Protodepalladation as a Strategic Elementary Step in Catalysis

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Abstract

Protodepalladation is the redox-neutral conversion of a C-Pd(II) bond to a C-H bond promoted by a Brønsted acid. It can be viewed as the microscopic reserves of Pd(II)-mediated C-H cleavage. In the context of catalytic reaction development, protodepalladation offers a means of converting organopalladium(II) intermediates to organic products without a change in oxidation state at the metal center. Hence, when integrated into catalytic cycles, it can be a uniquely enabling elementary step. The goal of this Review is to provide an overview of protodepalladation, including exploration of different reactions types, discussion of literature examples, and analysis of mechanistic features. Our hope is that this review will stimulate other researchers in the field to pursue new applications of this underexploited step in catalysis.

Graphical Abstract
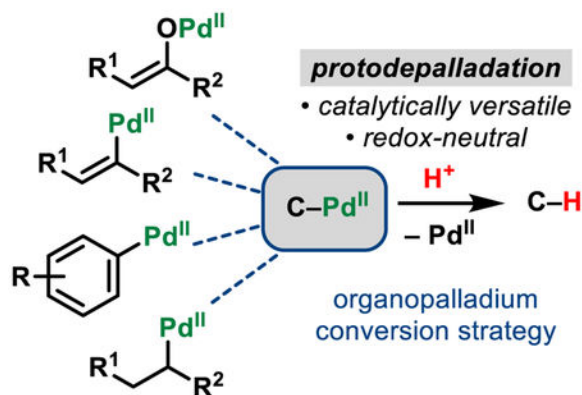
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Introduction

The interchange of C-H and C-M bonds has been a prominent topic of study throughout the history of organometallic chemistry.[2] C-H activation by transition metals, *i.e.* the conversion of a C-H bond to a C-M bond, is known to take place by a variety of mechanisms, and by the principle of microscopic reversibility, there exists an equally diverse set of mechanisms for transforming C-M bonds into C-H bonds (Scheme 1). While reactions to convert C-M into C-H bonds are intriguing from a mechanistic organometallic perspective, this mode of reactivity also offers exciting possibilities in the context of organic synthesis, given that organometallic (C-M) intermediates can be accessed from various classes of organic precursors during the course of catalysis. *Protodemetalation*, the redox-neutral conversion of a C-M bond to a C-H bond via reaction with a Brønsted acid (HX), is an elementary step that is of special interest, both mechanistically and synthetically (Scheme 1). In the literature, it has also been referred to as *protiodemetalation, protonolysis, protic cleavage* or simply *protonation.*

Mechanistically, it can be viewed as the microscopic reverse of a metal-mediated C-H activation process proceeding via electrophilic activation or concerted metalation/deprotonation (CMD). Protodemetalation is perhaps best precedented in the context of copper- and gold-catalyzed reactions. For example, copper-catalyzed 1,4-addition reactions to α,β-unsaturated carbonyl compounds involve protodecupration of a copper(I) enolate intermediate (Scheme 2A). Gold-catalyzed alkyne and alkene hydrofunctionalization reactions similarly involve protodeauration of vinyl- and alkylgold(I) intermediates, respectively (Scheme 2B). Palladium is among the most catalytically versatile transition metals, and organopalladium(II) intermediates can be accessed in a variety of ways, such as oxidative addition to aryl halides and activated carbon-heteroatom bonds or nucleometalation across C-C π-bonds. Protodepalladation, however, remains comparatively underexploited, despite its unique possibilities for bond construction. This review focuses on recent advances in protodepalladation as a productive and synthetically enabling step in catalysis that has intriguing potential for continued development.

In the field of C-H activation, proto/deuterodepalladation has routinely been studied to elucidate reaction mechanisms, as H/D scrambling at the reactive center gives valuable information about how a substrate interacts with the metal catalyst, specifically pertaining to the reversibility of the C-H activation step.[3] With the rise in current interest of medicinal chemistry in "heavy" drugs,[4] which can benefit from greater metabolic and shelf stability than their protonated equivalents, there has also emerged a renewed drive toward the development of novel deuteration methodology. Traditional strategies rely on acid or base mediated exchange reactions. Homogeneous palladium(II)-catalyzed C-H activation/deuteration—using deuterodepalladation as the crucial step—offers a mild, highly selective alternative[5] that can complement other mechanistically distinct approaches involving Ru,[6] Rh,[7] Ir,[8] Pd,[9] Pt,[10] and Fe catalysts.[11] As the number of catalytic reactions involving deuterodepalladation is somewhat extensive, this body of literature is outside of the current review. Instead we focus our attention on palladium-catalyzed C-C and C-heteroatom bond breaking or forming reactions involving a protodepalladation step. As such, this review will cover four main types of reactivity: (1) the functionalization of alkynes via alkenylpalladium

intermediates, arene functionalization, (3) conjugate addition to generate palladium-enolates, and (4) the reactivity of alkylpalladium species (Scheme 3).

Scheme 4 shows a general catalytic cycle for the hydrofunctionalization of unsaturated substrates using palladium(II) catalysis with a protodepalladation termination step: palladium(II) acts as a π-Lewis acid, coordinating to the C-C π-bond and activating the substrate towards nucleopalladation—either with an external nucleophile (NuH) or one previously installed on the palladium catalyst (R[1]). The challenge in designing such a system is that protodepalladation of the resulting palladium(II) complex **1** is often kinetically unfavorable due to competing side-reactions. If **1** is an alkylpalladium species, β-hydride elimination must be suppressed (*vide infra*), while in alkenylpalladium complexes oligomerization may dominate.[12] We hope that this review will give the reader useful strategies to favor protodepalladation over these competing elementary steps, making it a more accessible strategy for the synthetic community.

The reader will note that most of the catalytic protodepalladation examples are redox neutral and use Pd(II) as the active catalyst (Scheme 5i). Similar overall transformations can be achieved through a reductive elimination rather than a redox neutral protodepalladation with addition of formic acid, which leads to the formation of a palladium hydride intermediate via a decarboxylation event (Scheme 5ii) (*e.g.* Cacchi hydroarylations, see Scheme 6).[13] Since these reactions are not generally believed to involve a protodepalladation step, they will not be covered in this review except when illustrative of certain principles. Another interesting and relevant mode of reactivity that will not be covered in this review, since it is unclear in most cases whether it involves a protodepalladation step, is aryl-aryl, aryl-vinyl or aryl-benzyl palladium 1,4-migration (and the less common 1,5-migration) (Scheme 7).[14]

Examples of Synthetically Enabling Protodepalladation Reactions

(1) Alkenylpalladium Species

Protodepalladation of alkenylpalladium(II) species offers a powerful platform for the synthesis of substituted alkenes, particularly in the context of ring-closing reactions to prepare heterocycles. Alkenylpalladium(II) intermediates are commonly access from alkynes, which can be activated toward nucleophilic attack upon coordination of palladium(II), which acts as a π-Lewis acid.

Alkyne Cyclization for the Synthesis of Carbo- and Heterocycles—

Intramolecular nucleopalladation of these activated alkynes by pendant nucleophiles forms the kinetically favored five-membered rings which undergo protodepalladation to furnish the final product (Scheme 8A). This approach offers a useful synthetic route toward different carbo-[15] and heterocycles, including furans,[16] lactones,[17] coumarins,[18] isochromans,[19] indoles and pyrroles,[20] alkylidene indanones,[21] benzazepines[22] and multifused *N*-heterocycles[23] (Scheme 8B).

Alkynediol cycloisomerization allows access to interesting spirocycles (Scheme 9).[24] The addition of chiral ligands enables the enantioselective synthesis of heterocycles.[25] Polyfunctionalized quinolines can be synthesized by dimerization of *N*-aryl propargylamines

(Scheme 10).[26] The first step in this reaction is thought to be intramolecular palladium(II) catalyzed cyclization of the aromatic ring onto the alkyne, followed by hydroarylation of a second substrate molecule with the resulting quinolinylpalladium species. Intermolecular variants for the synthesis of oxindoles,[27] benzoxepines,[28] and thiadiazafluorenones[29] have been successful as well. An interesting variation of this chemistry was developed by Aurrecoechea and co-workers, who accessed trien-1-ols **3** by reduction of 4,5-epoxyalk-2-ynyl esters **2** with samarium iodide. In the presence of a palladium(II) catalyst and a proton source, these compounds underwent facile cycloisomerization to afford substituted furans (Scheme 11).[30]

Intermolecular Hydrofunctionalization of Alkynes—Aside from the palladium-mediated intramolecular cyclization of alkynes, another highly useful class of transformations is the reaction of alkenylpalladium intermediates that are formed upon outer-sphere attack by an external nucleophile. Oh *et al.* discovered that arylboronic acids undergo cross-coupling reactions with activated alkynes to afford alkenylpalladium species that lead to trisubstituted alkenes upon protodepalladation; however the regioselectivities observed in this reaction were low.[31] Pincer ligands were successful in directing hydroarylation and -vinylation to the more electron-rich carbon with regioselectivities of >9:1 (Scheme 12A).[32] The Engle group demonstrated that very high regio- and stereoselectivity can be achieved when a removable bidentate directing group is employed that coordinates strongly but reversibly to the catalyst (Scheme 12B), allowing for highly selective alkyne *syn*-hydroarylation[33] and *anti*-hydrochlorination.[34]

Fujiwara and co-workers discovered that electron-rich arenes undergo C-H activation in the presence of triflic acid and a Pd(II) or Pt(II) catalyst, affording *trans*-hydroarylation of C-C π-bonds (Scheme 13A).[13a,35] Arenes, arylboronic acids[31,36] and aryl sulfonates[37] have been successfully used as coupling partners in the Fujiwara hydroarylation reaction. The intramolecular variant furnishes coumarins, quinolinones[38] and fluorenes[15i] in good yields (Scheme 13B). Mechanistically, Fujiwara and co-workers proposed *trans*-carbopalladation of an arylpalladium species across the alkyne (Scheme 13C). KIE studies by Tunge and Forsee, however, showed an inverse KIE inconsistent with known C-H activation mechanisms with electrophilic palladium.[39] This suggests the alkenylpalladium species may instead be formed by electrophilic aromatic substitution, in which case the highly electrophilic cationic $[Pd(OCOCF_3)_nL_m]^+$ active catalyst formed *in situ* acts as a π-acid, increasing the electrophilicity of the alkyne. These findings were further supported by extensive ^{1}H NMR and mass spectrometry experiments carried out recently by the Eberlin and Correira groups.[13a]

Aside from hydroarylation, hydroamidation has been shown to selectively afford *Z*-enamides from terminal alkynes.[40] The Zhang and Yoshikai groups developed interesting three-component condensation approaches for the synthesis of highly substituted furans (Scheme 14).[41] Another elegant example of an intermolecular ring-synthesis involving deprotonation of an alkenylpalladium intermediated was demonstrated by Jarvo and co-workers who showed that allenylboronic esters can be used to access propargylpalladium species **5** which undergoes conjugate addition to alkenes bearing ester or nitrile groups (Scheme 15). The

resulting palladium enolate or imine intermediates cyclize under the reaction conditions to diastereoselectively afford cyclopentenes.[42]

In brief, the reaction of alkenes and alkynes with intra- or intermolecular nucleophiles under palladium(II) catalysis offers a useful strategy for the synthesis of carbo- and heterocycles as well as highly substituted alkenes. Rational design of substrates or ligands allows for high levels of regio- and stereoselectivity.

(2) Arylpalladium Species

Transformations involving protodepalladation of arylpalladium(II) species have been less extensively pursued than other categories of reactions described in this review. This is likely due at least in part to the fact that the common pathways for accessing arylpalladium(II) intermediates—oxidative addition (aryl halides), transmetalation (aryl boronates) and C-H activation (arenes)—involve starting materials that are more highly functionalized than the putative products (or equivalently functionalized starting materials in the case of C-H activation), which means protodepalladation is typically not a synthetically enabling step. Nevertheless, in recent years, creative applications of arylpalladium(II) protodepalladation have demonstrated the potential of this step in enabling unique transformations.

Aromatic Protodecarboxylation—Inspired by transition-metal catalyzed decarboxylative cross-coupling reactions, Kozlowski *et al.* hypothesized that it would be possible to intercept the arylpalladium species formed during these transformations with a proton source to afford mild aromatic protodecarboxylation. Indeed, they found that bis-*ortfto*-methoxy substituted aromatic substrates successfully underwent protodecarboxylation in the presence of a palladium(II) catalyst and trifluoroacetic acid (Scheme 16).[43] Detailed mechanistic studies found that the reaction proceeds by decarboxylative palladation via a 4-membered transition state, followed by protodepalladation via an electrophilic aromatic substitution mechanism.[44] This discovery paved the way for the use of carboxylic acids as traceless directing groups in palladium-catalyzed C-H activation that are easily removed following the functionalization of interest (Scheme 17).[45]

Norbornene-Mediated Arene-Functionalization—Directed functionalization of C-H bonds immediately adjacent to suitable directing groups is a well-known transformation in transition-metal catalysis.[46] Remote functionalization of unactivated C-H bonds is more challenging and has become the focus of several research groups.[46g,47] Since the discovery by Catellani and co-workers in 1997 that norbornene (**6**) reversibly inserts into Pd-C(sp^2) bonds under mild conditions and subsequently acts as a powerful transient *ortho*-directing auxiliary,[48] this strategy has been used for a diverse range of *ipso*-, *ortho*- and *meta*-functionalization reactions of arenes.[46f,49] Mechanistically, these methods rely on a relay of oxidative addition and reductive elimination steps, which are usually terminated by a Heck-, Sonogashira-, or Suzuki-Miyaura cross-coupling reaction (Scheme 18). The Yu group realized that a Catellani-type catalytic cycle could be entered through directed *ortho*-C-H activation and terminated by a protodepalladation step. Addition of norbornene to amide-directed arene C-H alkylation and arylation reactions thus switched the selectivity from *ortho*- to *meta*-functionalization, enabling very selective remote C-H functionalization

(Scheme 19i).[50] A similar approach was concomitantly developed by Dong *et al.* using amine directing groups (Scheme 19ii).[51]

(3)   Palladium-Enolates

Among all types of organopalladium species covered in this review, palladium(II)-enolates are perhaps the best precedented intermediates in the context of protodepalladation reactivity. Palladium(II)-enolates are mostly commonly generated via 1,4-conjugate addition of organopalladium species to α,β-unsaturated carbonyl compounds or functional group equivalents, a process that can take place via either in an inter- or intramolecular fashion.

