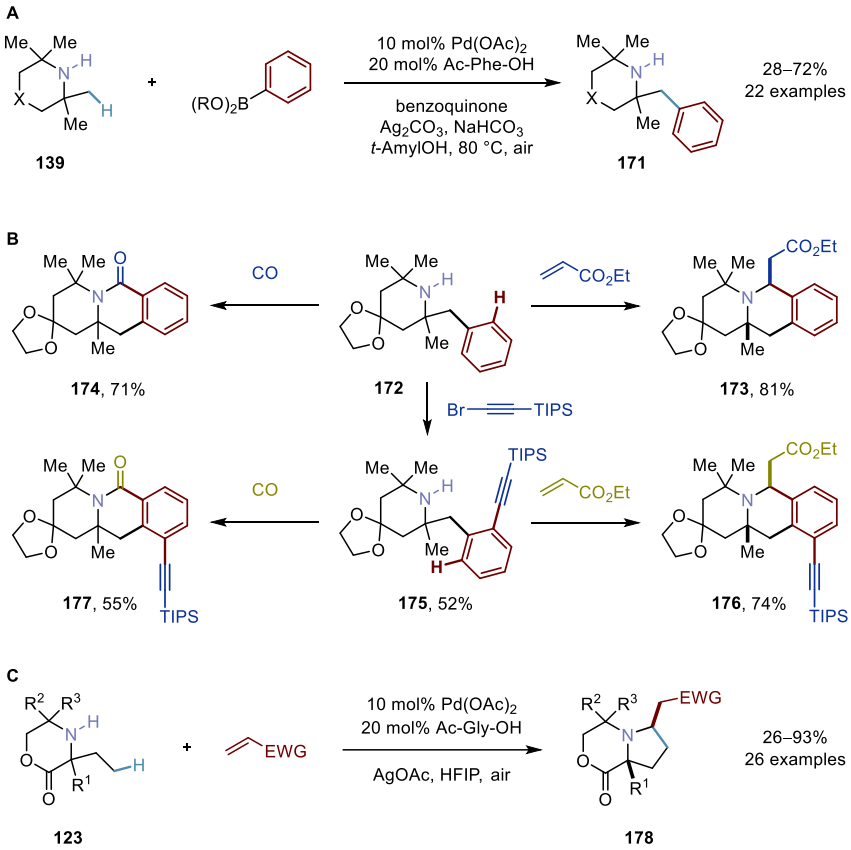
Scheme 37. Pd-Catalyzed Carbonylation and Alkenylation of Amino Alcohols using a Steric Tethering Approach

More recently, hindered acyclic secondary alkylamines (**168**) were demonstrated to undergo diastereoselective C–H carbonylation to *trans*-substituted γ-lactams (**169**, Scheme 38).[88] The reaction proceeds via the classical five-membered palladacycle (**170**), in which the branched substrates and a bulky benzoate additive (2,4,6-triisopropylbenzoic acid, TRIP–OH) were observed to favour γ-C–H activation over competing formation of the carbamoyl-Pd(II) complex and thus β-C–H activation. Notably, the ratio of β- to γ-C–H carbonylation could modulated by changing the concentration of CO and the electronics of the benzoate additive, with lower CO concentration and an electron-poor benzoate giving the highest preference for γ-C–H carbonylation.



Scheme 38. Diastereoselective γ-C–H Carbonylation to *trans*-Substituted γ-Lactams

Two further examples of C–H functionalization of hindered piperidine or morpholinone substrates using Pd(II)/Pd(0) catalysis were demonstrated, enabled by *N*-protected amino acid ligands. In the presence of an *N*-Ac-protected phenylalanine ligand, a Pd-catalyzed C–H arylation process successfully converted a range of hindered secondary amines (**139**) and arylboronic esters to highly substituted variants of the biologically relevant phenethylamine scaffold (**171**, Scheme 39A).[89] Interestingly, the arylated products provided a platform for further catalytic C(sp^2)−H functionalization, including carbonylation, alkenylation and alkynylation, to readily generate previously unexplored complex amines (**172–177**, Scheme 39B). Furthermore, an *N*-Ac-protected glycine ligand assisted a Pd-catalyzed C–H alkenylation process of morpholinone substrates (**123**), which generated a variety of functionalized pyrrolidines in good yields with perfect regio- and diastereoselectivity (**178**, Scheme 39C).[90] Mechanistic studies indicated that the amino acid ligand gives rise to a reversible C(sp^3)–H activation, as well as enabling an expanded substrate scope for the transformation.



Scheme 39. Pd-Catalyzed C(sp^3)−H Arylation and Alkenylation of Aliphatic Amines

CONCLUSION AND OUTLOOK

Over the past decade, Pd-catalyzed C–H functionalization of aliphatic amine derivatives have gradually maturated into a powerful tool for the synthesis of nitrogen-containing molecules. The use of a diverse range of amine-linked directing groups has delivered a plethora of new transformations through a variety of activation modes, which have been rapidly incorporated into synthetic routes to complex molecules. Many of the recent methods, in particular the transient and native amine directing group strategies, represent the most efficient methods for the synthesis of functionalized aliphatic amine compounds. However, there remains many challenges to improve the practicality and versatility of these remote transformations. First, selective functionalization of less substituted unprotected aliphatic amines is still difficult to achieve. Second, enantioselective C(sp^3)−H activation of aliphatic amines is still in its infancy. Third, relatively high amounts of Pd catalyst and combinations of various additives are commonly needed in the reactions. To overcome these shortcomings and provide more generally applicable synthetic methods, further mechanistic investigations and the development of new ligands and new catalytic systems will be needed.

AUTHOR CONTRIBUTIONS

C.H., W.G.W. and M.J.G. proposed the topic of the review. C.H. and W.G.W. wrote the manuscript.

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