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Transition metal catalyzed C–H bond activation by *exo*-metallacycle intermediates

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exo-Metallacycles have become the key reaction intermediates in activating various remote C(sp^2)–H and C(sp^3)–H bonds in the past decade and aided in achieving unusual site-selectivity. Various novel *exo*-chelating auxiliaries have assisted metals to reach desired remote C–H bonds of different alcohol and amine-derived substrates. As a result, a wide range of organic transformations of C–H bonds like halogenation, acetoxylation, amidation, sulfonylation, olefination, acylation, arylation, *etc.* were accessible using the *exo*-metallacycle strategy. In this review, we have summarized the developments in C–H bond activation *via* four-, five-, six-, seven- and eight-membered *exo*-metallacycles and the key reaction intermediates, including the mechanistic aspects, are discussed concisely.

1. Introduction

Transition metal-catalysed site-selective C–H bond activation has been a powerful tool for organic chemists to functionalize unactivated C(sp^2)–H and C(sp^3)–H bonds.[1–10] These reactions facilitate making unusual C–X bonds and provided an attractive approach for the construction of C–C bonds.[11–13] However, the presence of multiple chemically indistinguishable C–H bonds in an organic molecule makes it quite challenging to selectively activate the C–H bond of interest. The most successful strategy to achieve these transformations by overcoming this obstacle is the utilization of directing groups (DGs).[14–25] These chelating auxiliaries have been a reliable approach for the precise cleavage of the desired distal C–H bond even in the presence of other electronically and sterically biased C–H bonds and subsequent functionalization. The majority of these organic transformations occur *via* metallacycle intermediate formation and were considered as transient reactive intermediates in different metal-mediated transformations. However, only a few metallacyclic complexes were known in the literature with their potential for the catalytic

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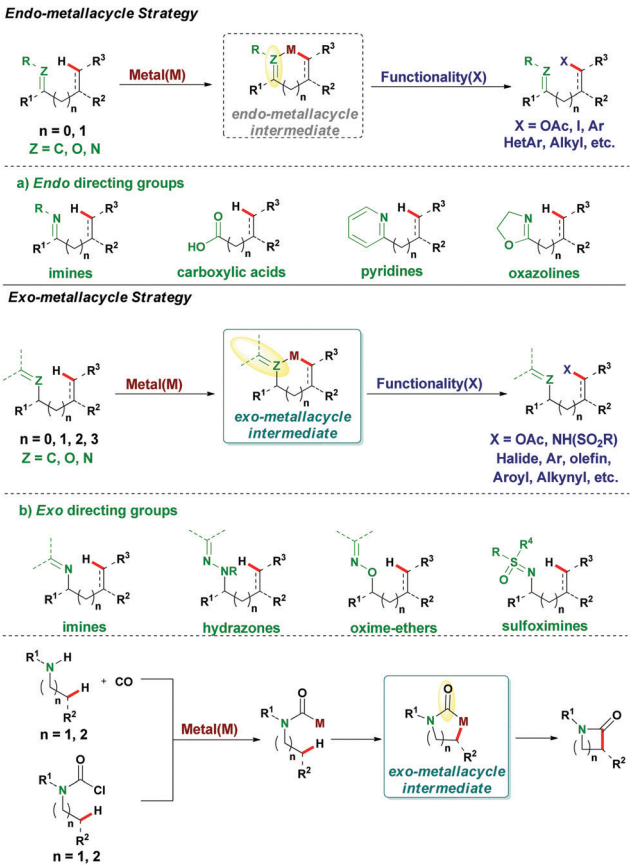
activation of the C–H bond being unexplored for a long time.[26] Nonetheless, the last decade witnessed an exponential increase in the development of metallacycle intermediates for various atom-economic transformations. Studying these metallacycle intermediates gives us a better understanding of the mechanistic aspects of C–H bond functionalization and a better control over the site-selective nature of C–H bond functionalization.

Metallacycles are mostly divided into two categories, namely, *endo* and *exo*, depending on the position of the π-bond (*endo*-π-bond inside the metallacycle and *exo*-π-bond outside the metallacycle) (Scheme 1). *endo*-Metallacycles are generated mostly by *endo*-DG (ketone-derived imines, carboxylic acids, pyridines and oxazolines) assisted cyclometallation, whereas *exo*-metallacycles are mostly formed *via* the activation of C–H bonds by *exo*-DGs (imines, hydrazones, oxime ethers and sulfoximines). Additionally, they are also formed either by the carbonylation of free amines or by the oxidative addition of acyl chlorides, followed by cyclometallation. *endo*-Metallacycles are thermodynamically more stable compared to their *exo*-counterparts due to the planarity.[27,28] Moreover, for a given ring size, the *endo* structure has one less rotatable bond than the corresponding *exo*-counterpart, increasing the conformational degrees of freedom and energy of the *exo*-counterpart. In some cases, *exo* is the kinetic product



Scheme 1 Overview of *exo*- and *endo*-metallacycles.

Shaeel A. Al-Thabaiti

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Mohamed Mokhtar

Prof. Dr Mohamed Mokhtar received his PhD in 1997 from Cairo University, Cairo, Egypt. He was a senior research fellow from DAAD at the Institute of Chemical Engineering and Processing, Karlsruhe University, Germany, in 1998–1999. He was invited as a research fellow to the Surface Chemistry and Catalysis Department, Ulm University, Ulm, Germany, in 2003 and to Chemical Reaction Technology, Erlangen-Nuremberg University (FAU), Germany, in 2007. He is currently a professor of physical chemistry at the Chemistry Department, KAU. Alternative catalytic techniques for organic synthesis are a prominent area of research for him.

Debabrata Maiti

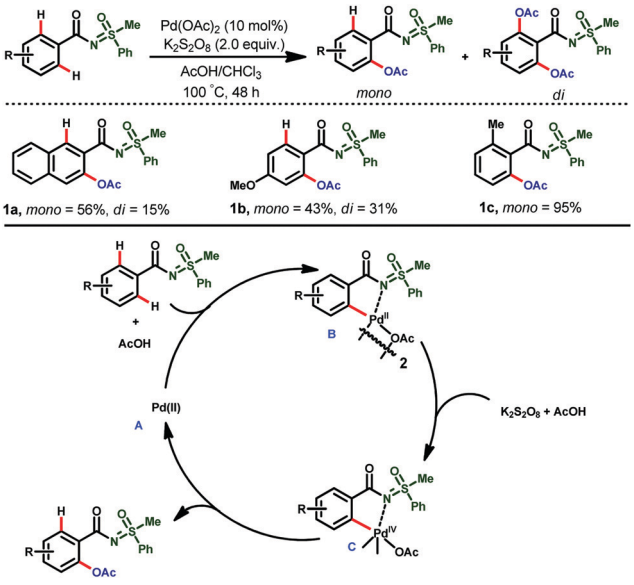
Prof. Debabrata Maiti received his PhD from John Hopkins University (USA) in 2008 under the supervision of Prof. Kenneth D. Karlin. After postdoctoral studies at the Massachusetts Institute of Technology (MIT) with Prof. Stephen L. Buchwald (2008–2010), he joined the Department of Chemistry at IIT Bombay in 2011, where he is currently a full professor. His research interests are focused on the development of new and sustainable synthetic and catalytic methods.

and isomerizes to the thermodynamically more stable *endo* product.[29] These above-mentioned facts ascribe to the extensive study on *endo*-metallacycles over the past few years,[30–35] whereas the *exo*-counterpart had minimal reports.[36–44] While the *endo*-metallacycle has adequate site-selectivity controls, it suffers from many drawbacks such as the need for a functional group with pre-existing π-bonds already being present in the starting material, for instance, aldehyde, ketone, carboxylic acid, pyridine, *etc.* (pre-functionalized substrates). This limits the substrate scope of the *endo*-approach. Thus, *exo*-counterparts have received significant attention in the past decade in order to address the functional group flexibility. The two pioneering stoichiometric reactions by Sames and co-workers in 2000 and 2002 laid the foundation for C–H bond activation *via exo*-metallacycle intermediates accessing natural products and drug molecules. Both reports are extensively discussed in their respective sections. By judicious choice of π-bond containing DGs, superior and unconventional site-selectivity can be achieved by the *exo*-metallacycle approach with a broad substrate scope. This is evident from the diverse organic transformation of C–H bonds such as fluorination, amidation, olefination, alkynation, acylation, acetoxylation, iodination, heteroarylation, *etc.*, reported using the *exo*-metallacyclic strategy in the last decade. However, the isomerization of *exo*-complexes into thermodynamically favoured *endo*-complexes under suitable conditions limits the formation of *exo*-metallacycles. A quick solution would be to either block the *endo*-reaction sites or by having more chelating centres favouring the *exo*-complex. Pioneered by Dong and Yu, several exotic *exo*-metallacycle species have evolved over the previous decade to activate inert C–H bonds of alkanes and alkenes. This review aims to discuss in detail all such reports of C(sp^2)–H and C(sp^3)–H bond activation where *exo*-metallacycles played a key role, which can be applied routinely in various pharmaceutical and agrochemical industries. This review is broadly divided into three parts: (i) C(sp^2)–H bond activation *via* five- and six-membered *exo*-metallacycles, (ii) C(sp^3)–H bond activation *via* five- and six-membered *exo*-metallacycles, and (iii) C(sp^2)–H and C(sp^3)–H bond activation *via* other than five- and six-membered *exo*-metallacycles. We have also included the methodologies where C(sp^2)–H and C(sp^3)–H bond activation take place *via exo*-metallacycles accessing multiple ring sizes and the only example of C(sp)–H activation *via exo*-metallacycle intermediates.

2. C(sp^2)–H bond activation *via* the *exo*-metallacycle strategy

2.1. Five-membered metallacycle

In 2012, Sahoo and co-workers reported a palladium-catalyzed *ortho*-C(sp^2)–H acetoxylation of arenes using a sulfoximine-based DG (Scheme 2).[45] Various *N*-benzoylated methyl phenyl sulfoximines underwent acetoxylation in the presence of $K_2S_2O_8$ as the oxidizing agent to afford both mono- and di-acetoxylated products. It is interesting to note that only the *ortho*-C–H bond of the *N*-benzoylated ring was acetoxylated without affecting the *ortho*-C–H bond of the phenyl ring of the DG. The synthetic

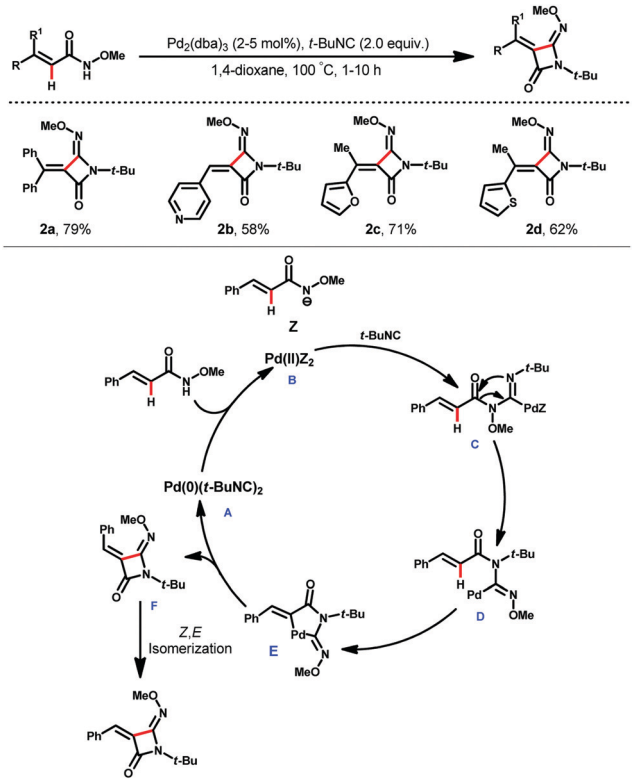


Scheme 2 Palladium-catalyzed *ortho*-C(sp^2)–H acetoxylation of arenes.