Conjugate addition to α,β-unsaturated carbonyls is a powerful reaction enabling C-C bond formation, and the use of palladium catalysis significantly expands the range of compatible carbon nucleophiles. The first palladium-catalyzed conjugate addition was reported by Yamamura in 1978, who showed that benzene undergoes conjugate addition with bulky, electron-poor α,β-unsaturated ketones in the presence of stoichiometric amounts of $Pd(OAc)_2$ to afford predominantly protodepalladated alkane products, with small amounts of alkene by-products arising from β-hydride elimination (Scheme 20A).[52] Catalytic variants were developed soon thereafter by Cacchi and Lu for the conjugate addition of arylmagnesium, aryltin and arylboronic acid coupling partners to α,β-unsaturated aldehydes and ketones (Scheme 20B).[53] Nucleopalladation of the alkene occurs selectively to deliver the aryl group to the β-carbon, with formation of a stabilized palladium enolate intermediate (**7**). This intermediate can undergo either β-hydride elimination, or protodepalladation to afford the desired products (Scheme 20C). Steric bulk on the β-carbon as well as conformationally rigid cyclic structures were found to favor protodepalladation, presumably by restricting rotation around the C-C bond necessary to obtain the correct conformation for *syn-β*-hydride elimination.[13c] Bidentate nitrogen-containing ligands such as 2,2'-bipyridine and excess halide anions were also found to suppress β-hydride elimination, while simultaneously stabilizing the palladium enolate intermediate **7** and favoring protodepalladation.[53d,54]

Minaard *et al.* demonstrated that the use of a chiral DuPHOS ligand afforded highly chemo-, regio-, and entantioselective conjugate addition of arylboronic acids to cyclic alkenes under palladium(II) catalysis (Scheme 21i).[55] Selectivities for linear substrates, however, were low. Similar results were obtained with BINAM-based NHC ligands[56] and pre-formed palladacycles bearing chiral naphylphosphine ligands.[57] Chiral pyridinooxazoline (PyOX) (Scheme 21ii)[58] and bisoxazoline (BOX)[59] ligands were effectively used to construct chiral quaternary centres. Miyaura and co-workers found that addition of a silver salt greatly enhanced the enantioselectivity in linear substrates, presumably by accelerating the transmetalation step of the arylboronic acid onto palladium (Scheme 21iii).[60] Alternatively, a chiral amine co-catalyst can be used to activate the carbonyl and impart enantioselectivity.[61] Finally, addition of 4-*tert*-butyloxazolidin-2-one to the carbonyl as a chiral auxiliary also afforded enantioselective conjugate addition of arylboronic acids to linear alkenes with moderate to high *ee*'s.[62] Recently, Yang and Zhang demonstrated the use of nitrostyrene and dienes derived from Meldrum's acid as viable Michael acceptors for the asymmetric conjugate addition of arylboronic acids under Pd(II) catalysis using Pyox-derived ligands

(Scheme 21iv and v).[63] Alkoxylation, acetoxylation and amidation of alkenes have been developed with alcohols, acetic acid and Cbz-protected amines as external nucleophiles, respectively.[64] Panda and Yadav recently adapted an aza-Wacker reaction developed by Lloyd-Jones and Booker-Milburn[65] for the synthesis of benzoxazolidines by forming a stabilized palladium(II) enolate intermediate which could be trapped by protodepalladation to afford the desired products (Scheme 22).[66] In a similar vein, Wang and Shi developed an elegant synthesis of chiral [3.3.1]-bicyclic ketals and spiroketals via a Pd(II) catalyzed cascade of conjugate addition reactions in the presence of a chiral BINAP ligand (Scheme 23).

Widenhoefer demonstrated that 1,3-diketones intramolecularly add to unactivated alkenes in the presence of catalytic $PdCl_2(MeCN)_2$, giving alkane rather than alkene products. Subsequent mechanistic studies were consistent with chain-walking of the palladium to afford a stabilized palladium(II) enolate which undergoes protodepalladation rather than *beta*-hydride elimination (Scheme 24).[67]

Furthermore, the alkenylpalladium species introduced in the previous section can be used as nucleophiles, opening up an interesting range of tandem reactions for the synthesis of *beta*-alkylated ketones and heterocycles (Scheme 25).[68] An impressive asymmetric *oxa*-Diels-Alder/nucleophilic substitution cascade under cooperative Pd[II] and chiral phosphoric acid catalysis was reported by Yao *et al.* (Scheme 26).[69] Ligand exchange of the chiral phosphoric acid onto palladium after intramolecular nucleopalladation of the alkyne allows for enantioselective [4+2]-cyclization with the styrene coupling partner, forming three stereogenic centers with good to excellent *ee*'s. The resulting intermediate **9** undergoes cyclisation to form a stabilized palladium enolate which—upon protodepalladation—yields the desired products.

Palladium enolate chemistry has furthermore been exploited to achieve enantioselective protodecarboxylation protocols for cyclic ketones. Treatment of β-keto allyl esters with a palladium(II) catalyst in the presence of acid affords clean protodecarboxylation. The first example of this transformation was reported by Tsuji in 1985,[70] followed by an asymmetric variant developed by Hénin and Muzart who used ephedrine as a chiral proton source to achieve moderate *ee*'s.[71] Excellent enantioselectivities were attained by the Stoltz group with a chiral phosphinooxazoline (PHOX) ligand, which presumably leads to the formation of an asymmetric palladium enolate intermediate (**10**) that can be intercepted with acid before it undergoes β-allylation.[72] Guiry and co-workers discovered that expedient choice of acid allows for enantiodivergent protodecarboxylation, the exact mechanism of which is still under investigation (Scheme 27).[73]

(4)   Alkylpalladium Species

The aforementioned reactions all proceed through organopalladium intermediates (alkenyl, aryl, or enolate) that contain $C(sp^2)$-Pd or O-Pd bonds. These species are comparatively stable owing both to the hybridization and polarity of the bonding atom and to the absence of accessible β-H atoms. In contrast, protodepalladation to alkylpalladium(II) systems is comparatively difficult for several reasons, including the typically rapid nature of

competitive β-H elimination and the more sterically encumbered nature of because C(sp^3)-Pd bonds.

Protodepalladation of π-allyl palladium(II) species—π Allyl/benzylpalladium(II) species are a special case owing to the presence of adjacent π-bond which enables adoption of a stabilizing η^3-coordination mode and are not covered here in extensive detail. In an early representative example, Yoshida and co-workers demonstrated that stabilized π-allylpalladium complexes could also be accessed by treatment of conjugated dienes with stoichiometric amounts of PdCl$_2$ and a suitable nucleophile (Scheme 28).[74] Protodepalladation of these complexes with dimethylglyoxime in a protic solvent cleanly afforded sulfonylated *Z*-alkenes, presumably due to coordination of the sulfonyl group to palladium.

Protodepalladation of π-Allyl palladium(II) species—The stability and reactivity of σ-alkylpalladium intermediates is much harder to control, and therefore less well documented. One of the major challenges associated with this chemistry is the propensity for alkylpalladium species to undergo rapid *beta*-hydride elimination.[75] For a long time, only substrates in which *β*-hydride elimination was unfavorable were implicated in alkylpalladium chemistry. Examples include the hydroarylation and hydrovinylation of substrates that do not contain *β*-hydrogens,[76] as well as cyclic, strained alkenes—such as norbornene or porphyrins—in which *syn*-*β*-hydride elimination is geometrically impossible.[77]

The Anbarasan group exploited the first strategy in an elegant indoline synthesis: reaction of a palladium(II) catalyst with a diazonium salt is thought to form a palladium carbene which is trapped by a secondary amine to give the alpha-amino palladium enolate species **11**. Attack on a pendant alkene closes the indoline ring, forming alkylpalladium species **12** adjacent to a quarternary carbon center which therefore cannot undergo *beta*-hydride elimination. Instead, protodepalladation yields the desired indoline products in good yields (Scheme 29).[78]

β-Hydride elimination is initiated by the agostic interaction between a hydrogen atom's sigma bond and an open coordination site on the metal catalyst. While in certain cases bidentate nitrogen ligands have been shown to sufficiently stabilize the alkylpalladium intermediate,[44d,45] Michael and Chochran hypothesized that a tridentate pincer ligand would completely suppress undesired *beta*-hydride elimination by coordinatively saturating the metal.[79] This approach allowed them to develop an intramolecular alkene hydroamination proceeding through a truly unstabilized alkylpalladium intermediate (Scheme 30). In the presence of a strong base such as 2,6-lutidine, complex (**14$^+$**)(BF$_4^-$) was isolated and its structure determined by NMR and X-ray analysis, confirming the ability of the pincer ligand to prevent *beta*-hydride elimination. The Engle group was able to expand this reactivity to regioselective intermolecular hydroamination of unactivated alkenes by employing a removable bidentated 8-aminoquinoline directing group (Scheme 31).[80] It is believed that the stability and conformational rigidity imparted by the directing group to palladacycle intermediate **14** prevents *beta*-hydride elimination and allows protodepalladation to occur instead.[81] The concept was further expanded to hydrocarbofunctionalization of alkenes and

dienes (Scheme 32).[82] Chen *et al.* recently developed an asymmetric variant of this reaction using a chiral monodentate oxazoline ligand **L5**, achieving good to excellent *ee*'s (Scheme 32Aii).[83] Engle and co-workers further developed an elegant formal C-X bond activation (where X = O, N, C, F, S) based on this transformation, by accessing alkene substrates *in situ* via *β*-X elimination (Scheme 33).[84]

The reactivity and selectivity of these methodologies hinge on the kinetic and thermodynamic stability of 5-membered palladacycle intermediate **15** (Scheme 31). Remote functionalization—*e.g.* via the less stable 6-membered palladacycle intermediate—is more difficult, and usually only possible if the 5-membered intermediate is sterically inaccessible. [85] Rational design of removable, pincer-like tridentate directing groups allowed Engle *et al.* to access the less stable 6-membered palladacycle **16** by suppressing *beta*-hydride elimination, further expanding the scope of their methodology to include highly regioselective remote alkene functionalization (Scheme 34).[86]

Mechanistic Considerations

Protodepalladation can occur via two possible mechanisms: (1) protonation of the Pd^{II}-C bond with external acid through a three-center-two-electron transition state (i), or via a retro-CMD mechanism (ii) (Scheme 33A). Or (2) oxidative addition of HX to the palladium(II) intermediate to form a Pd^{IV} hydride, followed by reductive elimination (Scheme 35B).

One of the first mechanistic investigations into protodepalladation was carried out by Fryzuk and Bosnich, who developed an elegant stereospecific deuteration protocol for alkenes in 1979 using CF_3CO_2D as the deuterium source (Scheme 36):[87] Reaction of vinyl bromide **17** with stoichiometric amounts of $Pd(PPh_3)_4$ afforded oxidative addition complex **18** which was identified by NMR and X-ray[88] analysis. Treatment of this complex with CF_3CO_2D and trifluoroacetic anhydride afforded the deuterated alkene in 90% yield with retention of stereochemistry. This would suggest that the deuterated TFA is acting as an external proton source (mechanism A, Scheme 35).

Michael and Cochran carried out variable NMR studies of their pincer-ligand assisted, palladium-catalyzed hydroamination of alkenes in order to investigate whether protodepalladation was happening via an external deprotonation mechanism (mechanism A, Scheme 35) or via a palladium(IV) hydride (mechanism B, Scheme 35) (Scheme 37).[79b] Screening temperatures ranging from −78 °C to room temperature, they were never able to observe an NMR signal in the spectral region indicative of a late metal hydride (0 to −60 ppm). While these results cannot fully rule out a palladium hydride intermediate, they strongly suggest that protodepalladation is occurring through protonation of the C-Pd bond, possibly through intramolecular assistance of the carbamate group. 1n the presence of 2,6-lutidine, complex (**14**$^+$)(BF_4^-) was isolated and its structure confirmed by X-ray analysis. Treatment of the isolated alkylpalladium complex with different acids (TfOH, $HBF_4 \cdot Et_2O$, [Ph_2NH_2][BF_4], [Ph_2NH_2][OTf]) resulted in complete conversion to product **20** and catalytically competent complex **19** in less than 15 minutes at room temperature.

Computational studies on the protodepalladation mechanism of palladium enolates in methanol and acetic acid were carried out by the Houk (Scheme 38)[89] and Wu (Scheme 39)[90] groups, respectively. In both studies, the barrier toward intramolecular, solvent-assisted CMD-type protodepalladation was found to be lower than 15 kJ/mol. Furthermore, when comparing protodepalladation to competing *beta*-hydride elimination, Wu *et al.* found that the rate-determining step for the latter was isomerization to enable a Pd-H agostic interaction. While the energy of this transition state was relatively unaffected by ligand choice, the barrier for protodepalladation was significantly reduced by bidentate nitrogen or phosphine ligands on the palladium catalyst (compared to acetate). For example with a 2,2'-bipyridyl ligand, protodepalladation was found to be more favorable than *beta*-hydride elimination by 2.8 kcal/mol.[90] This confirmed the experimental observation that bidentate ligands can be successful at suppressing unwanted *beta*-hydride elimination. Engle and Liu found that for the tridentate directing groups they developed (Scheme 34), *beta*-hydride elimination is disfavored by 7.1 kcal/mol compared to protodepalladation, since the former requires partial dissociation of the directing group from the palladium catalyst (Scheme 40). [86] For similar reasons, intermolecular protodepalladation via a retro-CMD mechanism was strongly disfavored with these directing groups, since it would require association of HOAc to the palladium catalyst. Instead, intramolecular protodepalladation is thought to occur, with the nucleophile acting as a proton source (Scheme 40).

Based on the data presented in these studies, the authors of this review believe evidence points towards a retro-CMD-type protodepalladation mechanism with external acid for catalysts bearing mono- or bidentate ligands (Scheme 35A) and a novel, intramolecular mechanism with tridentate ligands (Scheme 40).

Conclusion

This review has described a series of catalytic transformations that involve protodepalladation of several different classes or organopalladium intermediates containing C(alkenyl)-, C(aryl)-, O(enolate)-, and C(alkyl)-Pd(II) bonds. In the context of synthetic methods development, this elementary step represents a unique means of converting organopalladium intermediates into organic products in a process that is redox-neutral at the metal center. The palladium(II) species that is thus generated can reenter the catalytic cycle in many cases without the need for oxidation or reduction.

We hope that the examples and mechanistic discussion covered in this review have demonstrated the synthetic utility of protodemetalation in palladium(II)-catalyzed C-C and C-heteroatom bond forming reactions, paving the way for further investigations into this field. By understanding how to favor this elementary step over competing side-reactions such as *beta*-hydride elimination or polymerization, we believe that this underappreciated mode of reactivity can be harnessed to enable invention of a plethora of interesting new transformations in the future.

Funding Information

Biographies

Miriam L. O'Duill grew up in Ireland and Germany. In 2011 she obtained her MChem from the University of Oxford. She carried out graduate work at the same university under the supervision of Véronique Gouverneur, earning a PhD in Organic Chemistry in 2015. After a two-year stint as a DAAD Postdoctoral Fellow with Keary M. Engle at the Scripps Research Institute, Miriam joined the School of Chemistry at the National University of Ireland, Galway as a lecturer in January 2018.

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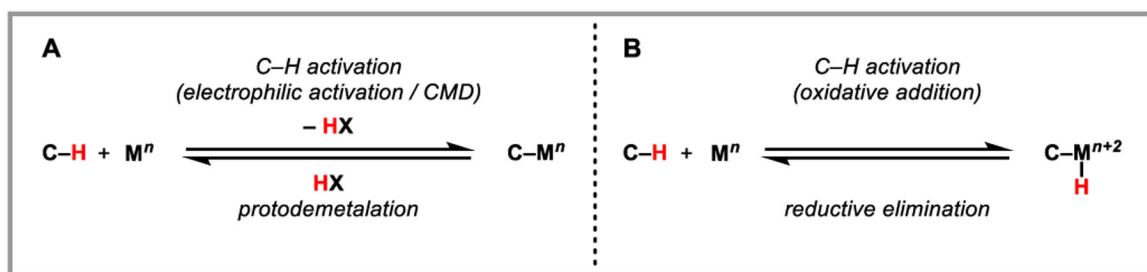
Scheme 1.
Microscopic reversibility of C-H activation.
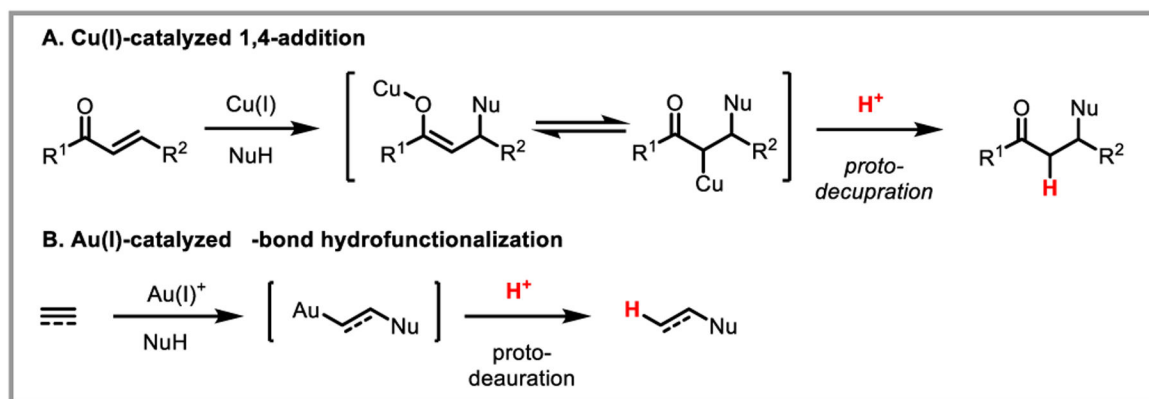
Scheme 2.
Examples of protodemetalation in Cu(I)- and Au(I)-catalyzed reactions.
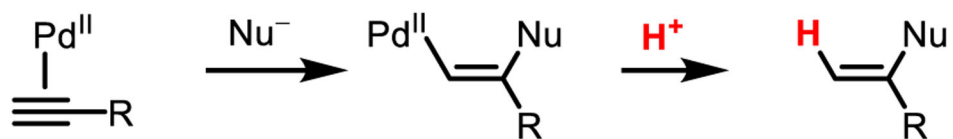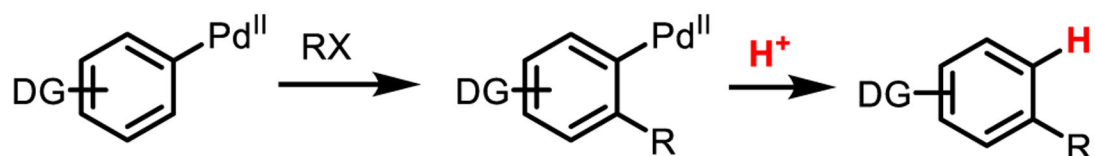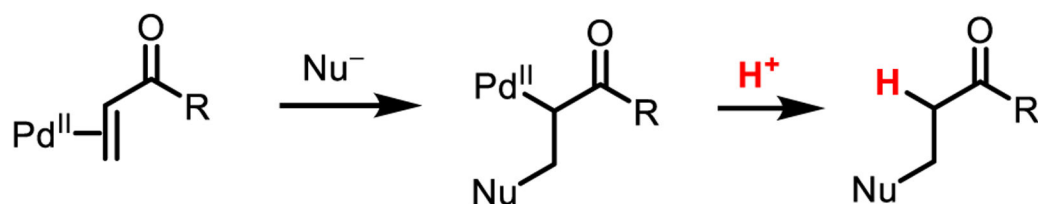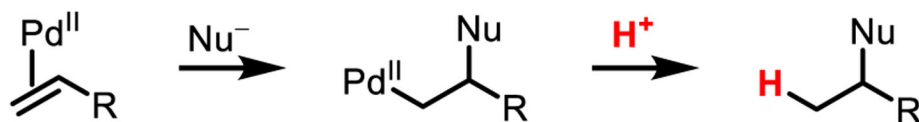
Scheme 3.
Pd-catalyzed reactions showcasing protodepalladation as an enabling transformation.
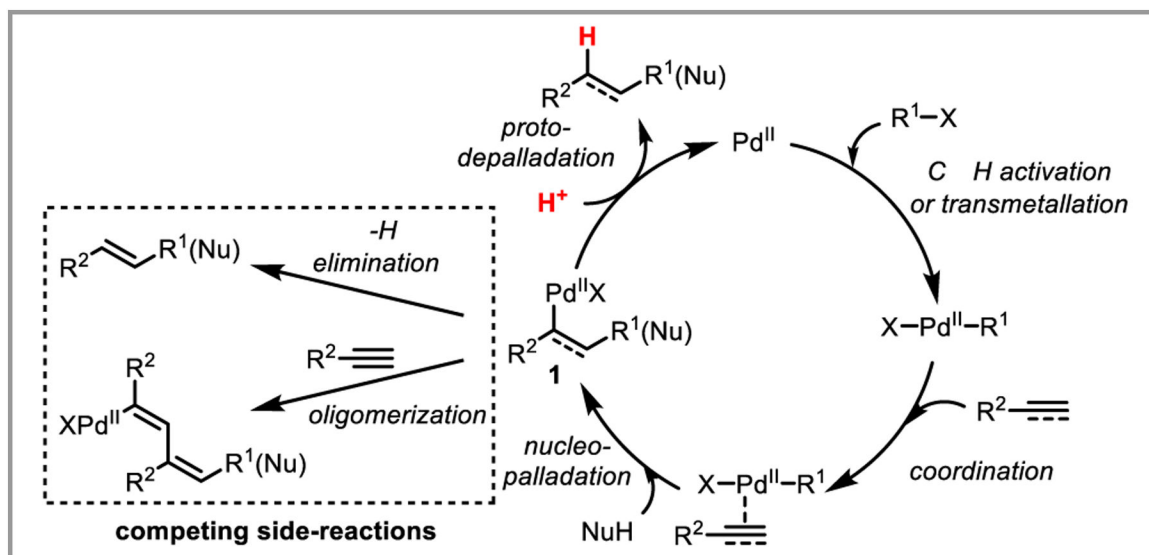
Scheme 4.
General catalytic cycle for Pd^{II}-catalyzed hydrofunctionalization of unsaturated substrates.