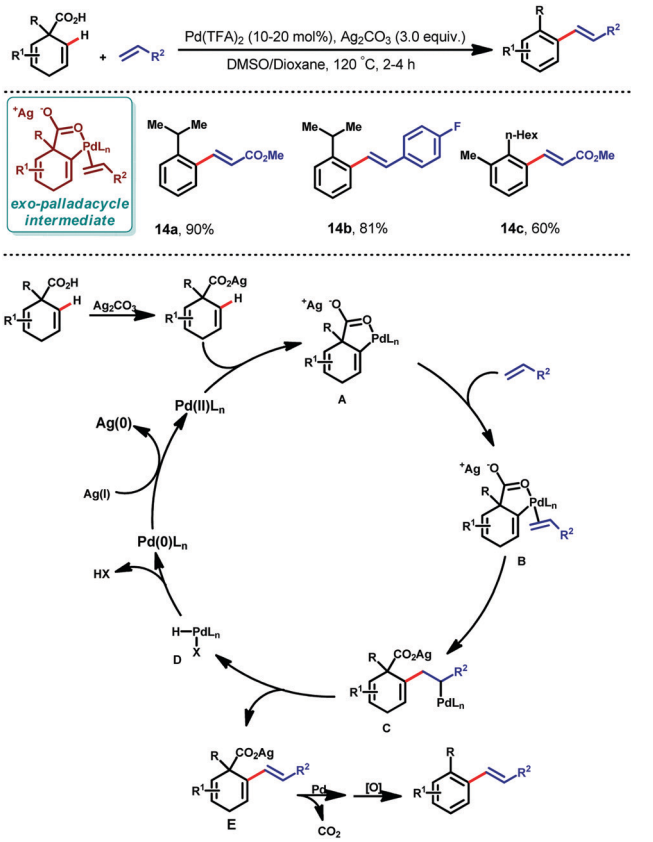
utility of the protocol lies in the effortless removal and the recovery of the DG *via* hydrolysis, which can later be reused. The authors were able to demonstrate the validity of the findings by proposing a suitable catalytic cycle (Scheme 2). The reaction commences with the binding of palladium to the nitrogen of sulfoximine followed by *ortho*-palladation, thereby resulting in the formation of a five-membered *exo*-palladacycle intermediate **B**. This intermediate undergoes oxidation with $K_2S_2O_8$ to form intermediate **C**. Subsequent reductive elimination of intermediate **C** leads to the formation of the desired product and regenerates the catalyst for the next catalytic cycle.

In 2016, palladium-catalyzed C(sp^2)–H bond activation of α,β-unsaturated olefins leading to the formation of 4-imino-β-lactam derivatives was reported by Yu and co-workers (Scheme 3).[46] Interestingly, air was used as the only oxidant and this methodology shows excellent compatibility with a wide range of heterocycles including thiophene, furan and pyridine at the β-position of the alkene, which is very important from the perspective of medicinal chemistry. A mechanistic blueprint was proposed by the authors where the reaction begins with the conversion of Pd(0) to PdZ_2 in the presence of air (Scheme 3). Subsequently, the PdZ_2 undergoes a 1,1-insertion of *t*-BuNC into the Pd–N bond followed by the acyl migration to afford intermediate **D**, which undergoes an alkene C–H bond activation to generate a five-membered *exo*-palladacycle intermediate **E**. Finally, the reductive elimination leads to product formation and regenerates the active catalyst for the next cycle.

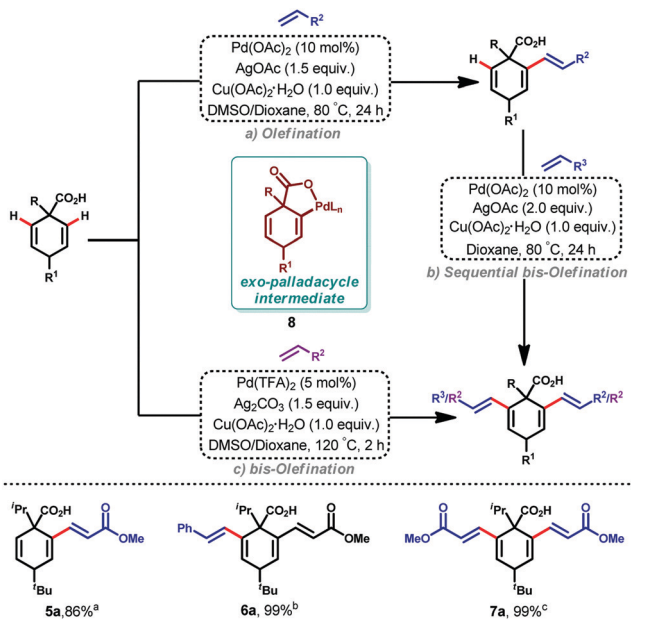
A palladium-catalyzed decarboxylative C(sp^2)–H bond olefination of cyclohexa-2,5-dienyl-1-carboxylic acids using a carboxylic acid group as the DG was reported by Chou and co-workers in 2017 (Scheme 4).[47] These substrates were prepared by the dearomatization of benzoic acids by Birch reductive alkylation. Various vinyl derivatives, including acrylates and styrenes, were installed by the decarboxylative olefination of different cyclohexa-2,5-dienyl-1-carboxylic acid substrates. Control experiments suggested that the Pd/Ag bimetallic system is essential for the cooperative



Scheme 3 Palladium-catalyzed C(sp^2)–H bond activation of α,β-unsaturated olefins.



Scheme 4 Palladium-catalyzed decarboxylative C(sp^2)–H bond olefination of cyclohexa-2,5-dienyl-1-carboxylic acids.



Scheme 5 Palladium-catalyzed proaromatic C(sp^2)–H olefination of 1,4-cyclohexadiene.

decarboxylation of the olefinated product. The authors proposed a mechanistic cycle which begins with the attack of the Ag-substrate complex to the palladium catalyst, leading to the formation of a five-membered *exo*-palladacycle intermediate **A** generated by the carboxylate group-assisted C–H activation. Subsequently, the olefin co-ordinates to the intermediate **A** and undergoes 1,2-migratory insertion, followed by β-hydride elimination to form intermediates **D** and **E**. Further reductive elimination of **D**, followed by reoxidation with Ag(I), regenerates the active Pd(II) catalyst. On the other hand, a subsequent decarboxylation of intermediate **E** in the presence of the palladium catalyst followed by re-aromatization produces the desired product.

Similar to their own report, Chou's group developed a palladium-catalyzed pro-aromatic C(sp^2)–H olefination of 1,4-cyclohexadiene using a carboxylic acid as the DG (Scheme 5).[48] Various pro-aromatic acids were readily mono-olefinated using different alkenes, including styrene, acrylate, vinyl phosphonate, vinyl sulfone, *etc.* The authors also reported a one-pot bis-olefination of various pro-aromatic acids by slightly modifying the initial reaction conditions (using Ag_2CO_3 in place of AgOAc and elevating the temperature to 120 °C). Subsequently, they investigated the sequential bis-olefination of sterically-hindered mono-olefination products. Both symmetrical and unsymmetrical bis-olefinated proaromatic acids were obtained from mono-olefinated styrenes in excellent yields. A plausible mechanistic cycle was proposed by the authors (Fig. 1). The reaction begins with the coordination of palladium with the substrate followed by the crucial C–H activation step leading to the formation of a five-membered *exo*-palladacycle intermediate **C**. Then, the alkene coordinates with the metal-center and undergoes a 1,2-migratory insertion to form intermediate **E**. A subsequent β-H elimination

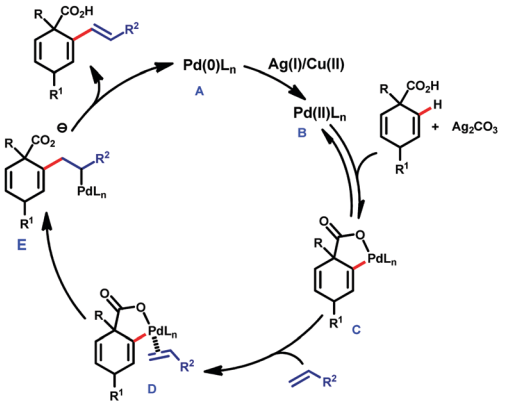


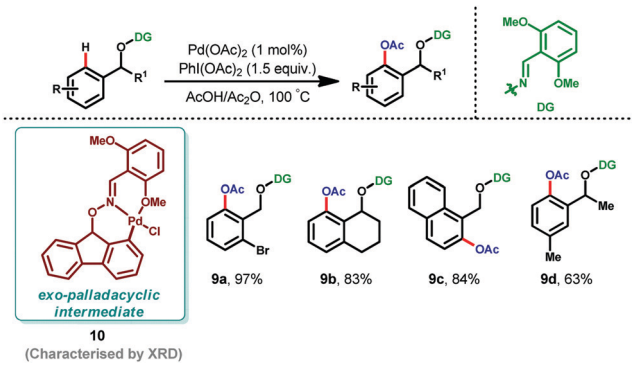
Fig. 1 Mechanism for proaromatic C(sp^2)–H olefination.

generates the product and forms Pd(0) species, which further gets oxidized by Ag(I)/Cu(II) to regenerate the active catalyst.

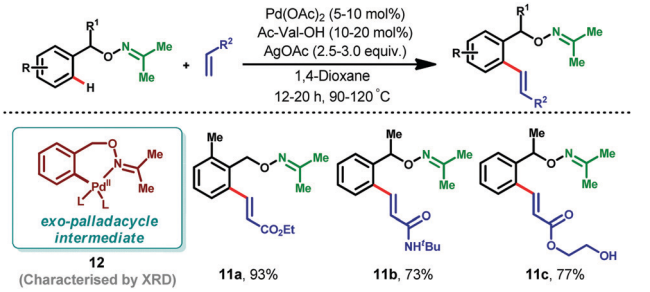
2.2. Six-membered metallacycle

In 2015, Dong and co-workers reported a palladium-catalyzed *ortho*-C(sp^2)–H acetoxylation of benzyl alcohols using a 2,6-dimethoxyl benzaldoxime based DG (Scheme 6).[49] A wide range of 2-hydroxyalkylphenol derivatives was obtained in good yields from different primary and secondary alcohols with a high catalyst TON > 1000. The reaction proceeds through the formation of a six-membered mononuclear pseudo square planar *exo*-palladacycle intermediate **10**. The authors were able to isolate the intermediate **10** by HCl workup after the reaction. X-ray crystallographic studies further characterized the intermediate **10**. The high catalyst TON was attributed to the presence of a methoxy group in the DG, which plays a crucial role in assisting the chelation process. The DG can be removed by treating with zinc and acetic acid.

Zhao's group in 2015 reported a palladium-catalyzed *ortho*-C(sp^2)–H olefination of benzyl alcohols using an acetone-oxime-ether-based DG (Scheme 7).[50] Various masked benzyl alcohols were readily olefinated at the *ortho* position with moderate to good yields. This methodology is compatible with a wide range of functional groups, including NO_2, CF_3, MeS, CO_2Me, F, Cl, OMe, and *tert*-butyl. A six-membered *exo*-palladacycle intermediate **12** was found to be the key intermediate for the



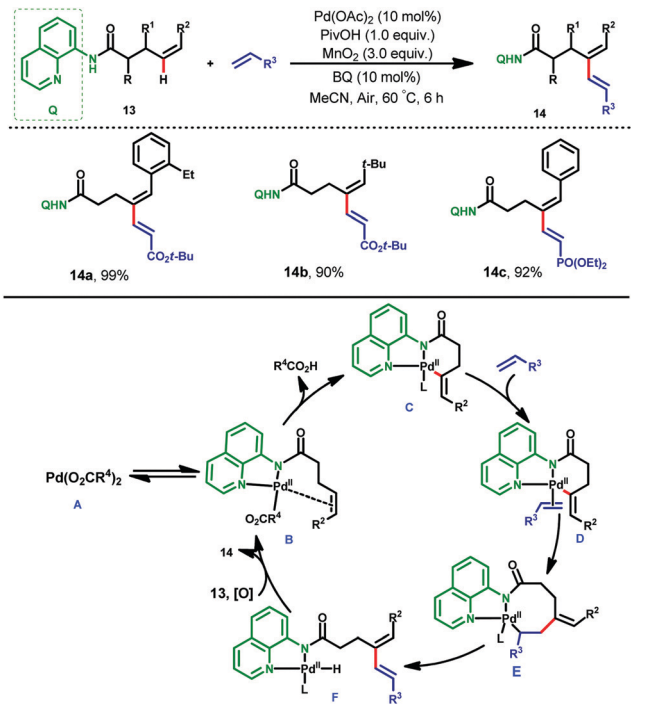
Scheme 6 Palladium-catalyzed *ortho*-C(sp^2)–H acetoxylation of benzyl alcohols.



Scheme 7 Palladium-catalyzed *ortho*-C(sp^2)–H olefination of benzyl alcohols.

above transformation. The authors were able to synthesize the intermediate **12** and obtained an orange-red color crystal characterized by X-ray crystallographic studies. The crystal structure clearly depicts the acetone-oxime-ether-based *exo*-DG directed C–H transformation. The DG can be removed by treating with molybdenum hexacarbonyl.

In 2018, Engle and co-workers developed a palladium-catalyzed C(sp^2)–H activation of alkenes using an 8-aminoquinoline based DG and a combination of benzoquinone and MnO_2 as the oxidant (Scheme 8).[51] A wide range of substituted 1,3-dienes was prepared by coupling the DG containing alkene with electron-deficient alkenes. The substrate scope spans three different classes of alkenes (allyl alcohols, 4-pentenoic acids, and bishomoallylic amines), and explicit site-selectivity was obtained in substrates containing internal non-conjugated alkenes. Nickel-mediated methanolysis conditions can remove the DG. The authors proposed a catalytic cycle (Scheme 8) supported by DFT calculations. The reaction begins with the substrate's coordination with palladium, giving rise to an

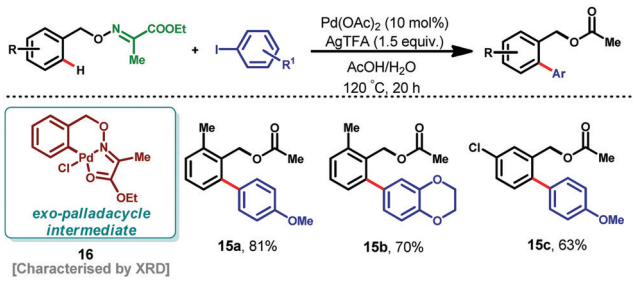


Scheme 8 Palladium-catalyzed C(sp^2)–H activation of alkenes.