| (i) | C−Pd(II) + **H⁺** | ⟶ | C−**H** + Pd(II) |
| (ii) | C−Pd(II) + **H** | ⟶ | C−**H** + Pd(0) |
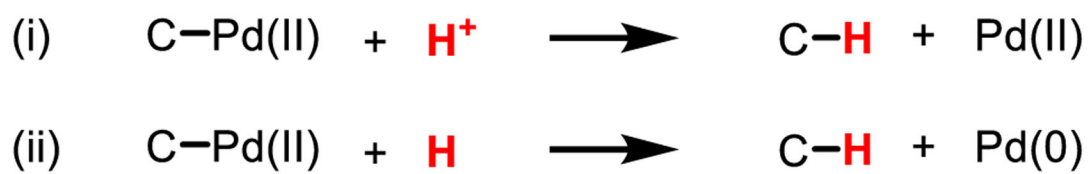
Scheme 5.
Conversion of C-Pd(II) to C-H via (i) protodepalladation (this review) and (ii) palladium hydride formation (not covered).
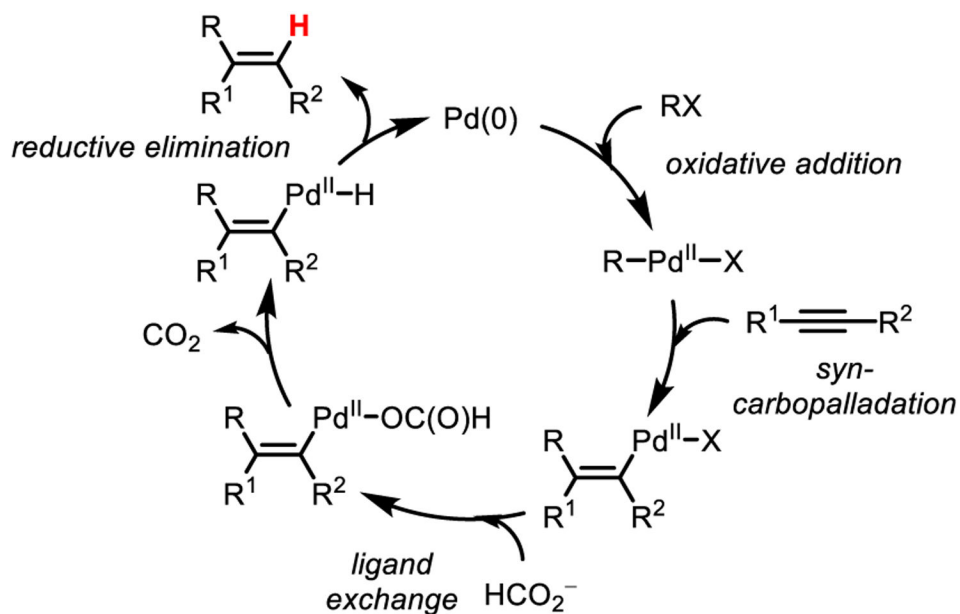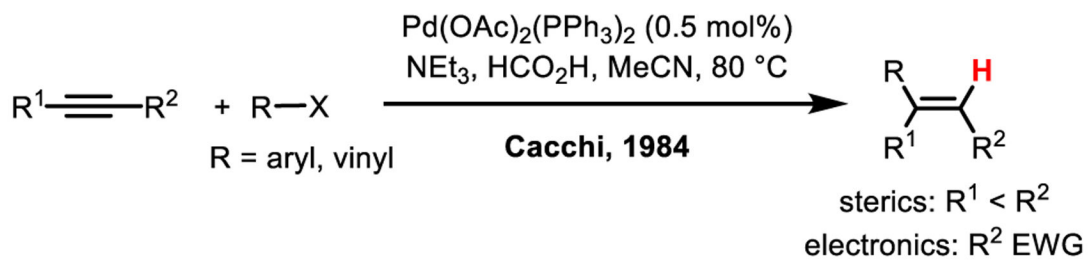
Scheme 6.
Cacchi *syn*-hydroarylation of alkynes via palladium-hydride intermediates.
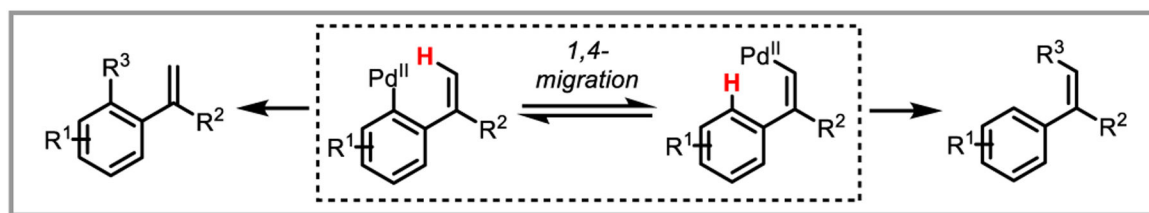
Scheme 7.
Aryl-vinyl palladium 1,4-migration.
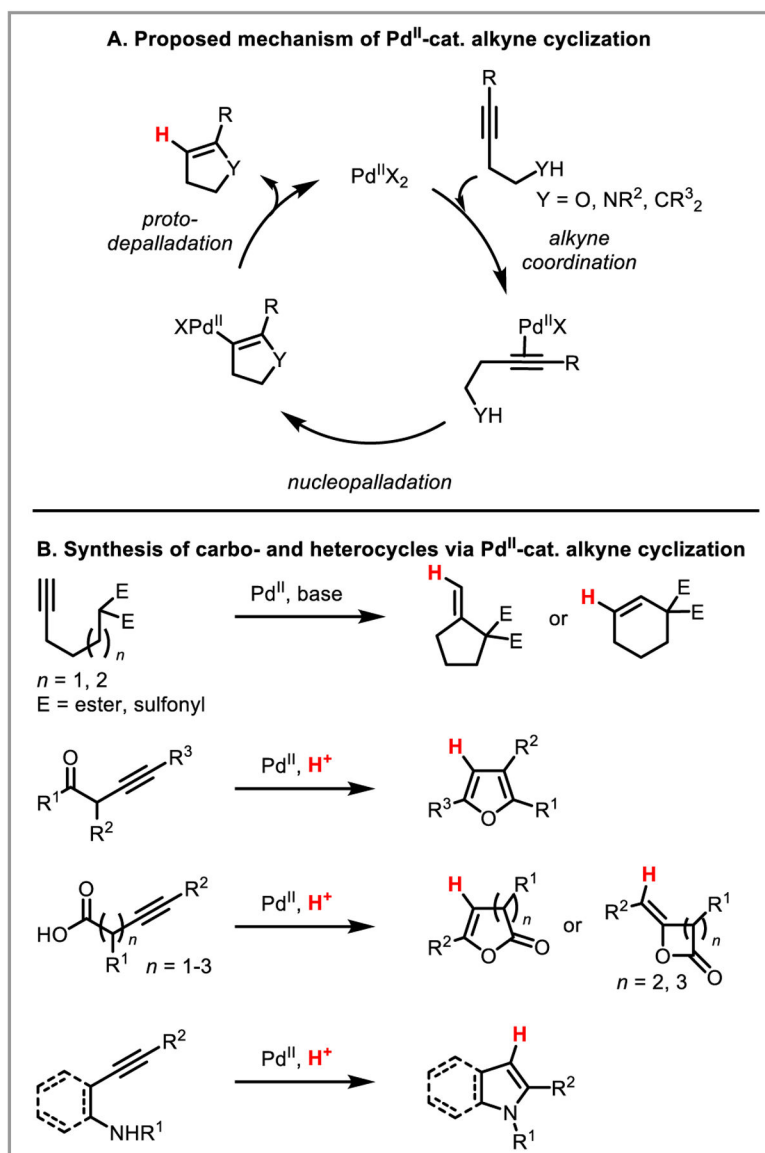
Scheme 8.
Synthesis of various carbo- and heterocycles via Pd^{II}-catalyzed alkyne cyclization.
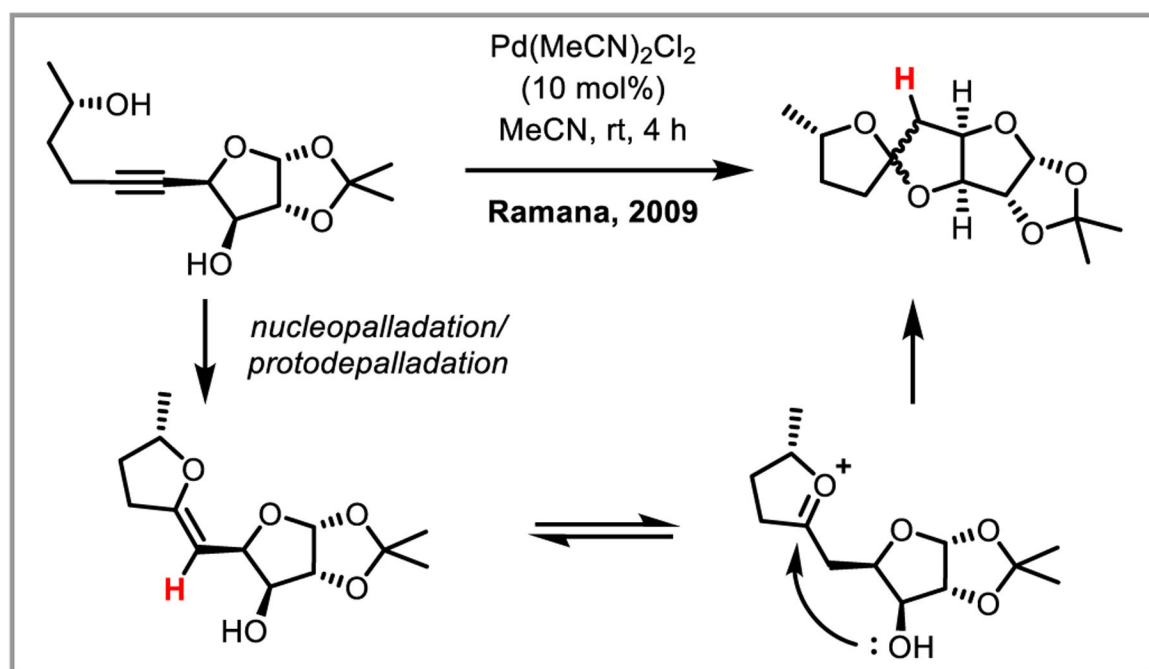
Scheme 9.
Spirocycle synthesis by Pd^{II}-catalyzed cycloisomerization.