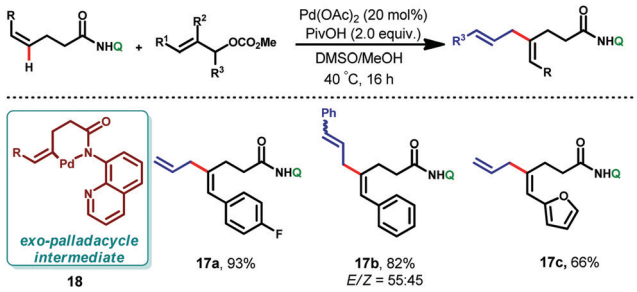
alkene–palladium complex intermediate **B**. The authors prepared an analogue of intermediate **B** by treating 2-NapCO$_2$H instead of PivOH and Pd(OAc)$_2$ with the alkene substrate and characterized it by X-ray crystallographic studies. Subsequent activation of the C(sp^2)–H bond of the alkene leads to the formation of a six-membered *exo*-palladacycle intermediate **C**. Then, the electron-deficient alkene coordinates with palladium and undergoes 2,1-migratory insertion to form intermediate **E**. The intermediate **E** undergoes β-H elimination followed by reoxidation to give the product and regenerate the active catalyst.

Ji and co-workers in 2018 reported a palladium-catalyzed *ortho*-C(sp^2)–H arylation of aryl methyl alcohols using a pyruvic-ketoxime-ester-based DG (Scheme 9).[52] A wide range of biaryl-2-methyl acetates were obtained in moderate to good yields by coupling various aryl methyl alcohols with different aryl iodides followed by the benzylic C–O bond solvolysis in the same pot. This methodology was also compatible with various other functional groups like halogens, pyridyl, CF_3, aryl methyl acetate, 1,4-dioxane, ether and methoxy. Kinetic isotope exchange experiments revealed that the C(sp^2)–H bond cleavage/carbopalladation might be the rate-determining step for the above transformation. Control experiments showed that metal salt is necessary for the C–O bond solvolysis, which implies that the palladium catalyst plays dual role, activates the *ortho*-C(sp^2)–H bond and assists the solvolysis of the benzylic C–O bond. The reaction proceeds through the formation of a six-membered *exo*-palladacycle intermediate **16**. The authors successfully crystalized palladacycle **16** and characterized it by X-ray diffraction, which proved the DG assisted C(sp^2)–H bond activation *via exo*-carbopalladation.

A palladium-catalyzed C(sp^2)–H allylation of alkenes using allyl carbonates and an 8-aminoquinoline based DG was reported by Zhong's group in 2019 (Scheme 10).[53] Various unactivated alkenes were effectively allylated under oxidant free conditions, and branched 1,4-dienes were obtained in good yield. This methodology well-tolerated different functional groups such as furan, halogens, CF_3, thiophene, methoxy and naphthalene. The reaction occurs *via* the formation of a six-membered *exo*-palladacycle intermediate **18** generated by the *N*,*N*-bidentate chelation directed C(sp^2)–H bond activation. Kinetic isotope experiments suggested that the C(sp^2)–H bond cleavage is the rate-determining step for the above transformation. The DG can be removed and recovered easily by a nickel-catalyzed methanolysis adding to the synthetic utility of the scheme.

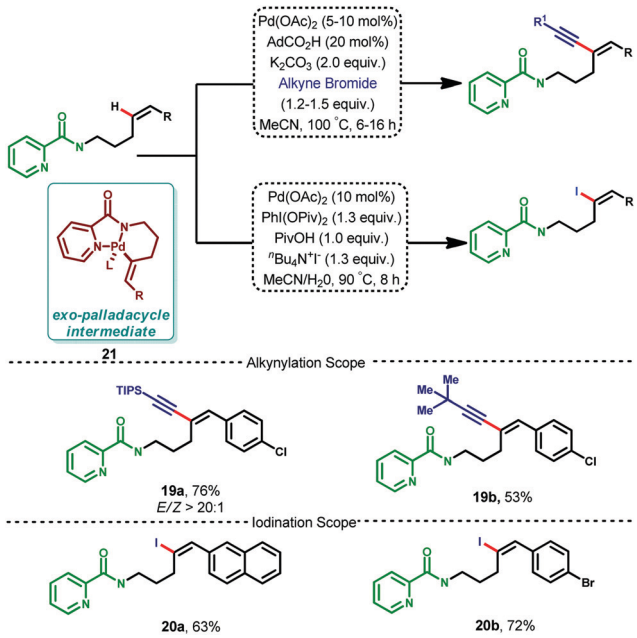


Scheme 9 Palladium-catalyzed *ortho*-C(sp^2)–H arylation of aryl methyl alcohols.

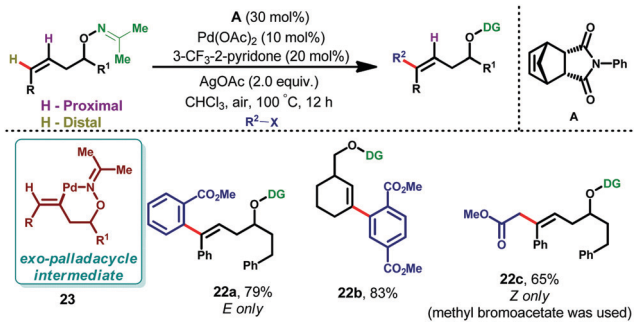


Scheme 10 Palladium-catalyzed C(sp^2)–H allylation of alkenes.

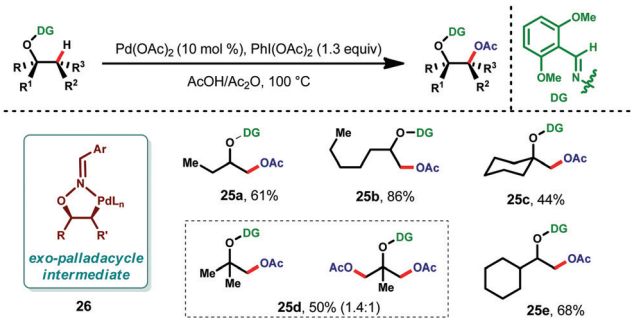
In 2019, Carreira and co-workers reported a palladium-catalyzed C(sp^2)–H iodination of alkenes using a picolinamide based DG (Scheme 11).[54] A combination of di(pivaloyloxy)-iodobenzene and tetrabutylammonium iodide was used as an oxidative iodinating agent and various acyclic and cyclic alkenes were readily iodinated in moderate yields. The methodology is highly regioselective as in the case of substrates containing multiple alkene motifs, mono-iodinated products were obtained selectively. The authors proposed that a six-membered *exo*-palladacycle **21** is the key intermediate for the above transformation, which is formed *via* the *N*,*N*-bidentate chelation assisted C(sp^2)–H bond activation. Furthermore, the reaction of the intermediate **21** with any electrophilic iodine source (NFSI) led to the formation of a mono-iodinated product. The same group in 2020 reported a palladium-catalyzed C(sp^2)–H alkynylation of olefins using the same picolinamide-based DG (Scheme 11).[55] A wide range of substituted 1,3-enynes were obtained in good yields from the alkynylation of various unactivated alkenes using different bromoalkynes. In this case as well, the reaction occurs *via* the formation of the six-membered *exo*-palladacycle intermediate **21**. Subsequently, the



Scheme 11 Palladium-catalyzed C(sp^2)–H iodination and alkynylation of alkenes.



Scheme 12 Palladium-catalyzed distal C(sp^2)–H arylation of olefins.



Scheme 14 Palladium-catalyzed β-C(sp^3)–H acetoxylation of alcohols.

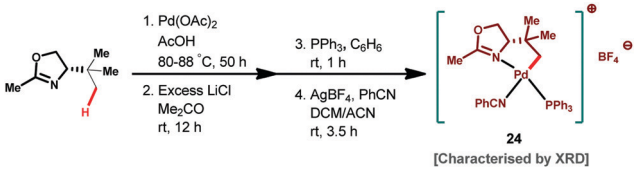
bromoacetylene undergoes carbopalladation with intermediate **21**, followed by retro-bromopalladation, leading to the formation of the desired enyne product. The DG can be easily removed by treating with zinc and HCl.

Dong's group in 2020 reported a palladium-catalyzed distal C(sp^2)–H arylation of olefins using an oxime-ether based DG and norbornene (NBE) based co-catalyst (Scheme 12).[56] Various cyclic and acyclic *cis*-olefins were readily arylated at the distal alkenyl C–H position with good yield and excellent regio-selectivity using different alkyl and aryl halides. This methodology well-tolerated various functional groups like ester, nitro, ketone, amide, halides, pyridine and thiophene. The DG can be removed by the addition of zinc and acetic acid. The reaction proceeds through a six-membered *exo*-palladacycle intermediate **23** formed *via* DG-assisted proximal C(sp^2)–H palladation. Subsequent NBE insertion and distal C(sp^2)–H palladation, followed by the reaction with aryl halide, led to the formation of the desired product. Deuterium labelling experiments in the absence of aryl halide led to the incorporation of deuterium in both the proximal and distal C–H positions which supports the reversible nature of cyclopalladation.

3. C(sp^3)–H bond activation *via* the *exo*-metallacycle strategy

3.1. Five-membered metallacycle

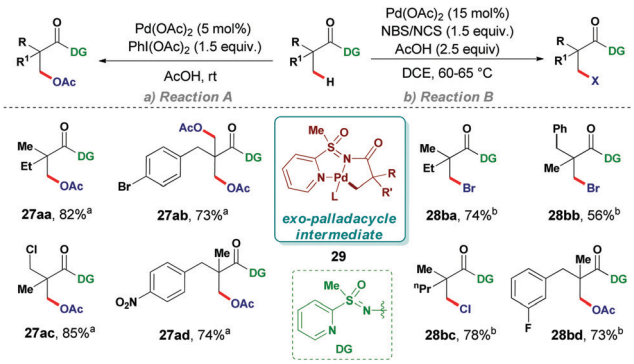
In 2005, Smoliakova and co-workers reported the cyclopalladation of (*S*)-4-*tert*-butyl-2-methyl-2-oxazoline, resulting in the formation of a five-membered *exo*-palladacycle **24** formed by the activation of the C(sp^3)–H bond of the *tert*-butyl group (Scheme 13).[57] X-ray crystallographic studies characterized the resulting *exo*-palladacycle complex, and it revealed an uncommon π–π interaction between the triphenylphosphine ligands and the phenyl rings of benzonitrile.



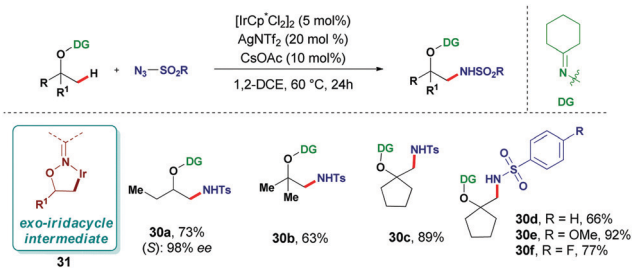
Scheme 13 Cyclopalladation of (*S*)-4-*tert*-butyl-2-methyl-2-oxazoline.

In 2012, a palladium-catalyzed β-C(sp^3)–H acetoxylation of alcohols using an oxime-based DG was reported by Dong and co-workers (Scheme 14).[58] The authors utilized 2,6-dimethoxybenzyl oxime as an *exo*-DG to activate the aliphatic C(sp^3)–H bond of masked alcohols, leading to the formation of a chemically differentiated 1,2-diol motif. A wide range of substrates including primary, secondary and tertiary alcohols were readily converted into their corresponding 1,2-diol motif in good yields, and functionalities like ether, oxime, ester, and aryl groups were tolerated. The reaction proceeds *via* a five-membered *exo*-palladacycle intermediate **26** formed by the cyclopalladation of the β-C–H bond. Further oxidation of this *exo*-palladacycle intermediate **26** by PhI(OAc)$_2$ in the presence of HOAc resulted in the formation of the corresponding 1,2-diol motif. Kinetic isotope experiments showed that the C–H bond cleavage was the rate-determining step. The *exo*-DG can be removed easily by using zinc and acetic acid.

A palladium-catalyzed β-C(sp^3)–H acetoxylation of sulfoximine-*N*-amides using an *S*-methyl-*S*-2-pyridyl-sulfoximine based DG was reported by Sahoo and co-workers in 2012 (Scheme 15a).[59] Various sulfoximine-*N*-amides were acetoxylated with moderate yields. In 2014, the same group reported a palladium-catalyzed β-C(sp^3)–H bromination and chlorination of sulfoximine-*N*-amides using the same DG (Scheme 15b).[60] A wide range of sulfoximine-*N*-amides were brominated and chlorinated using *N*-bromophthalimide (NBP) and *N*-chlorophthalimide (NCP), respectively, as the halogenating agent. The halogenation was compatible with functional groups like CF$_3$, halogens, and NO$_2$. They also carried out the sequential double C–H bond activation of β-C(sp^3)–H bonds.