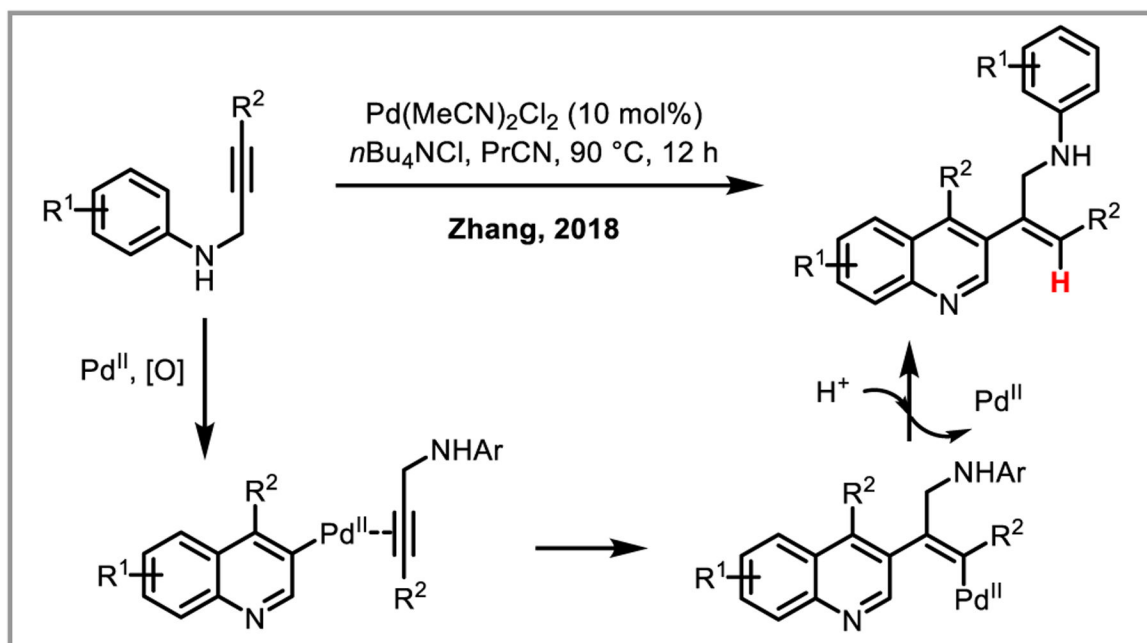
Scheme 10.
Pd^{II}-catalyzed dimerization of *N*-aryl propargylamines for the synthesis of quinolines.
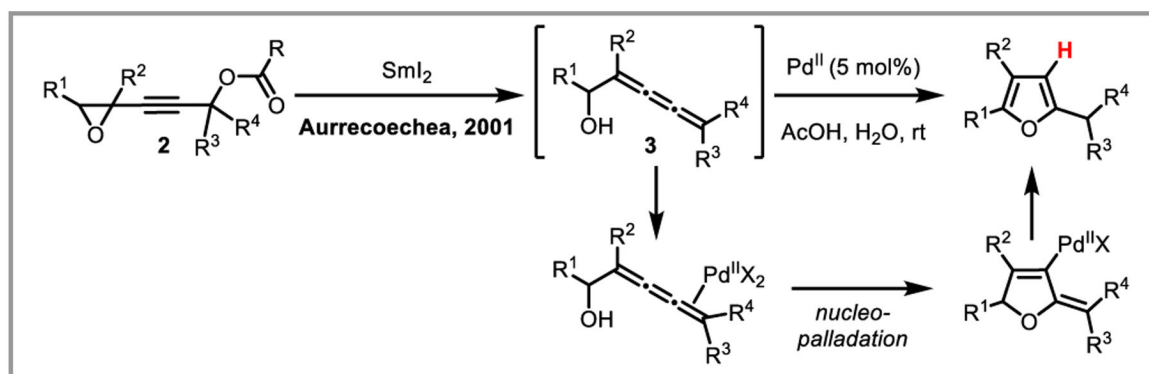
Scheme 11.
Synthesis of furans via Pd^II-catalyzed allene cyclization.
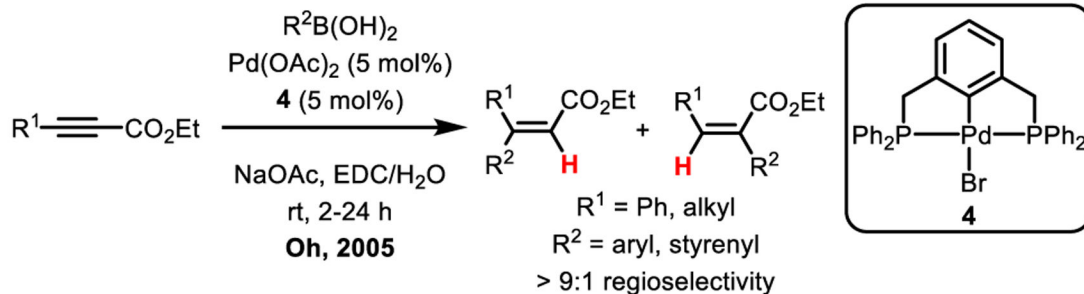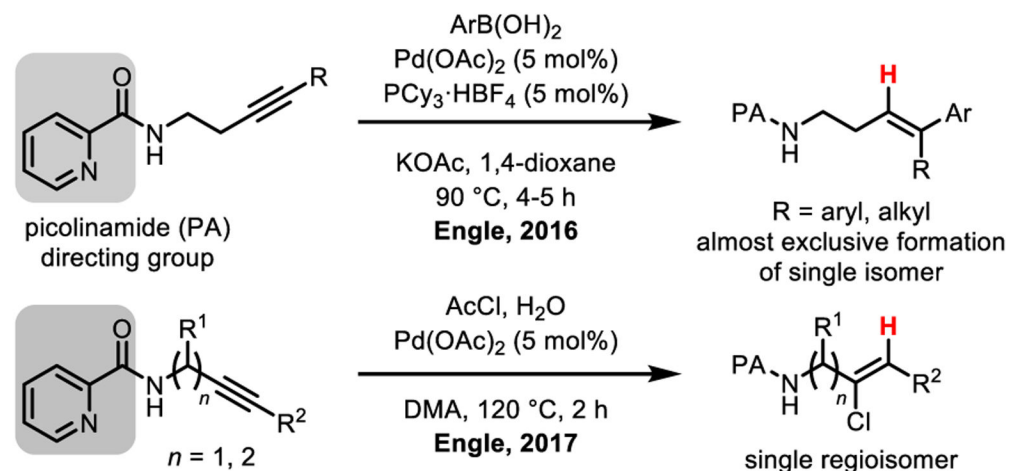
Scheme 12.
Regioselective *syn*-hydroarylation of alkynes.
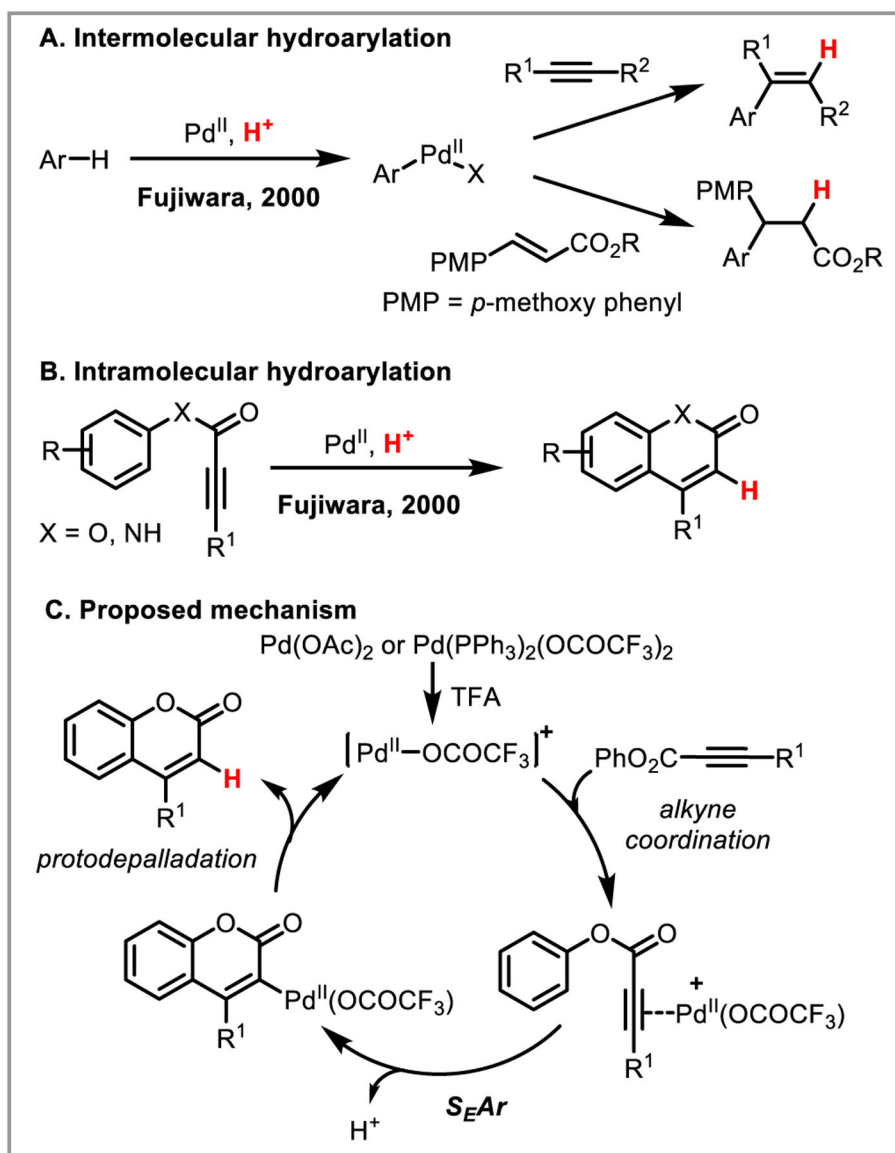
Scheme 13.
Fujiwara *trans*-hydroarylation of alkynes and alkenes.
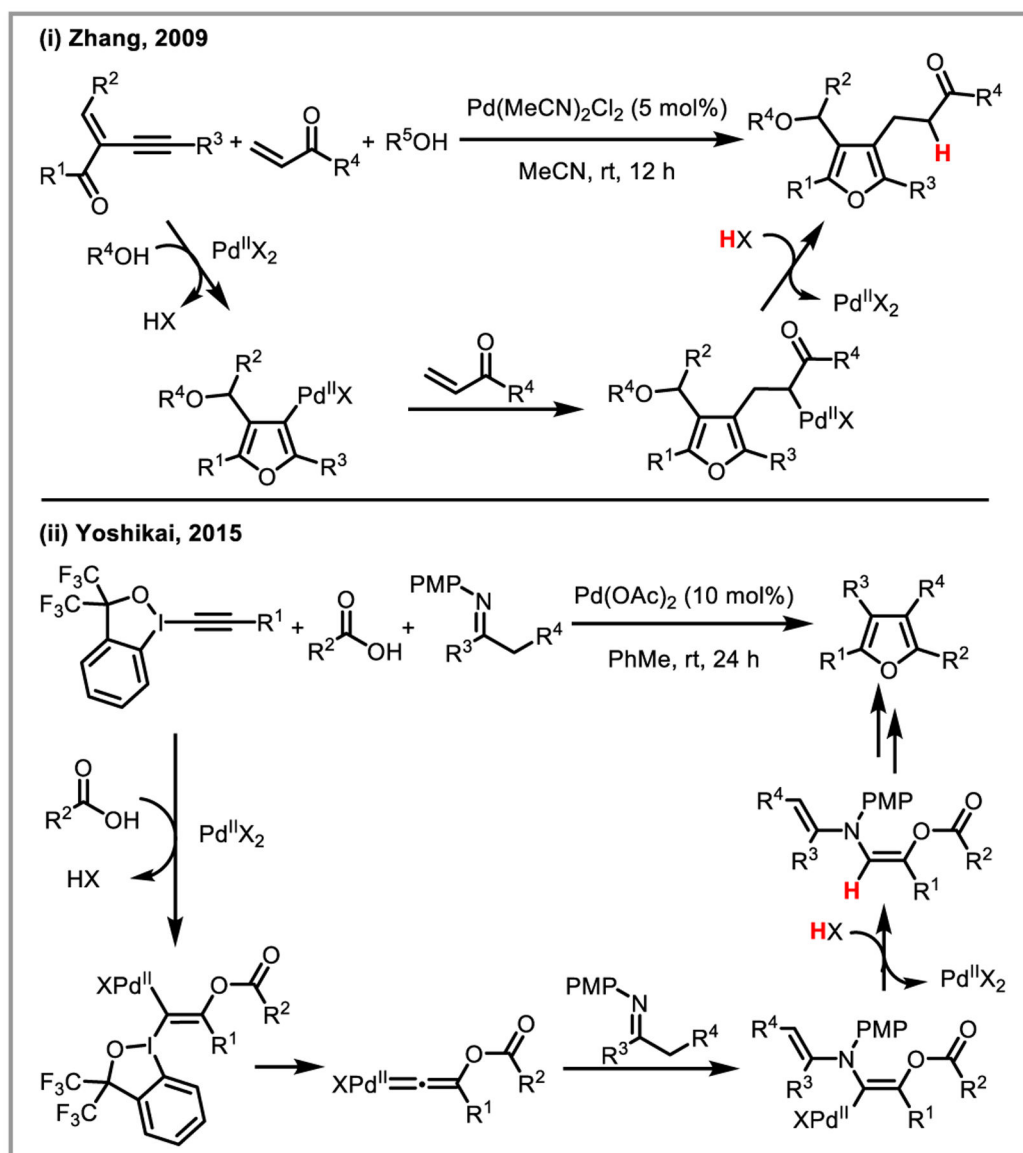
Scheme 14.
Pd^{II}-catalyzed three-component condensation for the synthesis of furans.
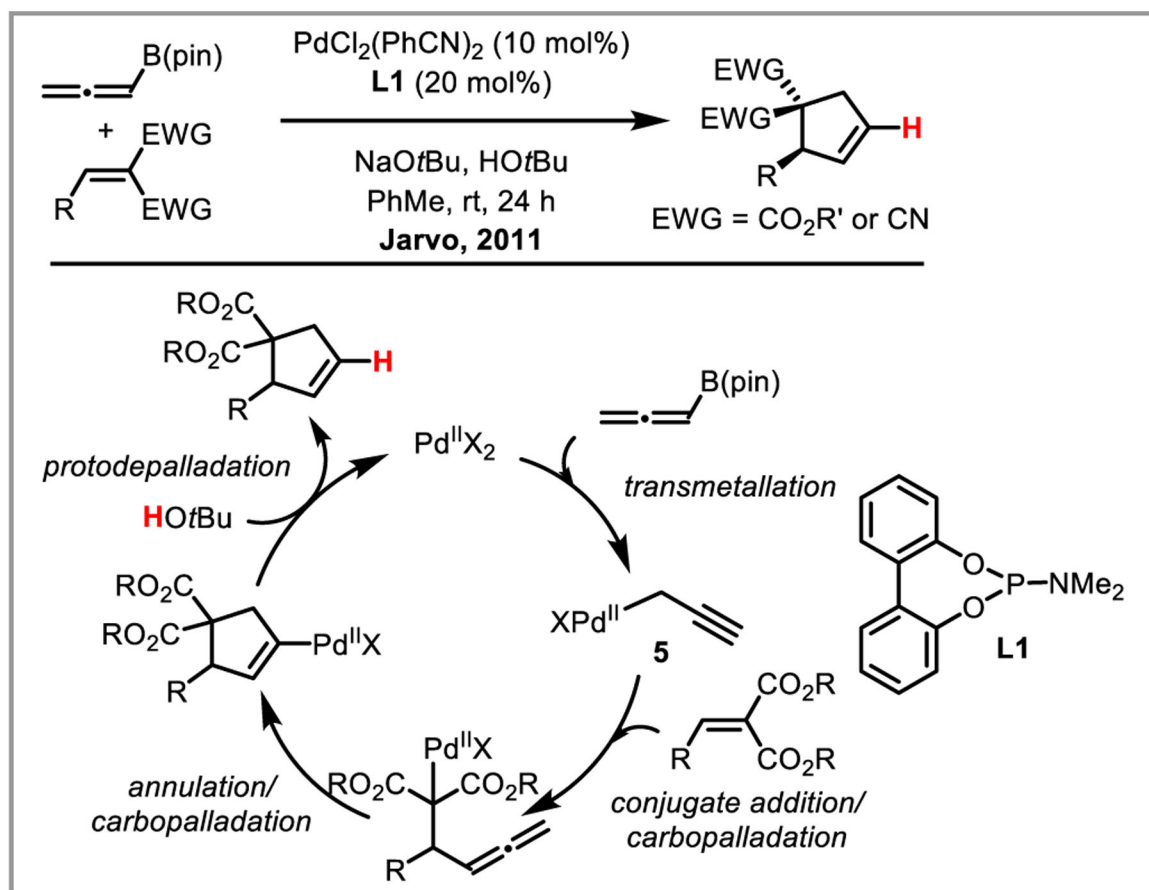
Scheme 15.
Pd^{II}-catalyzed diastereoselective cyclopentene synthesis.
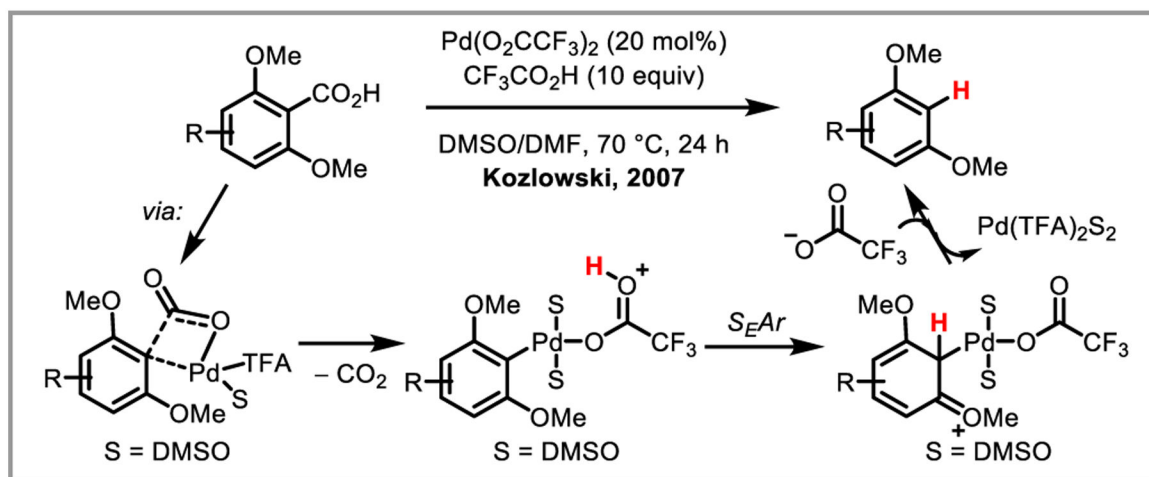
Scheme 16.
Palladium-catalyzed aromatic protodecarboxylation.
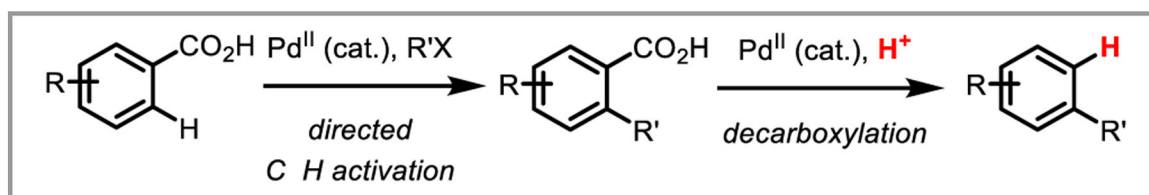
Scheme 17.
Carboxylic acids as traceless directing groups in Pd^{II}-catalyzed C-H activation.
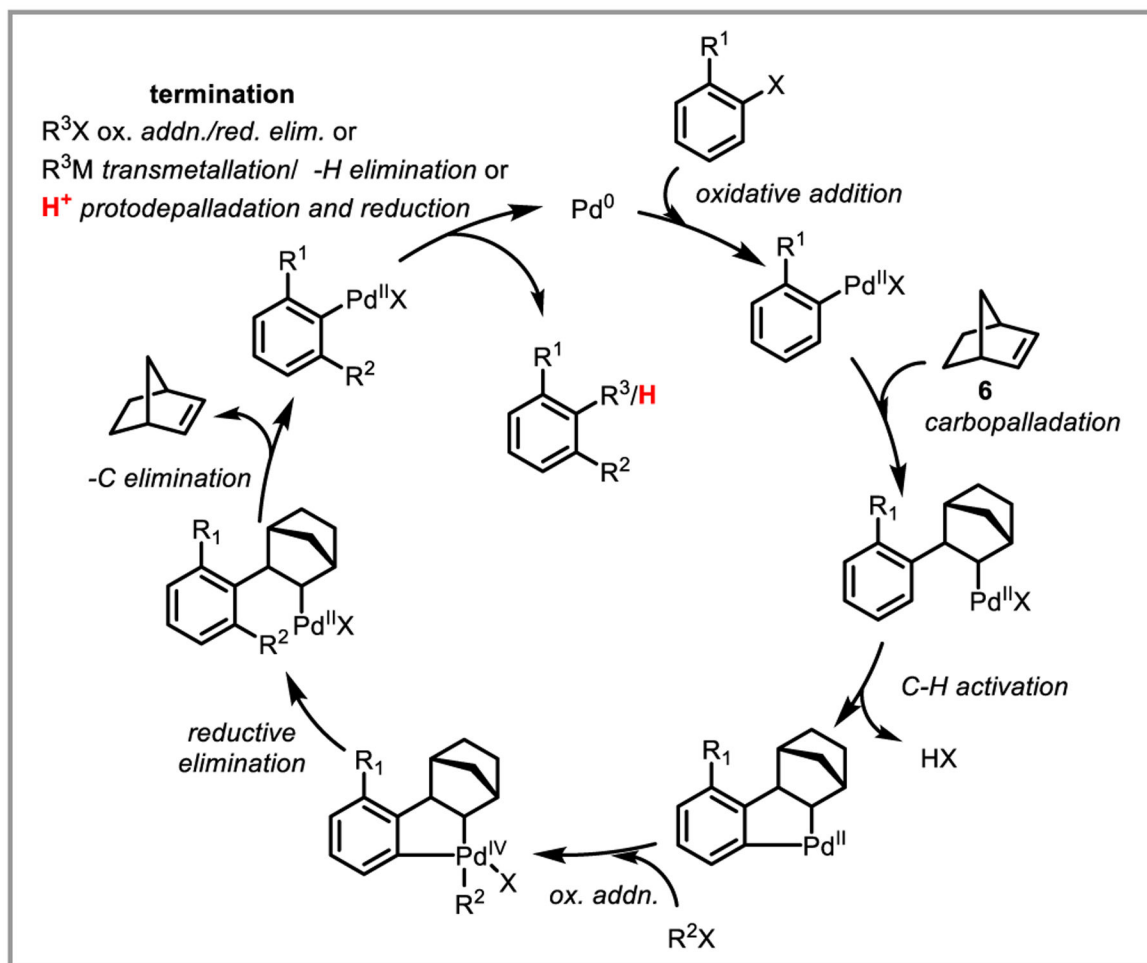
Scheme 18.
Mechanism of Catellani-type reactions.
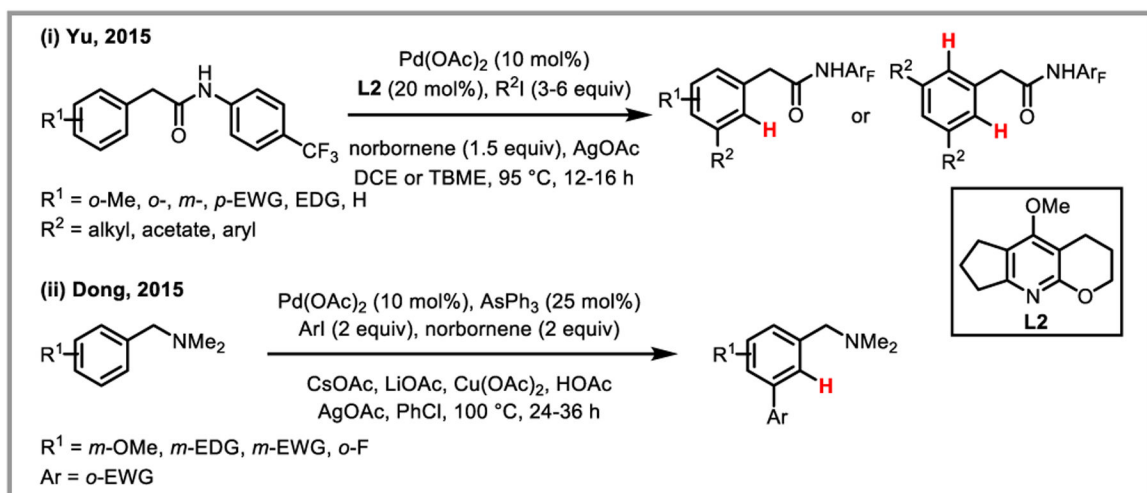
Scheme 19.
Directed, Catellani-type *meta*-C-H functionalization of arenes.
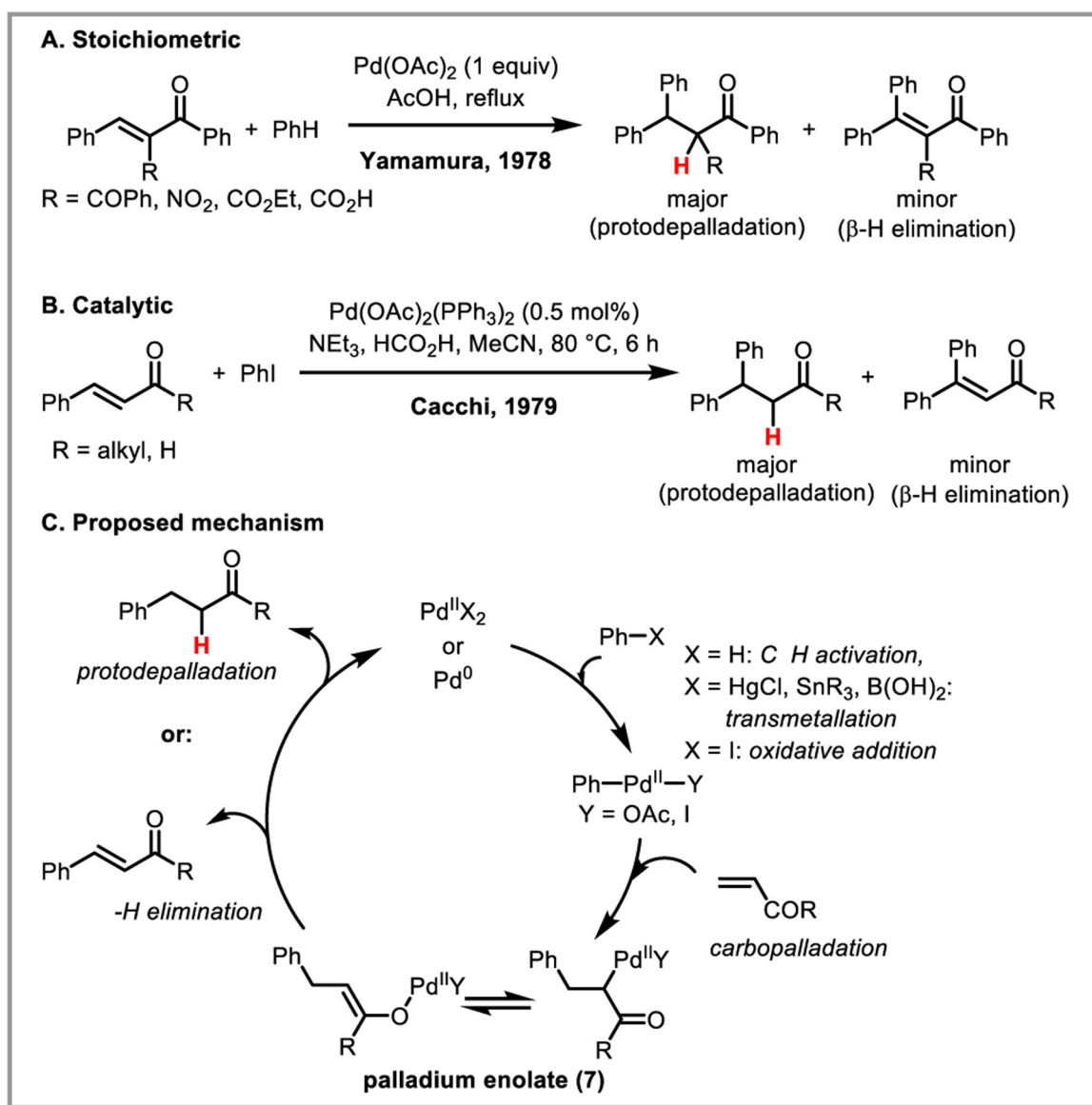
Scheme 20.
Pd^{II}-catalyzed conjugate addition of arenes to α,β-unsaturated ketones and aldehydes.
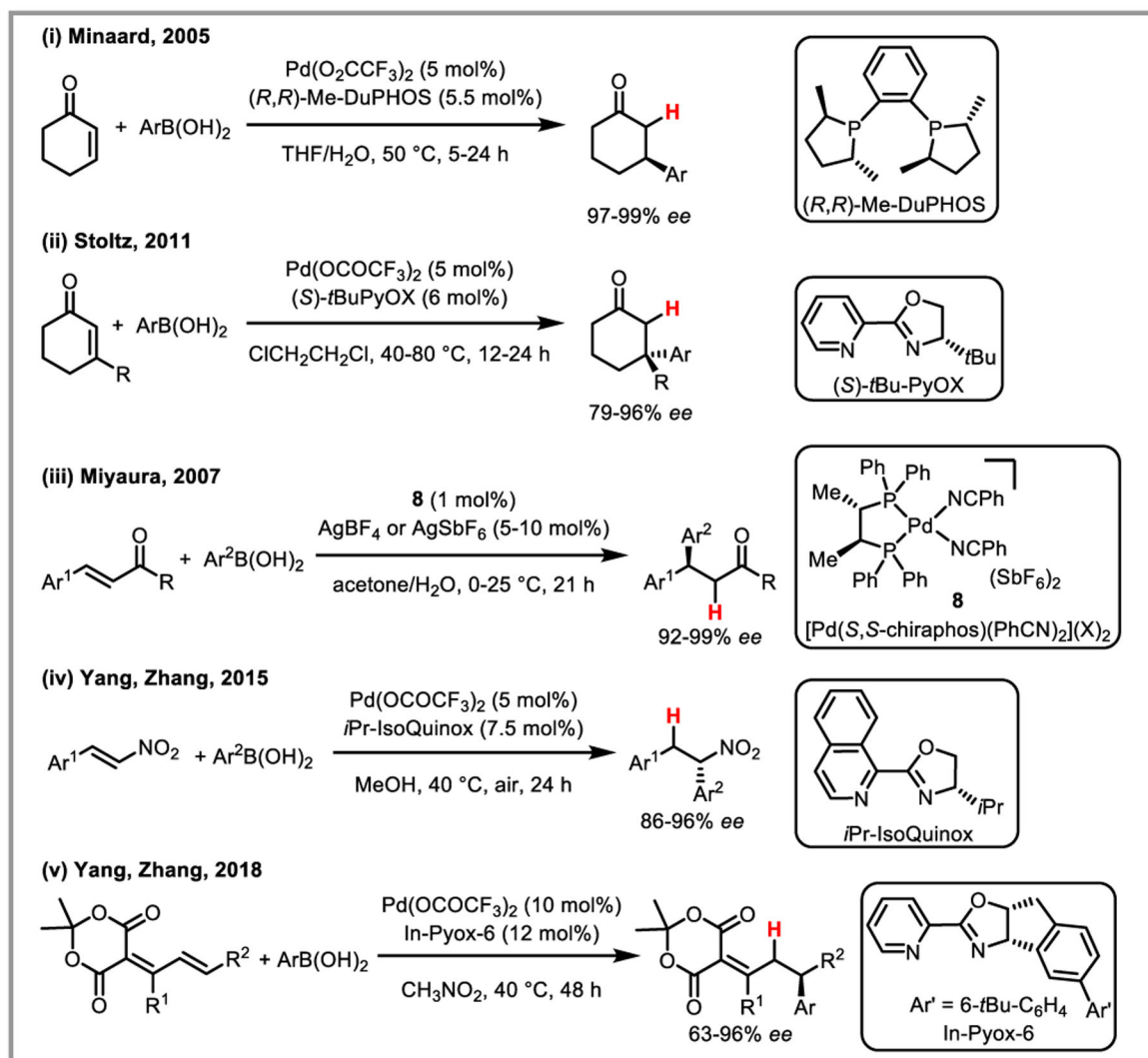
Scheme 21.
Enantioselective Pd^{II}-catalyzed conjugate addition of arylboronic acids.
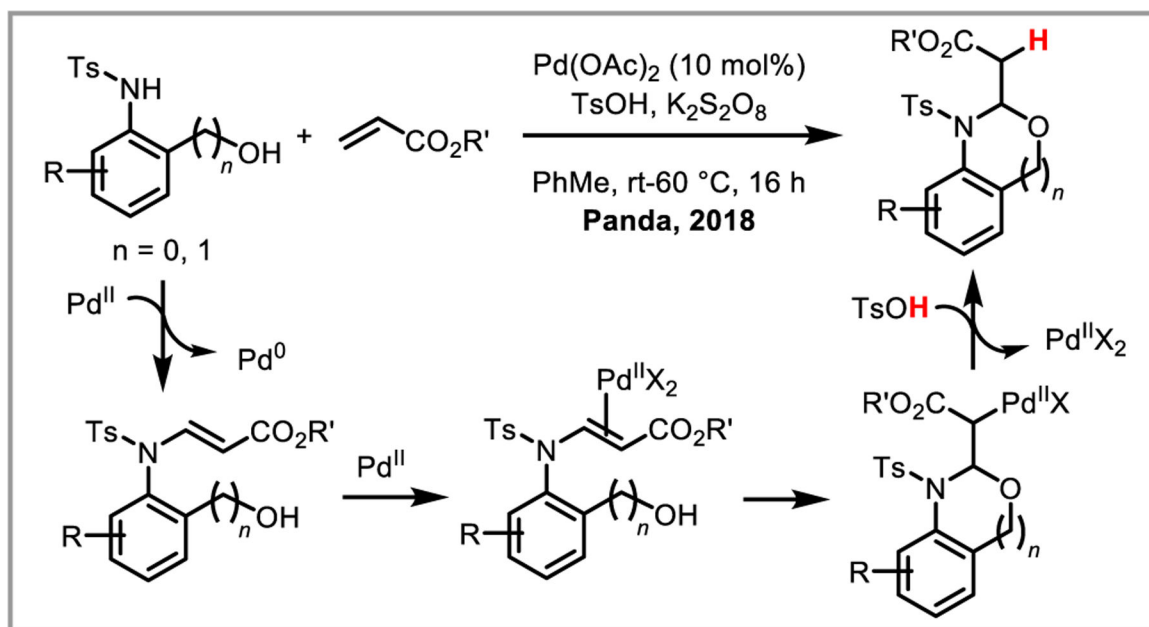
Scheme 22.
Benzoxazolidine synthesis via palladium enolate intermediates.