Scheme 15 Palladium catalyzed β-C(sp^3)–H acetoxylation and halogenation of sulfoximine-*N*-amides.

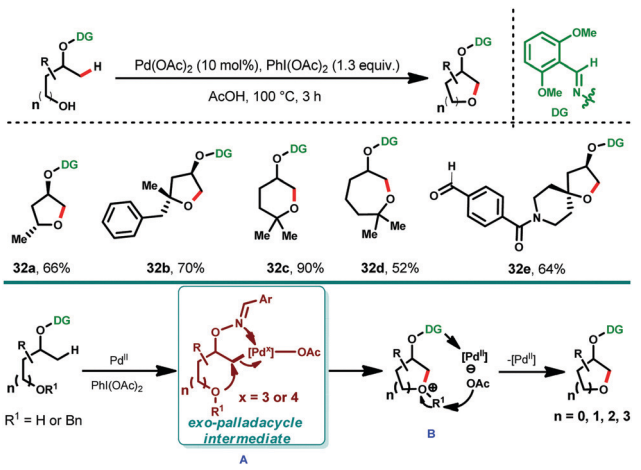


Scheme 16 Iridium-catalyzed intermolecular β-C(sp^3)–H amidation of alcohols.

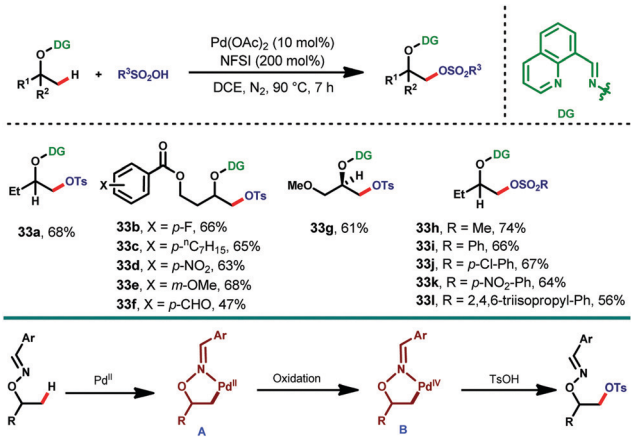
Both acetoxylation and halogenation proceed through a five-membered *exo*-palladacycle intermediate **29** formed by the chelation of sulfoximine *N*-atom and pyridine to the palladium catalyst, followed by the activation of the β-C(sp^3)–H bond of the substrate. It is interesting to note that the DG can be recovered by acid hydrolysis and can be recycled.

In 2014, Chang's group developed an Ir-catalyzed intermolecular β-C(sp^3)–H amidation of alcohols using a cyclohexyl ketoxime-based DG (Scheme 16).[61] Various primary, secondary, tertiary, cyclic, and acyclic alcohols were easily amidated using different sulfonyl azides as the amine source. $[IrCp^*Cl_2]_2$ and $AgNTf_2$ react *in situ* to generate an active catalyst Cp*Ir(III). A five-membered *exo*-iridacycle **31** formed by the chelation-assisted C–H metalation was found to be the key intermediate for the above transformation. The DG can be removed by using lithium aluminum hydride, which leads to the formation of 1,2-amino alcohols.

Dong and co-workers, in 2015, reported a palladium-catalyzed intramolecular dehydrogenative annulation at the β-C(sp^3)–H bond of diols using an oxime-based DG (Scheme 17).[62] Substrates containing primary, secondary, and tertiary hydroxyl groups readily cyclized to give the corresponding aliphatic cyclic ethers with 4–7 membered rings and tolerating functional groups like aryl aldehyde, ester, amide, carbonate, and urea. The authors proposed a mechanistic cycle, which is shown in Scheme 17. The reaction begins with the oxime-directed β-C(sp^3)–H bond



Scheme 17 Palladium-catalyzed intramolecular dehydrogenative annulation.

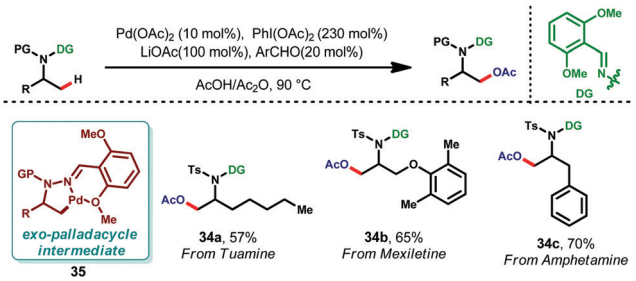


Scheme 18 Palladium-catalyzed β-C(sp^3)–H sulfonyloxylation of alcohols.

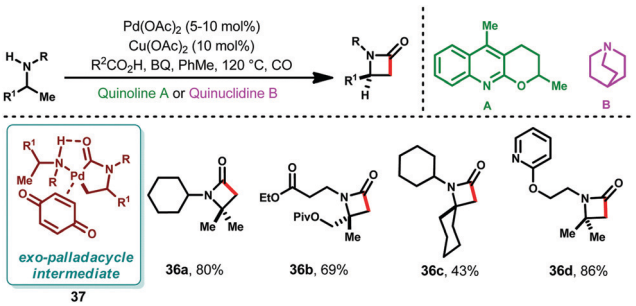
palladation to form a five-membered *exo*-palladacycle intermediate followed by the oxidation of the palladium by $PhI(OAc)_2$ to generate hypervalent species **A**. Subsequently, the intramolecular S_N2 reaction occurs to yield an oxonium intermediate **B** and reduce the palladium to Pd(II). Finally, an acetate ion undergoes deprotonation or de-benzylation to form the cyclic ether product. The DG can be easily removed by treating with zinc and acetic acid.

A palladium-catalyzed β-C(sp^3)–H sulfonyloxylation of alcohols was reported in 2015 by the same group, using an 8-quinolinecarboxaldehyde-oxime DG and *N*-fluorobenzenesulfonimide (NFSI) as the oxidant (Scheme 18).[63] A wide range of primary, secondary and tertiary alcohols, alcohols with an aromatic and hetero-aromatic group, and cyclic alcohols were readily sulfonyloxylated using various aromatic and aliphatic sulfonic acids. This methodology was compatible with various functional groups like aryl aldehyde, aryl halide, cyclopropane, nitroarene, amine, ester, and nitrile. A proposed catalytic cycle for the above transformation is shown in Scheme 18. The reaction starts with the cyclopalladation of the C(sp^3)–H bond leading to the formation of a five-membered *exo*-palladacycle intermediate **A**. Further oxidation of this palladacycle by NFSI leads to the formation of a Pd(IV) intermediate **B**, which upon reductive elimination gives the product and regenerates the active catalyst. The DG can be removed by using zinc and acetic acid or by hydrogenation using Pd/C.

In 2016, the same group reported a palladium catalyzed β-C(sp^3)–H oxidation of sulfonyl-protected primary amines using a hydrazone-based DG (Scheme 19).[64] Various primary amines with different functionalities and different protecting groups were efficiently acetoxylated using a 2,6-bismethoxyphenyl-hydrazone-based DG. Some of the amine substrates were directly derived from various approved drugs like tuamine (**34a**), mexiletine (**34b**), and amphetamine (**34c**). It is also interesting to note that in the case of an amphetamine substrate (**34c**), the β-C(sp^3)–H bond was preferentially acetoxylated without affecting the more reactive *ortho*-aryl C–H bonds. The authors proposed that the five-membered *exo*-palladacycle **35** was the key intermediate for the acetoxylation. The OMe group of the DG directs the metal to activate the β-C(sp^3)–H bond of the primary amine, leading to an *exo*-palladacycle intermediate **35**. The 2,6-bismethoxyphenyl



Scheme 19 Palladium catalyzed β-C(sp^3)–H oxidation of Ts-protected primary amines.

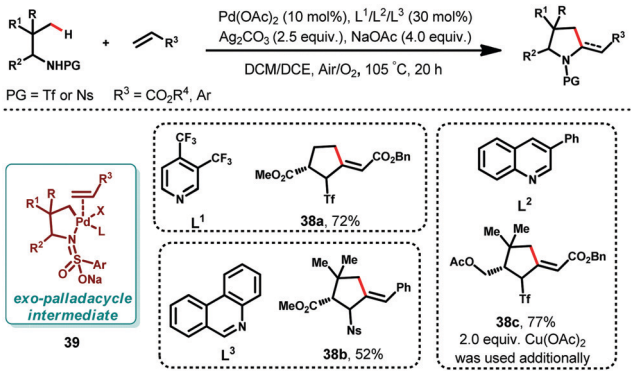


Scheme 20 Palladium-catalyzed β-C(sp^3)–H carbonylation of aliphatic amines.

DG also prevents the *endo*-metalation and stabilizes the metallacycle **35**. The DGs can be removed using zinc and acetic acid.

In 2016, Gaunt and co-workers reported a palladium-catalyzed β-C(sp^3)–H carbonylation of aliphatic amines using carbon monoxide and a sterically hindered carboxylate ligand like adamantanoic acid ($AdCO_2H$) (Scheme 20).[65] A wide range of aliphatic secondary amines underwent carbonylation in good yields to form β-lactams with tolerance of different functional groups like alkenes, sulfones, heterocycles, and esters. The sterically hindered carboxylate ligand adamantanoic acid was necessary to overcome the incompatible nature of the Pd(II) catalyst and aliphatic amines with the free NH bond. Kinetic isotope studies (KIE = 1.14) showed that the C–H bond cleavage is not the rate-determining step. Deuterium scrambling experiments resulted in incorporating deuterium in the lactam product at the carbon close to the carbonyl of the lactam and no hydrogen–deuterium scrambling in the recovered starting material, which shows the reversible nature of C–H activation that occurs after an irreversible step. The authors proposed that the reaction occurs *via* a five-membered *exo*-palladacycle intermediate **37** formed by the activation of the β-C–H bond of the amine with the carbamoyl palladium motif.

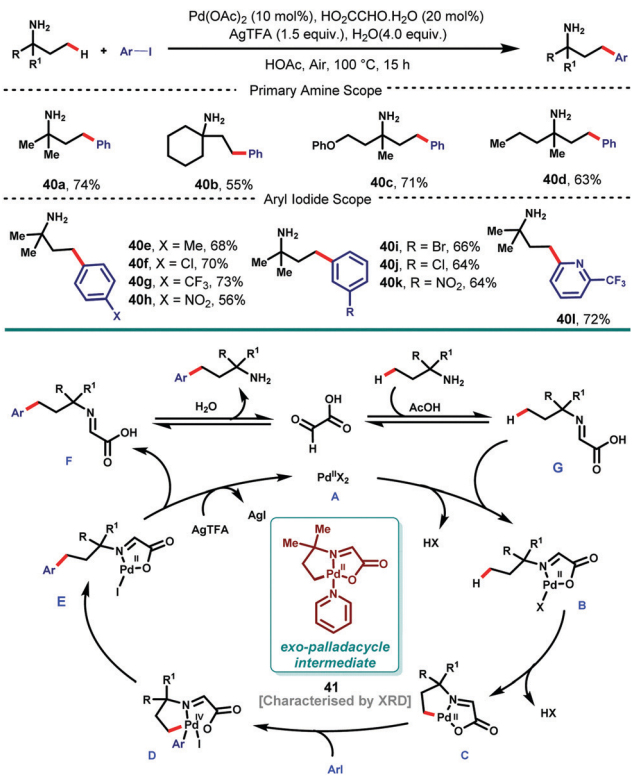
Yu's group in 2016 developed a palladium-catalyzed γ-C(sp^3)–H olefination of amines using triflyl (Tf) and 4-nitrobenzenesulfonyl (Ns) protecting groups (Scheme 21).[66] Phenanthridine ligand $\mathbf{L^3}$ was used for the olefination of Ns protected amine ester derivatives. 3-Phenylquinoline ligand $\mathbf{L^2}$ and 3,4-bis(trifluoromethyl)pyridine ligand $\mathbf{L^1}$ were used for the olefination of Tf protected alkyl amines and Tf protected amino esters with different alkenes, including styrenes. The protecting group acts as a DG and guides the metal to



Scheme 21 Palladium-catalyzed γ-C(sp^3)–H olefination of amines.

activate the γ-C(sp^3)–H bond of the amines selectively, resulting in the formation of a five-membered *exo*-palladacycle intermediate **39**. The intermediate **39** coordinates with an alkene and undergoes 1,2-migratory insertion followed by β-hydride elimination to form the olefinated product *in situ*, which subsequently undergoes aza-Wacker oxidative cyclization to form the corresponding pyrrolidine products.

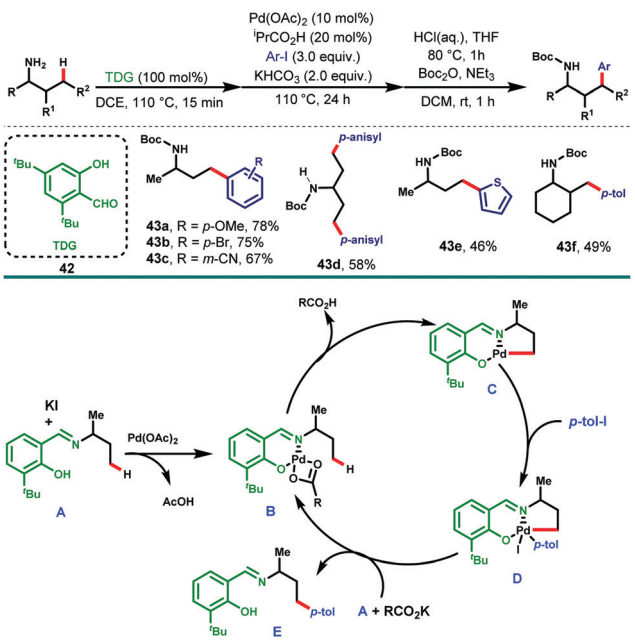
A palladium-catalyzed γ-C(sp^3)–H arylation of primary aliphatic amines using a glyoxylic acid-based transient DG was reported by Ge and co-workers in 2016 (Scheme 22).[67] A wide range of primary amines, including cyclic and acyclic amines, were readily arylated at the γ position with different aryl iodide coupling partners. The methodology was compatible with various functional groups like



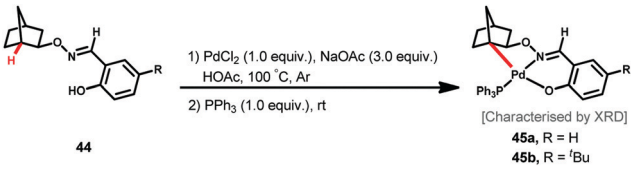
Scheme 22 Palladium-catalyzed γ-C(sp^3)–H arylation of primary aliphatic amines using glyoxylic acid.

nitro, alkoxyl, halides, trifluoromethyl, and alkoxycarbonyl. The authors were able to isolate one of the vital palladacycle intermediates **41** and characterized it by X-ray crystallographic studies. Based on the structure of palladacycle intermediate **41**, the authors proposed a catalytic cycle (Scheme 22). The reaction starts with the condensation of the glyoxylic acid with the amine to generate the imine intermediate **G**. The imine intermediate **G** coordinates with palladium and undergoes ligand exchange to form palladium complex **B**. Cyclometallation of this complex **B** leads to the formation of a five-membered *exo*-palladacycle intermediate **C**. Subsequently, the *exo*-palladacycle intermediate **C** undergoes oxidative addition with aryl iodide to generate the Pd(IV) species **D**, which upon reductive elimination followed by dissociation of the ligand and abstraction of the iodide by AgTFA forms imino-acid **F** and regenerates the catalyst. The imino-acid **F** produces the final product and glyoxylic acid in the presence of water.

In the same year, Murakami and co-workers independently developed a palladium-catalyzed γ-C(sp^3)–H arylation of primary amines using a salicylaldehyde-based transient DG (Scheme 23).[68] 3,5-Di-*tert*-butylsalicylaldehyde was employed as a transient DG in a catalytic amount to arylate various primary amines with different aryl iodides, including heterocyclic iodoarenes. It is interesting to note that the transient DG was recovered in 99% yield after the reaction. A catalytic cycle was proposed by the authors, which is illustrated in Scheme 23. The dehydration of amine with salicylaldehyde forms a salicylaldimine intermediate **A**. The salicylaldimine intermediate **A** chelates with palladium and replaces the acetate ligands to form a palladium chelate complex **B**. Subsequently, C–H palladation occurs at the γ-position and generates a five-membered *exo*-palladacycle intermediate **C**. The *exo*-palladacycle intermediate **C** then undergoes oxidative addition with the aryl iodide and forms palladacycle **D**, which undergoes



Scheme 23 Palladium-catalyzed γ-C(sp^3)–H arylation of primary amines using salicylaldehyde.

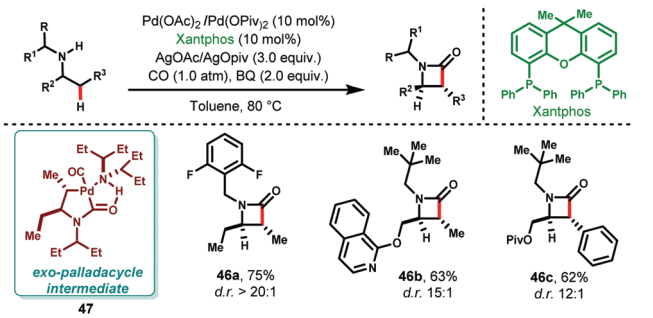


Scheme 24 Cyclopalladation of the tertiary C–H bond using a salicylaldehyde derived *exo* DG.

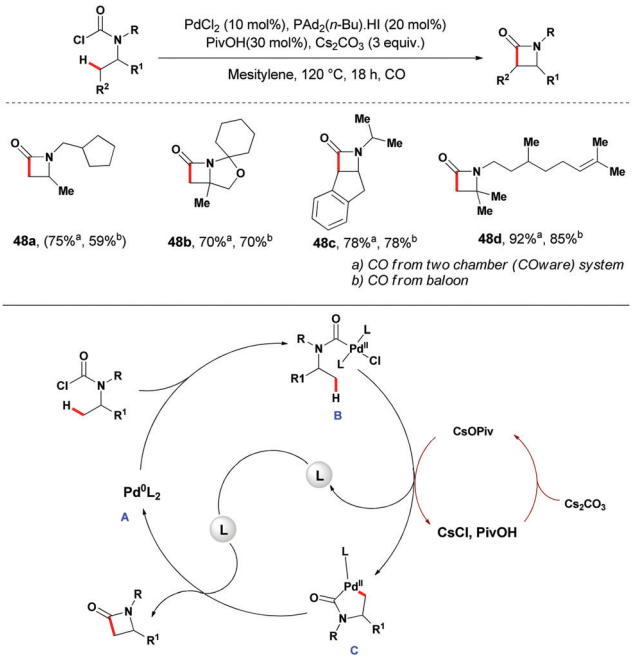
reductive elimination leading to the formation of arylated salicylaldimine **E**, as well as exchanging the iodide ligands with salicylaldimine **A** to regenerate the palladium chelate complex **B** for the next catalytic cycle. The arylated salicylaldimine **E** was treated with HCl and THF to afford the γ-arylated primary amine, which was then subjected to BOC protection to obtain the BOC-protected-arylated amine **43**.

In 2016, Dong's group demonstrated the cyclopalladation of the tertiary C–H bond using a salicylaldehyde derived *exo*-DG (Scheme 24).[69] Both salicylaldehyde derived aldoxime **44a** and 5-*tert*-butylsalicylaldehyde derived aldoxime **44b** underwent cyclopalladation at the tertiary bridgehead position in the presence of $PdCl_2$, NaOAc, and HOAc, followed by treatment with triphenylphosphine to furnish **45a** and **45b**, respectively. Both the cyclopalladated complexes **45a** and **45b** were characterized by X-ray crystallographic studies.

In 2017, Gaunt and co-workers reported a palladium-catalyzed β-C(sp^3)–H carbonylation of aliphatic amines using carbon monoxide and xantphos ligand (Scheme 25).[70] A wide range of *trans*-disubstituted β-lactams were obtained in good yields from the carbonylation of various aliphatic secondary amines. The authors were able to insert CO between the amine and the β carbon using this methodology. Gaunt's group proposed that the palladium catalyst first activates CO and then reacts with the amine to form a carbamoyl-palladium(II) species. Subsequently, β-C(sp^3)–H activation occurs by forming a five-membered *exo*-palladacycle intermediate **47**, which upon reductive elimination furnishes the lactam product. While the xantphos ligand's precise role is still uncertain, the authors postulated that the xantphos ligand most probably helps in the stabilization of Pd(0) species, which is formed towards the end of the catalytic cycle preceding the oxidation step which generates the Pd(II) intermediate.



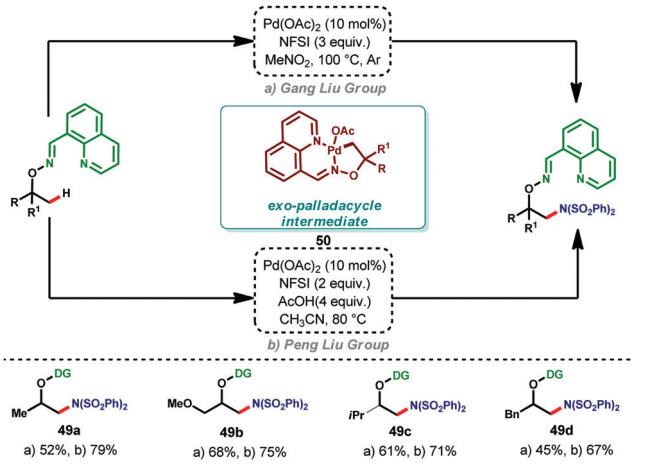
Scheme 25 Palladium-catalyzed β-C(sp^3)–H carbonylation of aliphatic amines.



Scheme 26 Palladium-catalyzed carbamoylation of the C(sp^3)–H bond of carbamoyl chloride.

A palladium-catalyzed carbamoylation of the C(sp^3)–H bond of carbamoyl chloride using carbon monoxide and phosphine ligand was reported by Baudoin and co-workers in 2017 (Scheme 26).[71] Primary, secondary, and tertiary C(sp^3)–H bonds of numerous carbamoyl chlorides were readily carbamoylated to furnish different β-lactams. The carbamoyl chlorides were obtained by the reaction of the corresponding secondary amine with triphosgene. The electron-rich phosphine ligand PAd$_2$(*n*-Bu) plays a crucial role in avoiding the deactivation of the catalyst by excess CO. The carbon monoxide was taken from two different sources, *i.e.*, in one case, it was taken from a balloon while in the other case, it was taken from a two-chamber (COware) system reported by Skrydstrup's group.[72] All the carbamoyl chlorides were subjected to two different carbon monoxide sources, and their yields were reported in both cases. The authors proposed a Pd^0 → Pd^{II} → Pd^0 catalytic cycle, which is shown in Scheme 26. The palladium catalyst undergoes oxidative addition with the carbamoyl chloride to form intermediate **B**. Subsequent C–H bond activation by the palladium metal leads to the formation of a five-membered *exo*-palladacycle intermediate **C**. Reductive elimination of the intermediate **C** leads to the formation of the product along with regenerating the catalyst.

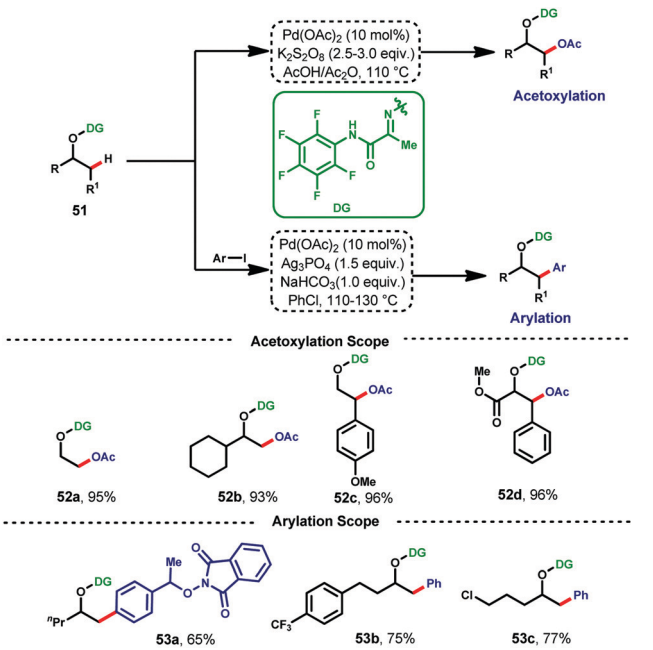
In 2017, Gang Liu and co-workers reported a palladium-catalyzed β-C(sp^3)–H sulfonamidation of alcohols using an 8-quinolyl aldoxime based DG to form a 1,2-amino alcohol derivative (Scheme 27a).[73] In that year, Peng Liu and co-workers independently reported the same reaction with the exact DG with a minor difference in the reaction conditions (Scheme 27b).[74] They used AcOH and CH_3CN in place of $MeNO_2$, and the reaction was carried out at 80 °C instead of 100 °C. NFSI was used as the oxidant and nitrogen source in both cases, and both the reactions proceed



Scheme 27 Palladium-catalyzed β-C(sp^3)–H sulfonamidation of alcohols.

via a five-membered *exo*-palladacycle intermediate **50** formed by the coordination of the substrate with the palladium catalyst, followed by a DG assisted C(sp^3)–H bond activation. In both cases, 1,2-amino alcohol derivatives were formed readily with a broad substrate scope and an excellent functional group tolerance. The DG can be removed under hydrogenation conditions catalyzed by Pd/C.