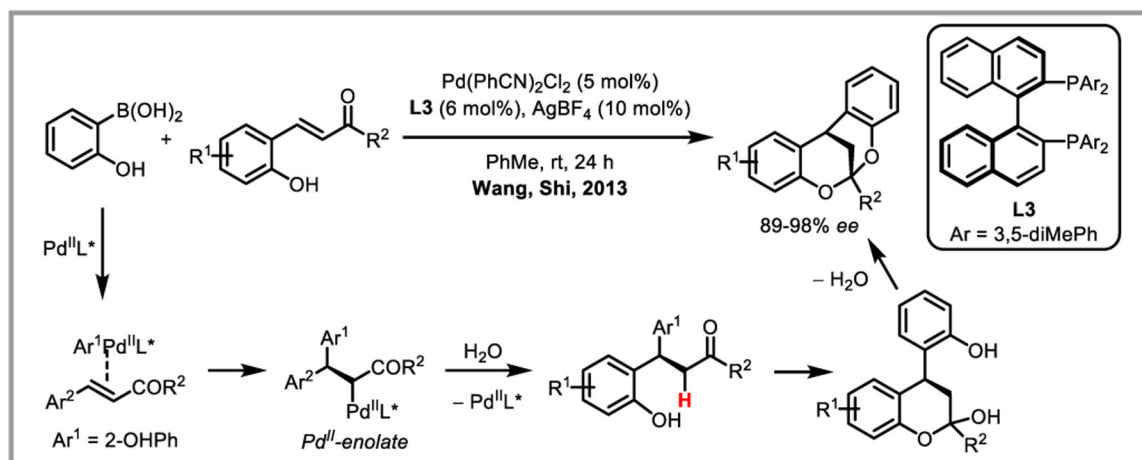
Scheme 23.
Pd(II) cascade for the synthesis of chiral [3.3.1]-bicyclic ketals.
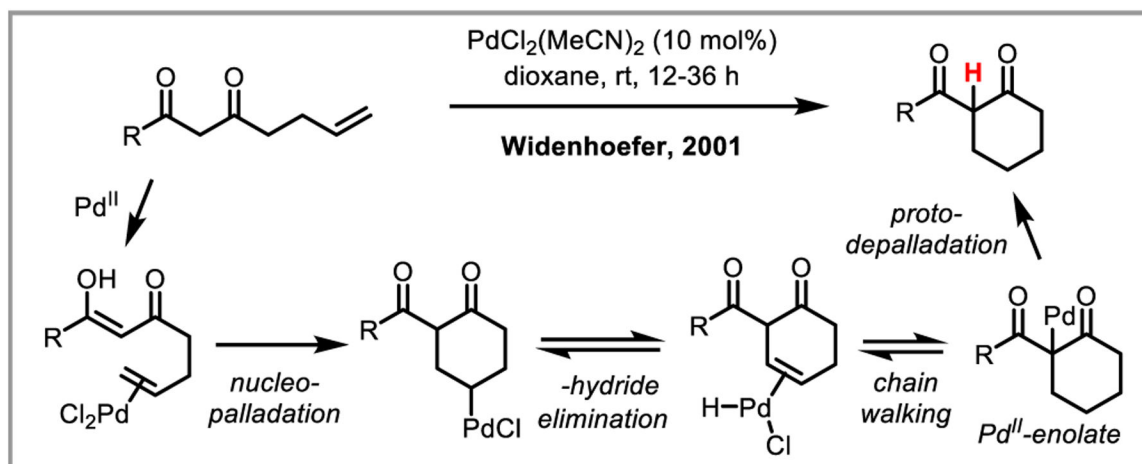
Scheme 24.
Intramolecular hydrocarbofunctionalization of unactivated alkenes.
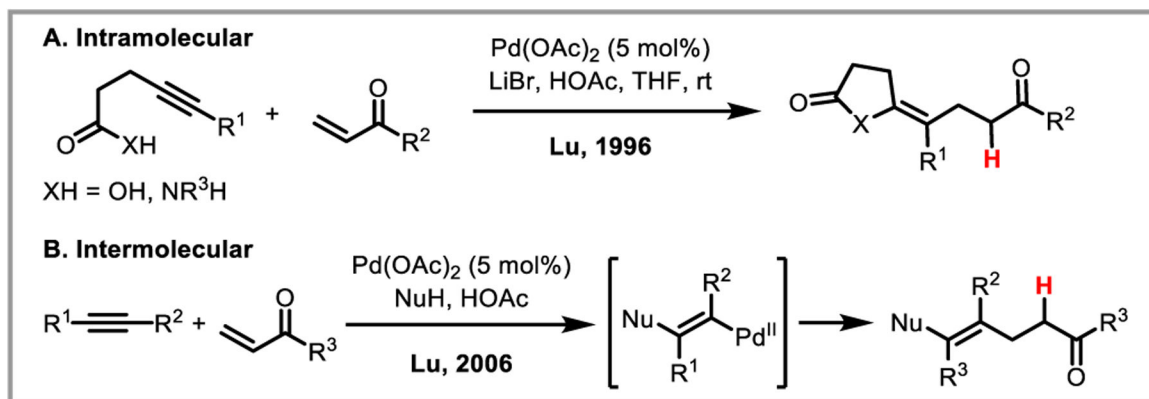
Scheme 25.
Tandem alkenylpalladium - palladium enolate chemistry.
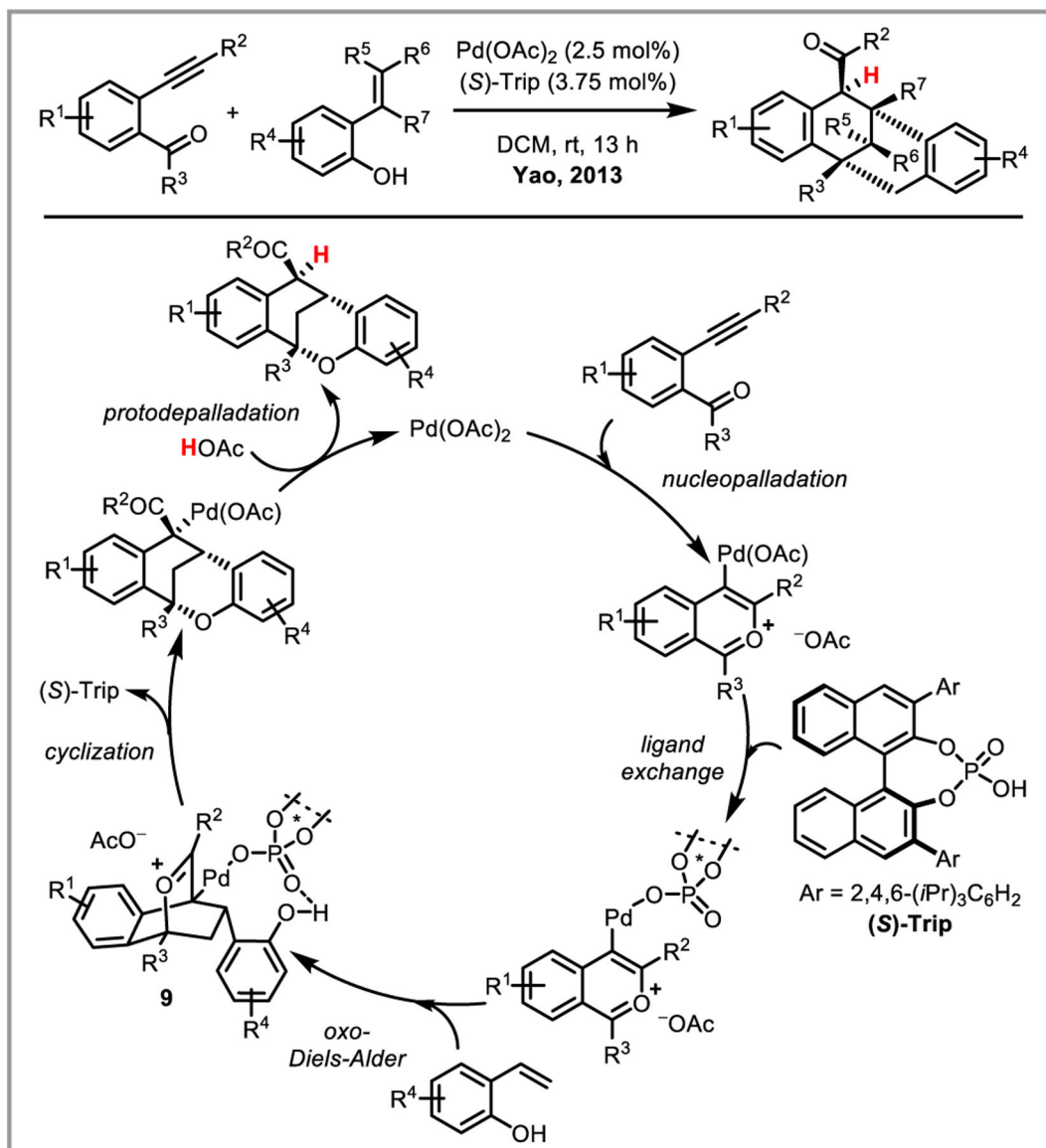
Scheme 26.
Cooperative Pd^{II}/chiral phosphoric acid catalysis.
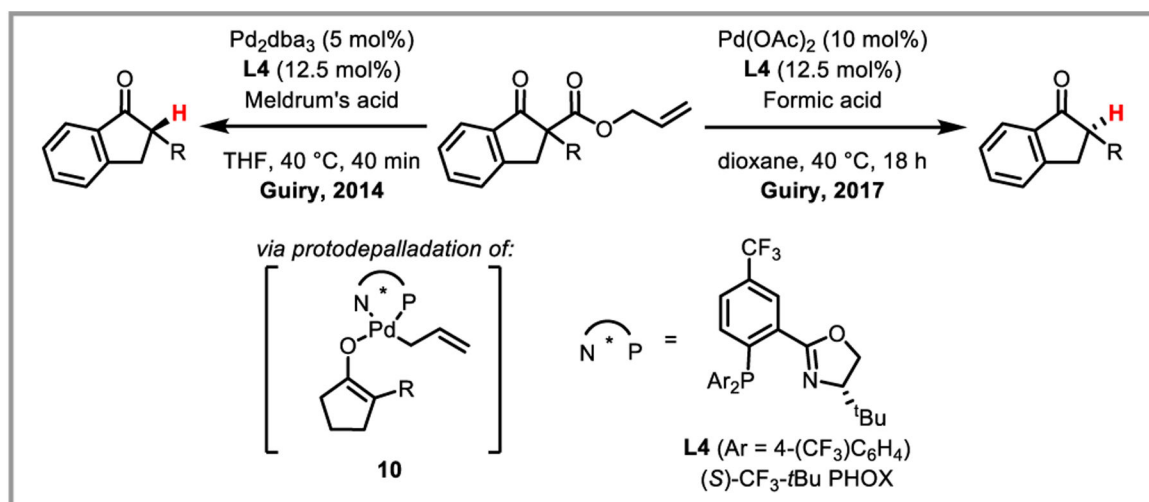
Scheme 27.
Enantioselective protodecarboxylation of cyclic ketones.
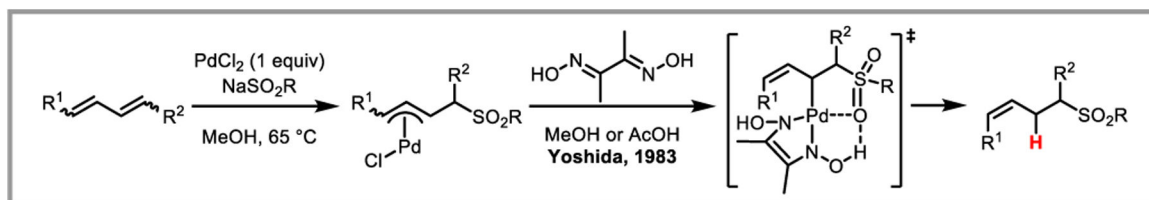
Scheme 87.
Hydrosulfonylation of conjugated dienes.
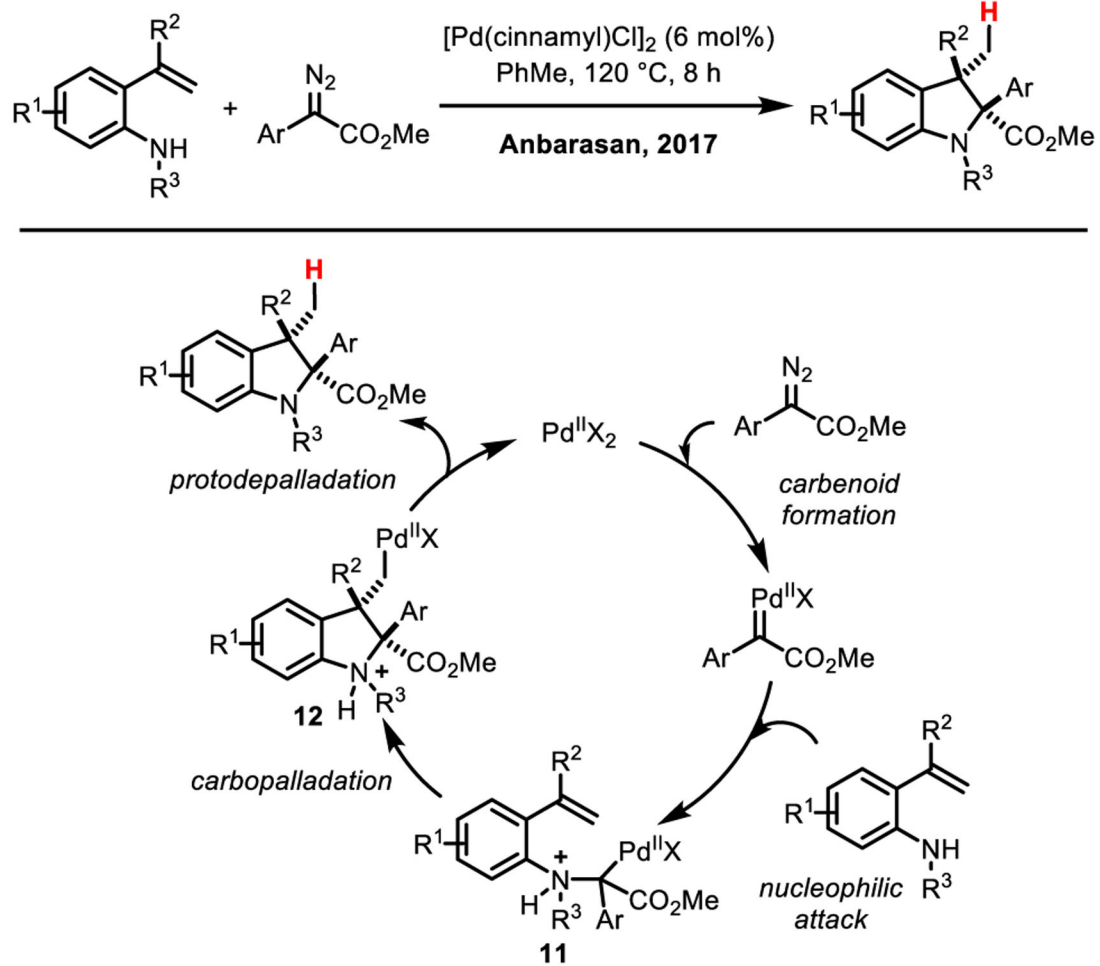
Scheme 29.
Indoline synthesis via palladium enolate chemistry.