In 2019, Xu's group reported a palladium-catalyzed β-C(sp^3)–H acetoxylation and arylation of alcohols using an *N*-pentafluorophenyl pyruvamide derived DG (Scheme 28).[75] Various secondary alcohols were selectively mono-arylated in moderate yields using different iodoarenes, and various functional groups like carbonyl, methoxy, trifluoromethyl, trifluoromethoxy, nitro and halide were well tolerated. Similarly, a wide



Scheme 28 Palladium-catalyzed β-C(sp^3)–H acetoxylation and arylation of alcohols.

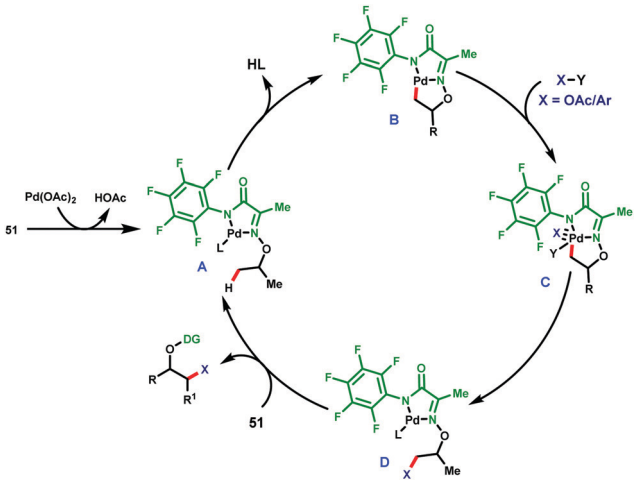
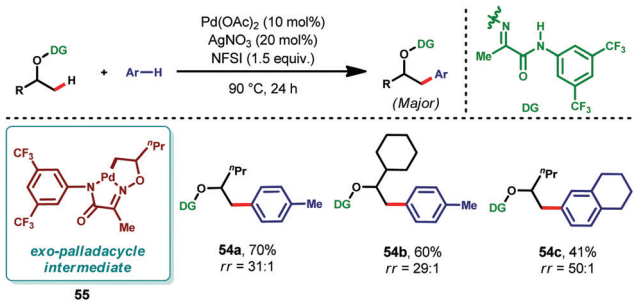


Fig. 2 Catalytic cycle for the palladium-catalyzed β-C(sp^3)–H acetoxylation and arylation of alcohols.

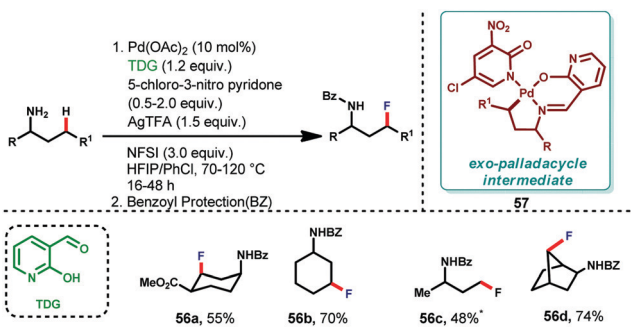
range of primary and secondary alcohols were acetoxylated in excellent yields using $K_2S_2O_8$ as the oxidant. The DG can be easily removed by refluxing with molybdenum hexacarbonyl and acetonitrile. Moreover, the –Ac group can be removed by hydrolysis to furnish chemically differentiated 1,2-diols. Kinetic isotope experiments (KIE = 2.0) showed that the C(sp^3)–H bond cleavage is the rate-determining step. Based on this study, the authors proposed a plausible catalytic cycle depicted in Fig. 2. The substrate undergoes a de-protective coordination and a subsequent C(sp^3)–H bond activation to give the five-membered *exo*-palladacycle intermediate **B**. Consequently, the intermediate **B** undergoes oxidative addition with aryl iodides or oxidation/ligand exchange with $K_2S_2O_8$ to form intermediate **C**. This intermediate **C** then undergoes reductive elimination to furnish the products and regenerate the active intermediate **A** for the next catalytic cycle.

In 2020, Xu and co-workers developed a palladium-catalyzed dehydrogenative β-C(sp^3)–H arylation of alcohols with simple arenes using NFSI as the oxidant (Scheme 29).[76] *N*-(3,5-Ditrifluoromethylphenyl)pyruvamide oxime was used as a DG to arylate various secondary alcohols with different substituted arenes. There were small traces of the β-C(sp^3)–H bond fluorinated product along with the arylated product. But, in most cases, excellent arylation selectivity was detected. Excellent *para*-selectivity was also observed for the substituted arenes. The DG can be removed by refluxing with molybdenum hexacarbonyl and acetonitrile, furnishing the corresponding β-aryl alcohols. Deuterium labeling experiments in the absence of NFSI showed that deuterium was selectively incorporated at the β-C(sp^3)–H position without affecting the aromatic C(sp^2)–H bonds, which indicates the reversible nature of the C(sp^3)–H bond cleavage in the absence of NFSI. However, deuterium labelling experiments revealed no deuterium incorporation either in the product or in the recovered starting material. These experiments suggest the irreversible nature of the C–H bond cleavage under catalytic conditions. Kinetic isotope experiments (KIE = 3.5) showed that the C(sp^3)–H bond cleavage might be the rate-determining step. The authors proposed that the reaction proceeds *via* a five-membered *exo*-palladacycle intermediate **55** formed by the deprotonation coordination of alcohols with the palladium catalyst, followed by the activation of the C(sp^3)–H bond of alcohols through concerted metalation–deprotonation.

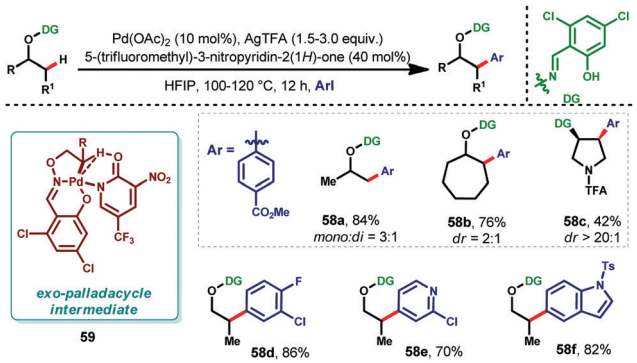
In 2020, Yu and co-workers reported a palladium-catalyzed γ-C(sp^3)–H fluorination of amines using 2-hydroxynicotinaldehyde as the transient directing group (TDG) (Scheme 30).[77] Numerous cyclic and acyclic free amines were efficiently fluorinated at the γ-position, and their corresponding benzoyl protected counterparts were isolated in good yields. 5-Chloro-3-nitropyridone was used as a ligand, and NFSI was used as the fluorine source for the activation of γ-methylene C(sp^3)–H bonds, whereas the fluorination of γ-methyl C(sp^3)–H bonds occurred in the absence of any silver additive and 1-fluoro-2,4,6-methylpyridinium tetrafluoroborate and 3-bromo-5-trifluoromethyl-2-pyridone were used instead of NFSI and 5-chloro-3-nitropyridone, respectively. DFT studies showed that the reaction proceeds through the formation of a five-membered *exo*-palladacycle intermediate **57** resulting from the coordination of imine (formed by the condensation of the amine with the TDG) with the palladium catalyst, followed by the TDG assisted γ-C(sp^3)–H bond activation by palladium. Computational studies showed that for methylene C(sp^3)–H activation, the oxidative addition step is the turnover determining step, whereas for the methyl C(sp^3)–H activation, the C(sp^3)–H bond cleavage is the turnover determining step. Kinetic studies illustrated that both the palladium catalyst and the substrate are involved in the rate-determining step.



Scheme 29 Palladium-catalyzed β-C(sp^3)–H arylation of alcohols.



Scheme 30 Palladium-catalyzed γ-C(sp^3)–H fluorination of amines.



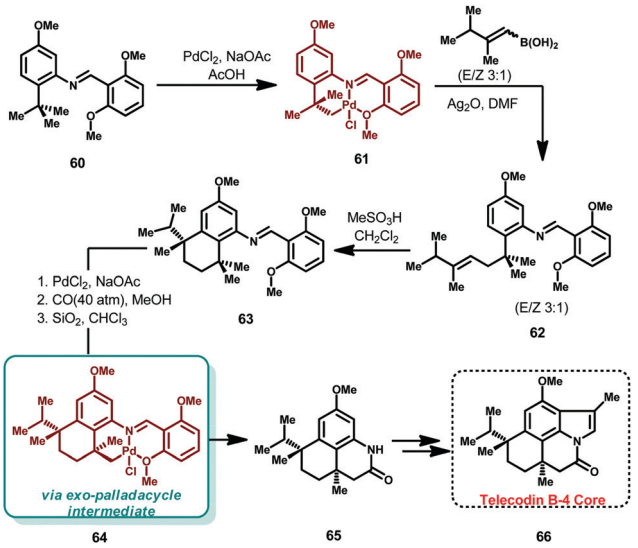
Scheme 31 Palladium-catalyzed β-C(sp^3)–H arylation of aliphatic alcohols.

In the same year, Yu's group developed a palladium-catalyzed β-C(sp^3)–H arylation of aliphatic alcohols using a salicylic aldehyde derived DG and a 2-pyridone ligand (Scheme 31).[78] A wide range of cyclic and acyclic alcohols, including aza-heterocyclic alcohols, were readily arylated using various aryl iodides and different functional groups like amino alcohols, carboxylate, acetoxy, amide, cycloalkanol, alkoxy, ester, cyano, nitro, aldehyde, halide, and trifluoromethyl were well tolerated. Various heteroaryl iodides containing pyridine, thiophene, quinoline, quinoxaline, indole, and oxindole were used as aryl iodide coupling partners. The DG can be removed under palladium catalyzed hydrogenation conditions. The reaction occurs *via* a five-membered *exo*-palladacycle intermediate **59** formed by the coordination of the substrate with the palladium catalyst, followed by the DG assisted activation of β-C(sp^3)–H bond of alcohols. The electron-deficient pyridone ligand helps to lower the energy of the transition state for C(sp^3)–H activation.

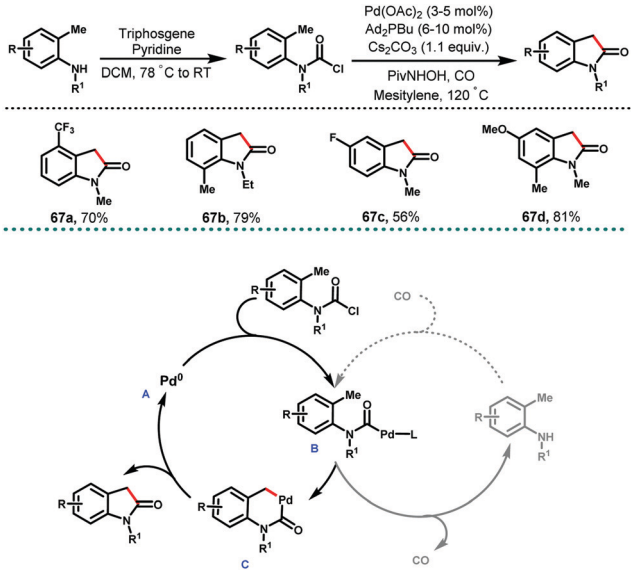
3.2. Six-membered metallacycle

In 2002, Sames and co-workers reported a palladium mediated C(sp^3)–H activation of *tert*-butyl groups during the total synthesis of teleocidin B4 core (Scheme 32).[79] A six-membered *exo*-palladacycle **61** was formed by the cyclopalladation of **60** with stoichiometric amounts of $PdCl_2$ in the presence of NaOAc. The OMe group blocks the *endo*-site and acts as a DG to activate the *tert*-butyl group. Then, *exo*-palladacycle **61** underwent alkenylation with vinyl boronic acid to form compound **62**. The Friedel–Crafts reaction of compound **62** with methanesulfonic acid leads to the formation of compound **63**. This compound was again treated with $PdCl_2$ and NaOAc, which leads to the activation of the methyl group *via* the formation of a six-membered *exo*-palladacycle intermediate **64**, followed by treatment with CO/MeOH, furnishing the carbonylation product **65**.

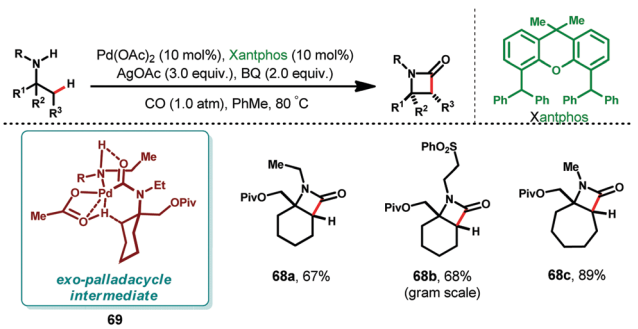
Takemoto and co-workers in 2012 developed a palladium-catalyzed C(sp^3)–H amidation of carbamoyl chloride leading to the formation of oxindoles (Scheme 33).[80] The carbamoyl chlorides were prepared by treating the corresponding anilines with pyridine and triphosgene. A wide range of oxindoles were obtained in moderate yields from the corresponding carbamoyl chloride with broad functional group compatibility. A catalytic cycle was proposed by the authors, which is illustrated in Scheme 33. The carbamoyl chloride undergoes oxidative addition with palladium to form the intermediate **B**. CO elimination from **B** was



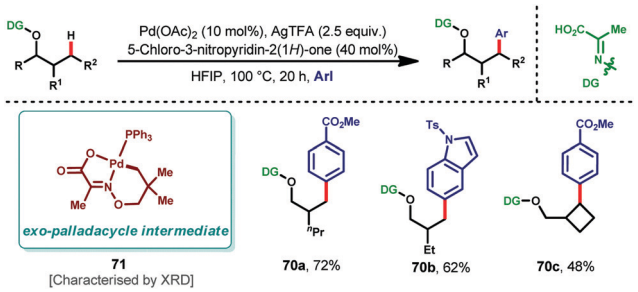
Scheme 32 Total synthesis of teleocidin B4 core.



Scheme 33 Palladium-catalyzed C(sp^3)–H amidation of carbamoyl chloride.



Scheme 34 Palladium-catalyzed β-methylene C(sp^3)–H carbonylation of α-tertiary amines.



Scheme 35 Palladium-catalyzed γ-C(sp^3)–H arylation of aliphatic alcohols.

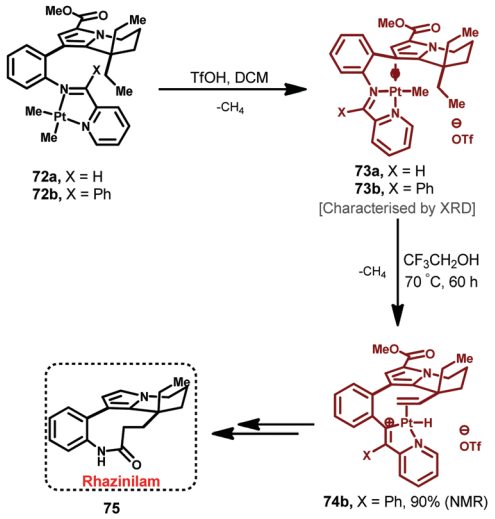
suppressed by carrying out the reaction in CO atmosphere. Subsequent C(sp^3)–H activation led to the formation of a six-membered *exo*-palladacycle intermediate **C**, which was then transformed into an oxindole product regenerating the active catalyst.

Gaunt's group in 2017 reported a palladium-catalyzed β-methylene C(sp^3)–H carbonylation of α-tertiary amines using carbon monoxide and xantphos ligand (Scheme 34).[81] Numerous substituted β-lactams, including bicyclic and tricyclic β-lactams, were obtained by the carbonylation of different α-tertiary amines. A six-membered *exo*-palladacycle intermediate **69** formed by the β-C(sp^3)–H bond activation by the carbamoyl palladium motif was the key intermediate for the above catalytic transformation. The authors proposed that hydrogen bonds between the carbonyl group of the carboxamide and the palladium coordinated amine play a crucial role in locking these two substituents' relative configuration. Hence, the sterically bulky α-tertiary amine motif places the C(sp^3)–H bond close to the palladium centre to prevent the steric clash with the other α-tertiary amine, which is ligated to the palladium centre. This is responsible for the preferential activation of the β-methylene C(sp^3)–H bond in the presence of the methyl C(sp^3)–H bond.

In 2019, Yu and co-workers reported a palladium-catalyzed γ-C(sp^3)–H arylation of aliphatic alcohols using a pyruvic acid-based DG and 3-nitro-5-chloro-2-pyridone ligand (Scheme 35).[82] A wide range of cyclic and acyclic alcohols containing primary and methylene C(sp^3)–H bonds were effectively arylated at the γ position with different aryl iodides. The authors were able to isolate a key six-membered *exo*-palladacycle intermediate **71** and characterize it by X-ray diffraction studies. The intermediate **71** is formed by the pyruvic acid directed remote γ-C(sp^3)–H bond activation by palladium. When deuterium labelling experiments were performed under the standard reaction conditions, deuterium incorporation was absent in the product, which indicated that the arylation was fast enough to outcompete the reversible nature of the C(sp^3)–H bond activation. Kinetic isotope experiments (KIE = 2.7) indicated that the C(sp^3)–H bond cleavage is involved in the rate-determining step and determines site-selectivity. The DG can be removed easily under Pd/C mediated reduction conditions.

4. Miscellaneous

In 2000, Sames and co-workers reported a platinum-induced activation of a remote ethyl group during the total synthesis of

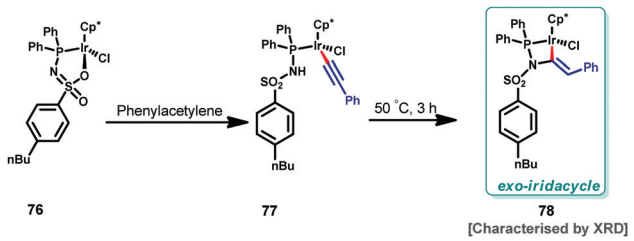


Scheme 36 Total synthesis of rhazinilam.

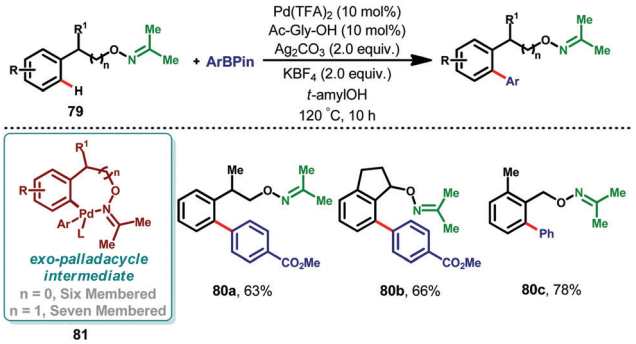
rhazinilam (Scheme 36).[83] Complex **72** was treated with triflic acid, which led to the formation of complex **73** by losing a methane moiety. Both **73a** and **73b** were crystallographically characterized. Furthermore, thermolysis of complex **73b** led to the activation (dehydrogenation) of the ethyl group with the assistance of a phenyl pyridyl ketimine based DG and loss of a methane moiety, followed by a β-H elimination to furnish the *exo*-metallacycle complex **74b**.

Reek and co-workers in 2015 reported an iridium-catalyzed, sulfonamidophosphine (METAMORPhos) ligand assisted C(sp)–H bond activation of phenylacetylene (Scheme 37).[84] This resulted in the formation of a four-membered *exo*-iridacycle complex **78** *via* an iridium-phenylacetylide complex **77**. The *exo*-iridacycle complex **78** could be characterized crystallographically. The reaction begins with the proton transfer to the ligand backbone from the phenylacetylene followed by an anti-Markovnikov hydroamination to the acetylide motif.

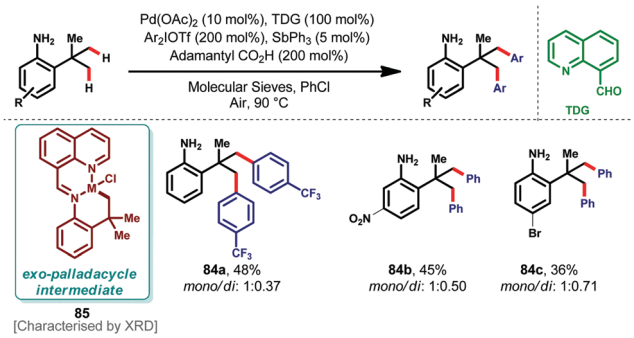
In the same year, Zhao and co-workers reported a palladium-catalyzed *ortho*-C(sp^2)–H arylation of aromatic alcohols using aryl boronic-acid-pinacol-esters and an acetone-oxime-based DG (Scheme 38).[85] Various *para* and *meta* substituted benzyl alcohol derivatives were efficiently mono-arylated with different aryl boronic-acid-pinacol-esters to give biaryl products in moderate to good yields. The methodology was compatible with various functional groups like halides, methoxy, acetate, trifluoromethyl, and nitro. The DG can be removed under RANEY® nickel catalyzed



Scheme 37 Iridium-catalyzed C(sp)–H bond activation of phenylacetylene.



Scheme 38 Palladium-catalyzed *ortho*-C(sp^2)–H arylation of aromatic alcohols.

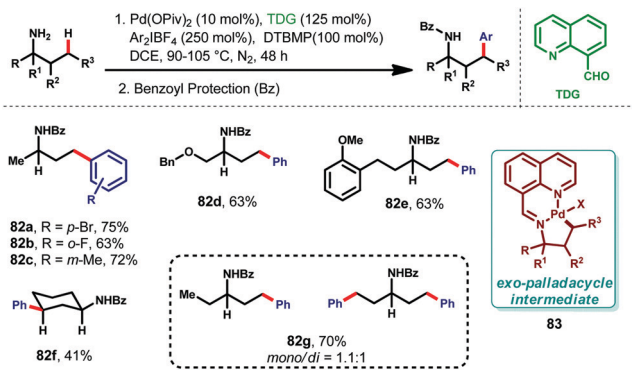


Scheme 40 Palladium-catalyzed δ-C(sp^3)–H arylation of aniline.

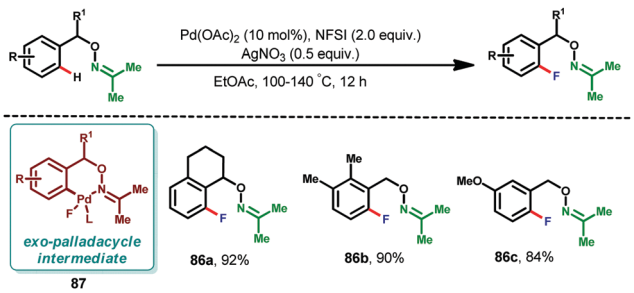
reduction conditions. The reaction takes place by forming either six- or seven-membered *exo*-palladacycle intermediate **81** resulting from the oxime directed *ortho*-C(sp^2)–H bond activation with palladium. Trans-metalation of intermediate **81** with aryl boronic-acid-pinacol-esters followed by reductive elimination furnishes the product. The authors proposed that KBF_4 acts as a pH buffer under reaction conditions and stabilizes the palladium intermediate.

In 2016, Dong and co-workers reported a palladium-catalyzed γ-C(sp^3)–H arylation of alkyl amines using an *in situ* generated 8-formylquinoline derived DG (Scheme 39).[86] The imine-based DG is formed *in situ* by the condensation reaction between quinoline-8-carbaldehyde and the alkylamine. To neutralize the *in situ* generated HBF_4, a bulky and non-coordinating substituted pyridine base (DTBMP) was used. Various primary, secondary, tertiary, cyclic, and acyclic alkyl amines were easily arylated, and several functional groups like ether, halide, nitro, cyano, and methylenedioxy were compatible with this methodology. The free amines could be isolated, but owing to the volatile nature of various alkylamines, the products were isolated as benzoylamide derivatives. The reaction occurs *via* a five-membered *exo*-palladacycle intermediate **83** resulting from the DG assisted γ-C(sp^3)–H palladation. When the authors tried for the arylation of aniline substrates using the same DG, surprisingly, δ-C(sp^3)–H bond arylation was observed (under modified conditions) instead of γ-C(sp^3)–H arylation (Scheme 40). Bulky 1-adamantanecarboxylic acid played a crucial role in promoting cyclopalladation. In this case, the authors could isolate a key six-membered *exo*-palladacycle intermediate **85** formed by the DG assisted δ-C(sp^3)–H bond cyclopalladation and characterized it by X-ray crystallography, which better explains the function and coordination mode of the *exo* DG. It is interesting to note that the DG can be easily recovered and recycled after the reaction.

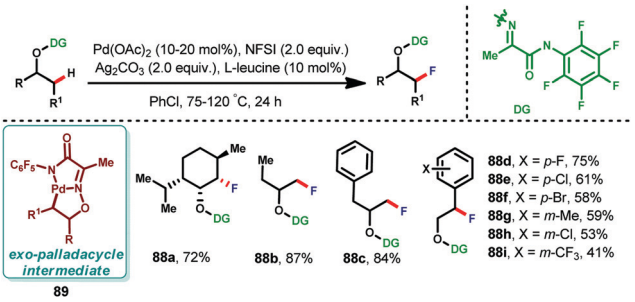
In 2018, Xu's group reported a palladium-catalyzed *ortho*-C(sp^2)–H fluorination of alcohols using an acetone-oxime-based DG and NFSI as the fluorine source (Scheme 41).[87] Various benzyl alcohol derivatives, including α-substituted benzyl alcohols, were readily mono-fluorinated with good to excellent yields using this methodology. This methodology was compatible with different functional groups like halogens, alkyl, phenyl, alkoxy, and OCF_3. The reaction occurs *via* the formation of a six-membered *exo*-palladacycle intermediate **87** formed by the *exo*-DG assisted C(sp^2)–H activation. The authors also showed the palladium-catalyzed β-C(sp^3)–H fluorination of aliphatic alcohols using NFSI as the fluorine source and *N*-pentafluorophenyl pyruvamide as the DG (Scheme 42). Various primary, secondary, tertiary, and cyclic alcohols were readily fluorinated at the β position with broad functional group tolerance. A five-membered *exo*-palladacycle **89** formed by the pyruvamide-assisted C(sp^3)–H bond activation was found to be the key intermediate in this case. Deuterium labeling experiments showed the reversible nature of the C–H bond cleavage in the absence of NFSI but the irreversible nature under the standard reaction conditions. Kinetic isotope experiments (KIE = 10.0) suggested that the C–H bond cleavage is involved in the rate-determining step. The DG can be removed under RANEY® nickel catalyzed reduction conditions or by treating with molybdenum hexacarbonyl and acetonitrile.



Scheme 39 Palladium-catalysed γ-C(sp^3)–H arylation of alkylamines.

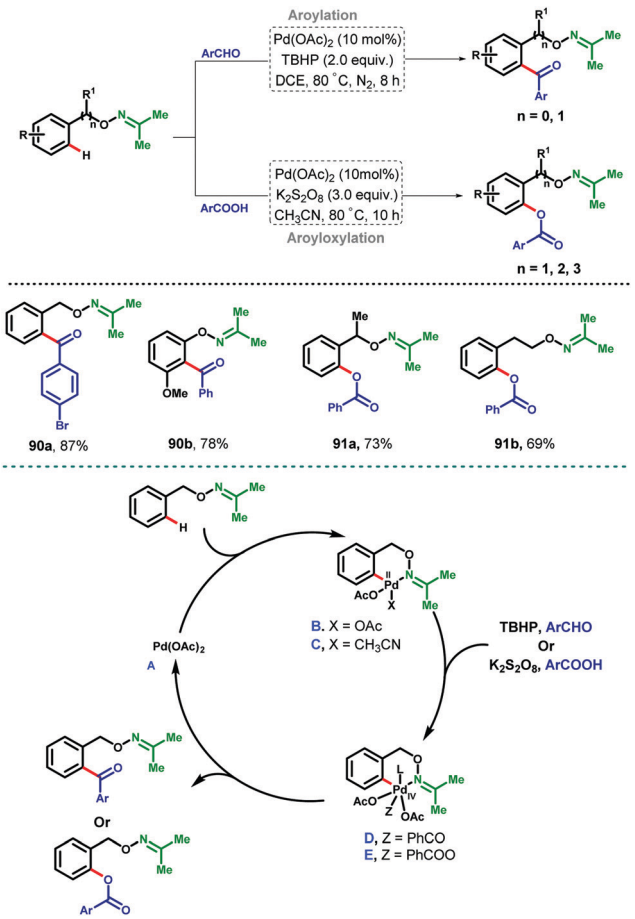


Scheme 41 Palladium-catalyzed *ortho*-C(sp^2)–H fluorination of alcohols.



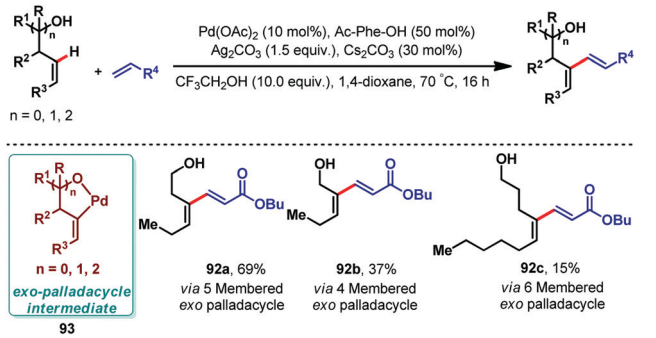
Scheme 42 Palladium-catalyzed β-C(sp^3)–H fluorination of aliphatic alcohols.

Ji and co-workers reported palladium-catalyzed *ortho*-C(sp^2)–H aroylation[88] and aroyloxylation (Scheme 43)[89] of aryl and arylalkyl alcohols using an acetone-oxime based DG. A wide range of aryl alkyl alcohols and aryl alcohols were readily aroylated and aroyloxylated using different aldehydes and carboxylic acids, respectively. Both the methodologies were compatible with different functional groups like halides, trifluoromethyl, alkoxy, and heterocycles, including thiophene and pyridine. The authors proposed a similar mechanism for both cases (Scheme 43). Aroylation begins by the oxime directed cyclopalladation of arene to form an *exo*-palladacycle intermediate **B**. Subsequently, the *in situ* generated aroyl radical (formed by the abstraction of a hydrogen atom by TBHP) reacts with **B** to form **D** *via* oxidative addition where the radical and Pd(II) participate in a SET, followed by the oxidation of Pd(III) to Pd(IV) with the help of TBHP. TBHP plays a dual role of an oxidant and a radical initiator. Reductive elimination of **D** furnishes the product and regenerates the catalyst. Similarly, the aroyloxylation begins with the oxime directed cyclopalladation of arene to form an *exo*-palladacycle intermediate **C**. Intermediate **C** undergoes oxidation with $K_2S_2O_8$ in the presence of benzoic acid to generate the palladacycle intermediate **E**. Subsequent reductive elimination of **E** furnishes the product by regenerating the catalyst. Aroylation takes place by the formation of five- or six-membered *exo*-palladacycles, whereas aroyloxylation proceeds *via* the formation of six-, seven- or eight-membered *exo*-palladacycles. The DG can be removed by treating molybdenum hexacarbonyl in the presence of acetonitrile and water.

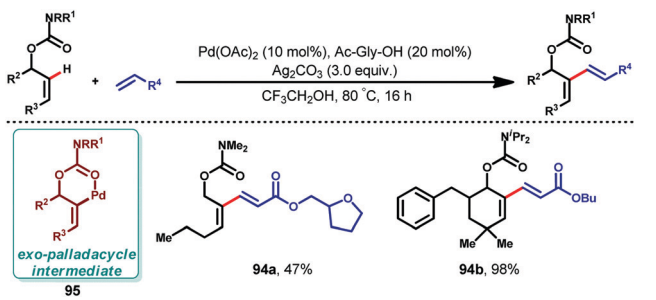


Scheme 43 Palladium-catalyzed *ortho*-C(sp^2)–H aroylation and aroyloxylation of aryl and arylalkyl alcohols.

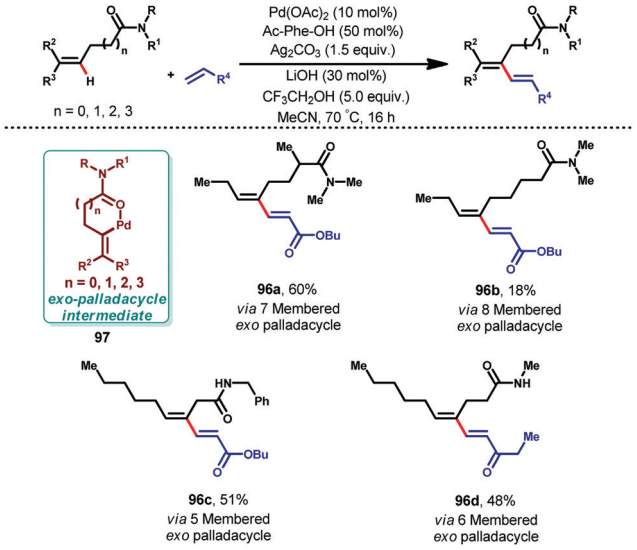
In 2019, Zhong and co-workers reported a palladium-catalyzed C(sp^2)–H alkenylation of olefins using a geminal functional group-based DG.[90] Various homoallyl alcohols, allyl alcohols, and bishomoallyl alcohols underwent alkenylation effectively with different olefins using the alcohol group as the DG (Scheme 44). The reaction proceeds through the formation of four-, five- or six-membered *exo*-palladacycle intermediates. Next, they showed the alkenylation of alkenyl carbamates using the carbamate group as the DG (Scheme 45). Various dialkyl carbamates were arylated using different acrylates. The alkenylation occurs *via* a six-membered *exo*-palladacycle intermediate **95**. They also performed the alkenylation of various secondary



Scheme 44 Palladium-catalyzed C(sp^2)–H alkenylation of allyl alcohols.



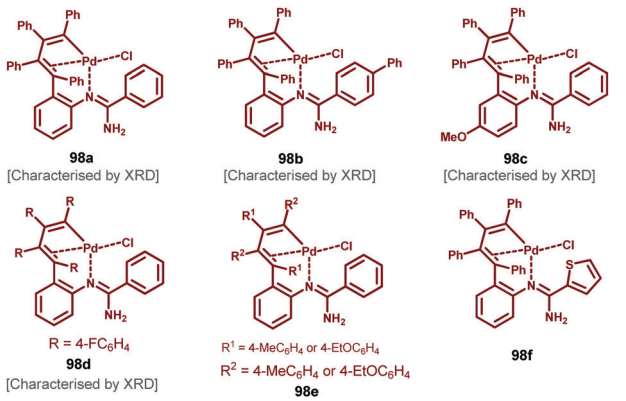
Scheme 45 Palladium-catalyzed C(sp^2)–H alkenylation of alkenyl carbamates.



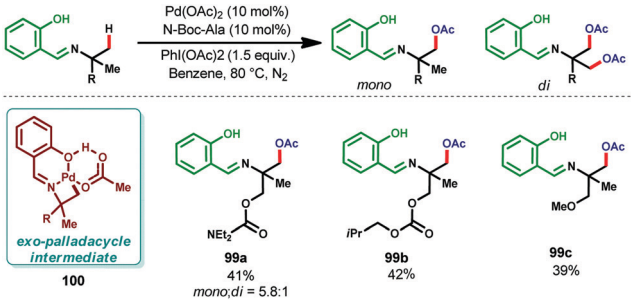
Scheme 46 Palladium-catalyzed C(sp^2)–H alkenylation of alkenyl amides.

and tertiary alkenyl amides using different styrenes, acrylates, and vinyl ketones (Scheme 46). The reaction occurs by the formation of five-, six-, seven- or eight-membered *exo*-palladacycles depending on the length of the substituents. The above methodology is compatible with a broad range of distances between the coordinating group and the olefinic C(sp^2)–H bond. Deuterium labelling experiments showed no deuterium incorporation in all three cases, which supports the irreversible nature of the C–H bond cleavage. A significant KIE value was obtained for all three cases, which indicates that the C–H bond cleavage step is involved in the rate-determining step and is responsible for such site-selectivity.

In 2020, Du's group reported a one-pot synthesis of eight-membered *exo*-palladacycles of amidines (Scheme 47).[91] A wide range of substituted *N*-phenylbenzimidamide derivatives were readily cyclopalladated in the presence of different alkynes. Deuterium labelling experiments and kinetic isotope experiments showed that the C–H bond activation step is reversible and involved in the rate-determining step. The reaction proceeds by the activation of *ortho*-C–H of the *N*-phenyl of amidines followed



Scheme 47 One-pot synthesis of eight-membered *exo*-palladacycles of amidines.



Scheme 48 Palladium-catalyzed β-C(sp^3)–H acetoxylation of primary alkylamines.

by a two-fold alkyne insertion into the Pd–C bond. A total of 32 eight-membered *exo*-palladacycle complexes were synthesized, and some of them (**98a**, **98b**, **98c**, and **98d**) were unambiguously characterized by the crystal structure. This methodology well-tolerated various functional groups like halogens, CF_3, OCF_3, and alkoxy.

Very recently, Hartwig and co-workers reported a palladium-catalyzed β-C(sp^3)–H acetoxylation of primary alkyl amines using a salicylaldehyde based DG (Scheme 48).[92] Various alkyl amines were acetoxylated in moderate yields, and this methodology easily tolerated a wide range of functional groups. Although the mono-acetoxylated amine was the major product, in some cases, a mixture of mono- and di-acetoxylated products were obtained. Deuterium incorporation experiments did not result in any incorporation of deuterium into the starting material, which indicates the irreversible nature of the C–H bond cleavage. The reaction occurs *via* the formation of a rare four-membered *exo*-palladacycle intermediate **100** resulting from the DG assisted β-C(sp^3)–H bond activation. The authors proposed that the hydrogen bond between the hydroxyl group of acetic acid and the oxygen of the DG is crucial for the stabilization of the *exo*-palladacycle intermediate **100**. The DG can be easily attached to the amine by the condensation reaction between the amine and salicylaldehyde, and it can also be easily removed and recovered by acid hydrolysis.

5. Conclusion

In conclusion, *exo*-metallacycles have clearly dominated the field of C–H bond activation and functionalisation in the past decade. The ability to achieve unconventional site-selectivity using different *exo*-DGs makes it an attractive approach for the functionalization of unactivated C(sp^2)–H and C(sp^3)–H bonds. Various alcohol and amine substrates were readily functionalized at the β-, γ- and δ-positions by utilizing the *exo*-metallacycle strategy. This review compiles all the complex organic transformations reported *via* the *exo*-metallacycle approach and the vital reactive intermediates along with the mechanistic investigation are discussed in great depth. *exo*-Metallacycles have not only conquered the area of C–H bond activation, but have also extended various other C–X bond activation chemistry recently.[93–95] Therefore, the compact knowledge presented in this review towards the behaviour of *exo*-metallacycles for C–H activation will be very

beneficial in devising better strategies for synthetic and practical applications.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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