Scheme 30.
Intramolecular hydroamination of alkenes.
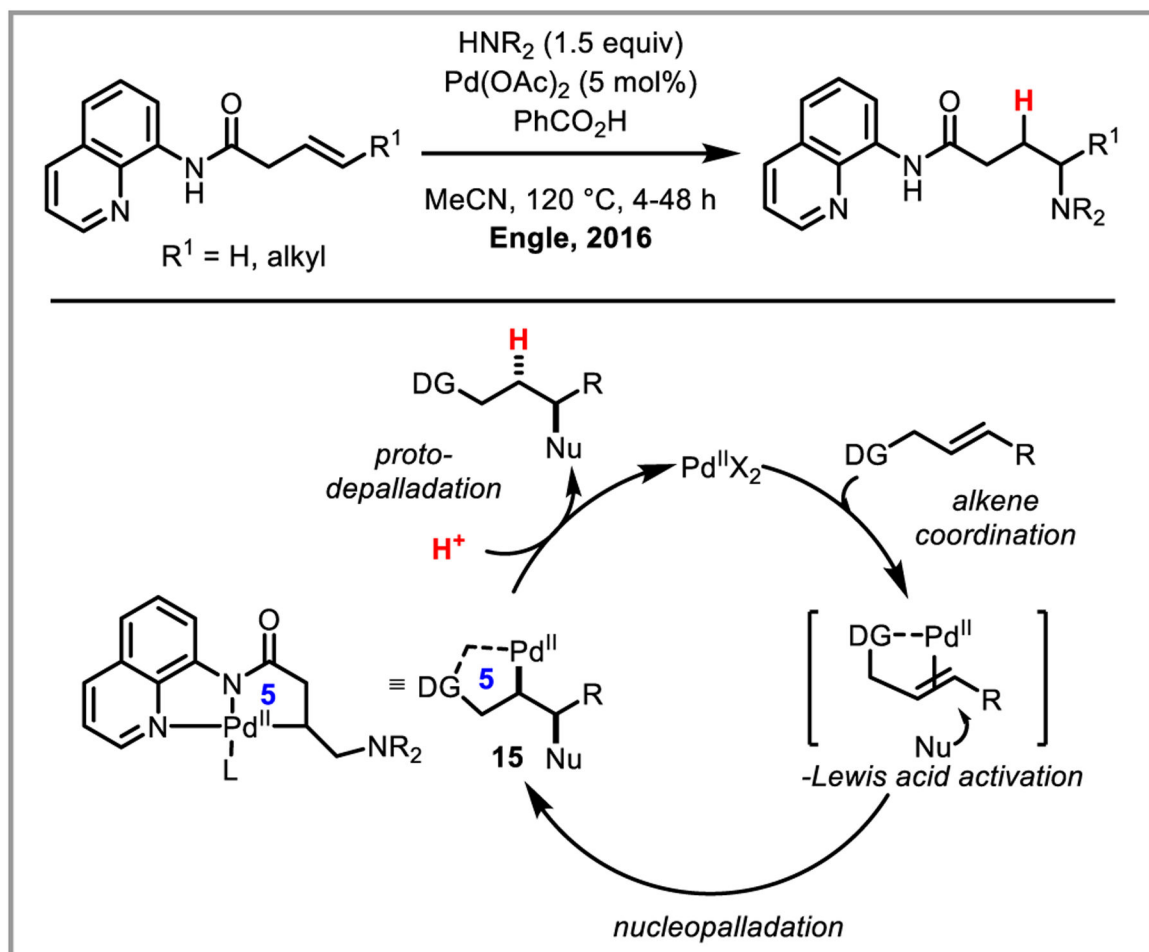
Scheme 31.
Intermolecular hydroamination of alkenes. (DG = directing group)
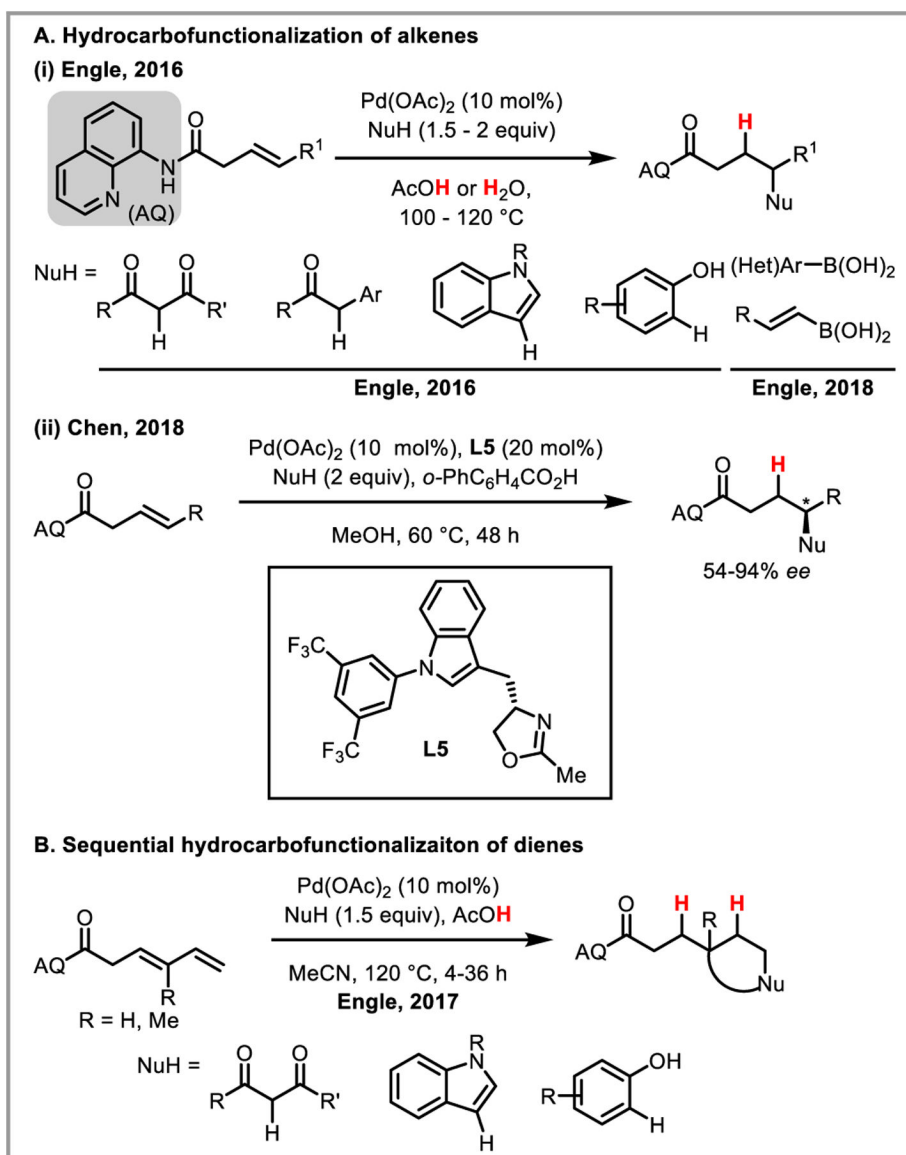
Scheme 32.
Hydrocarbofunctionalization of alkenes and conjugated dienes (AQ = 8-aminoquinoline).
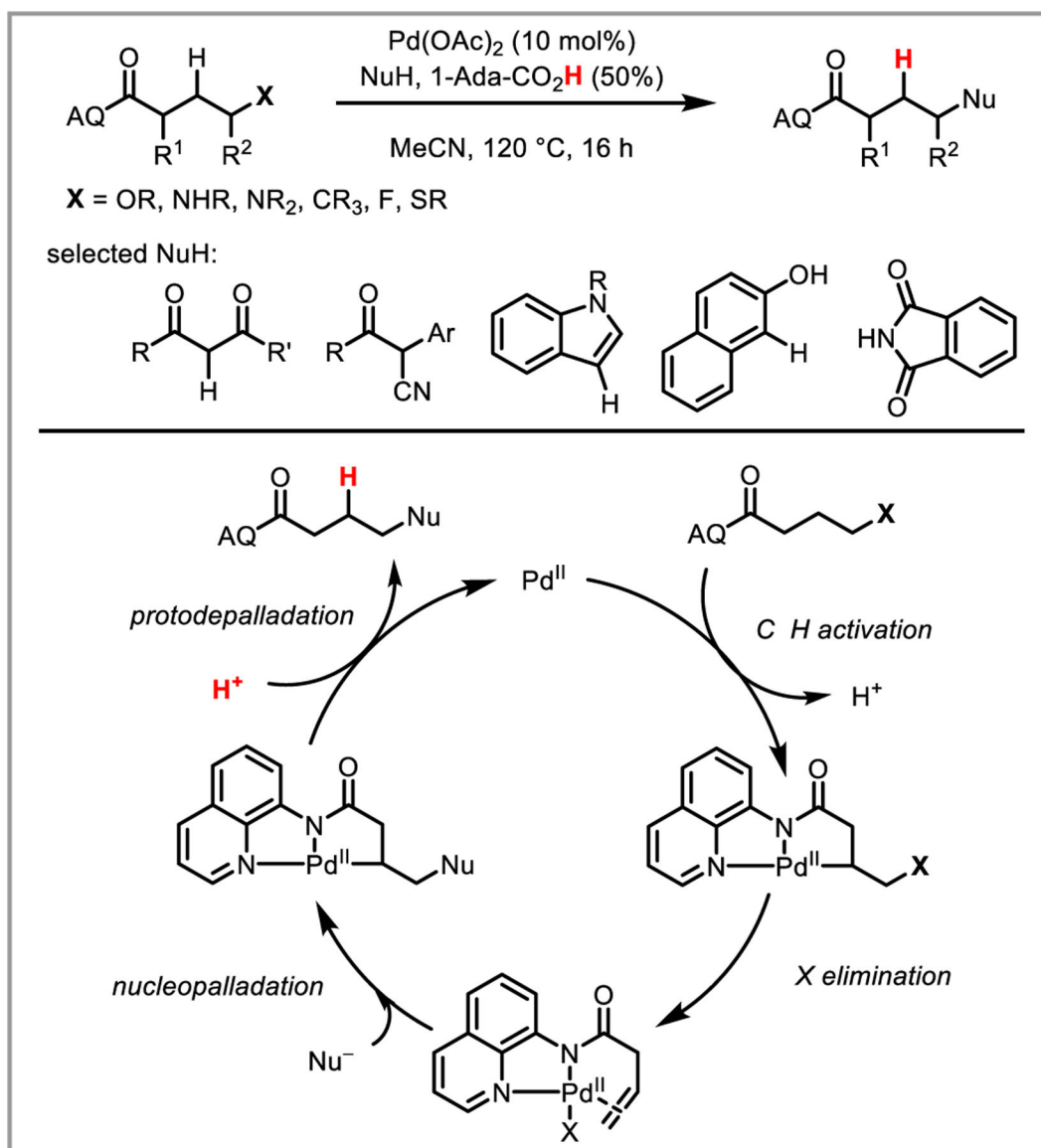
Scheme 33.
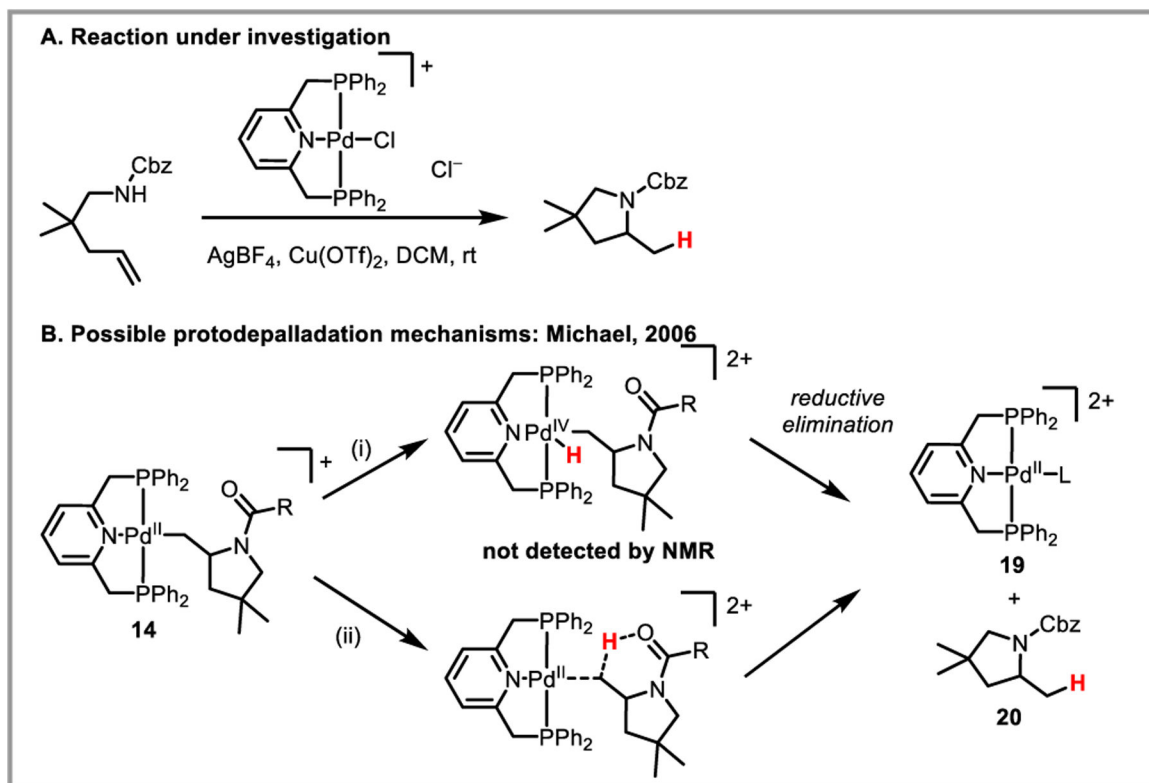Pd[II]-catalyzed C-X functionalization via β-X elimination.
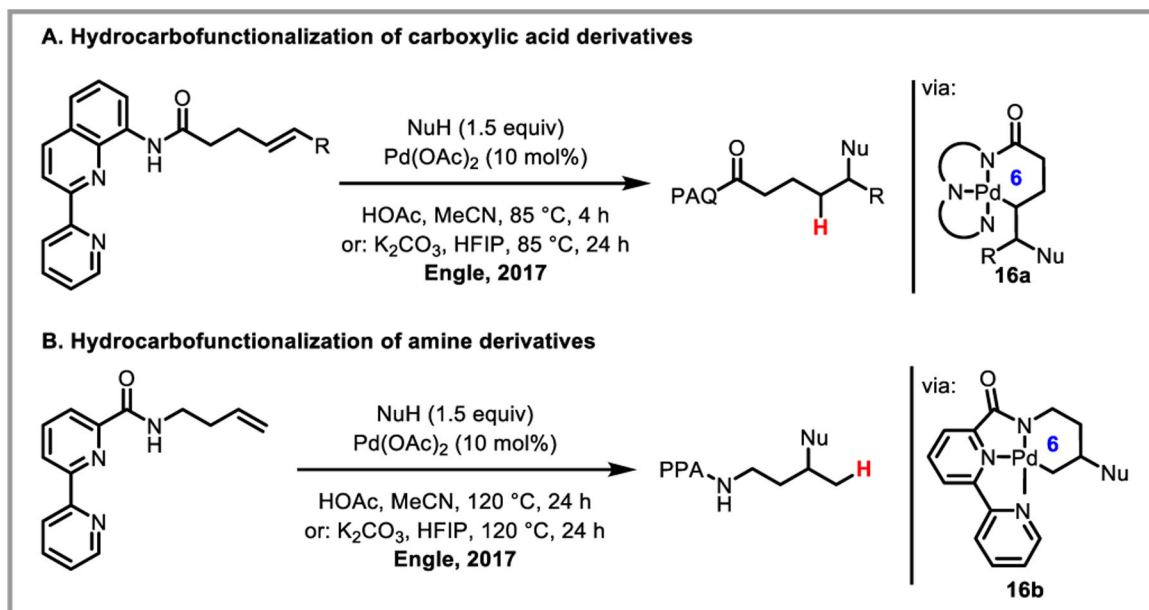
Scheme 34.
Tridentate directing groups for remote alkene hydrofunctionalization (PAQ = 2-pyridyl-8-aminoquinoline, PPA = 2,2'-bipyridylamide).
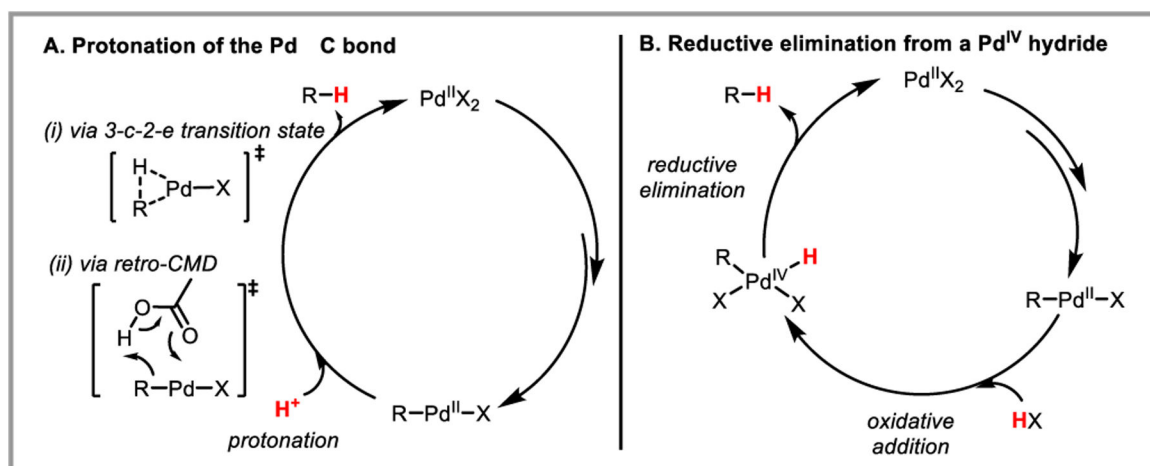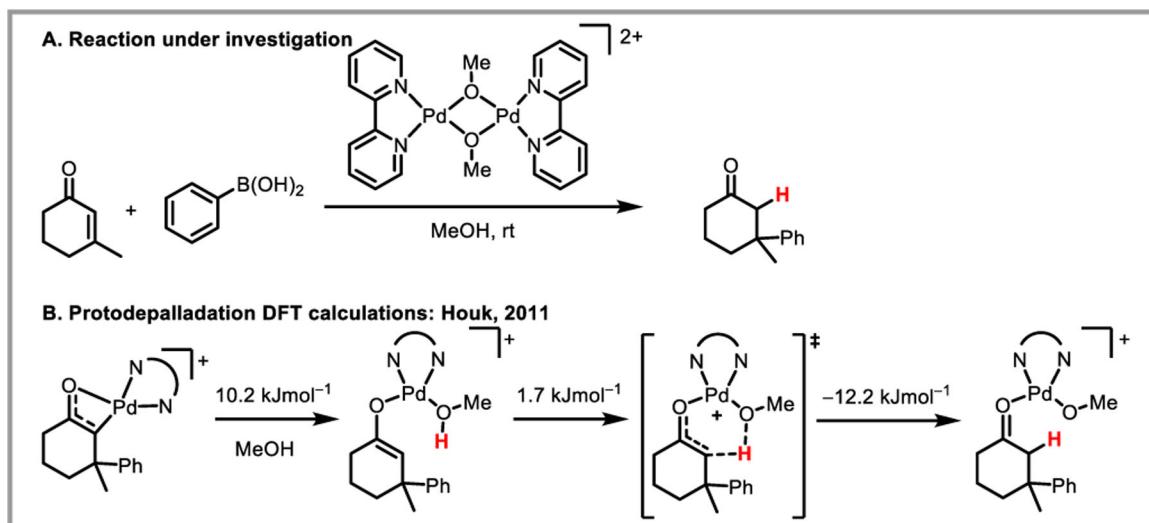
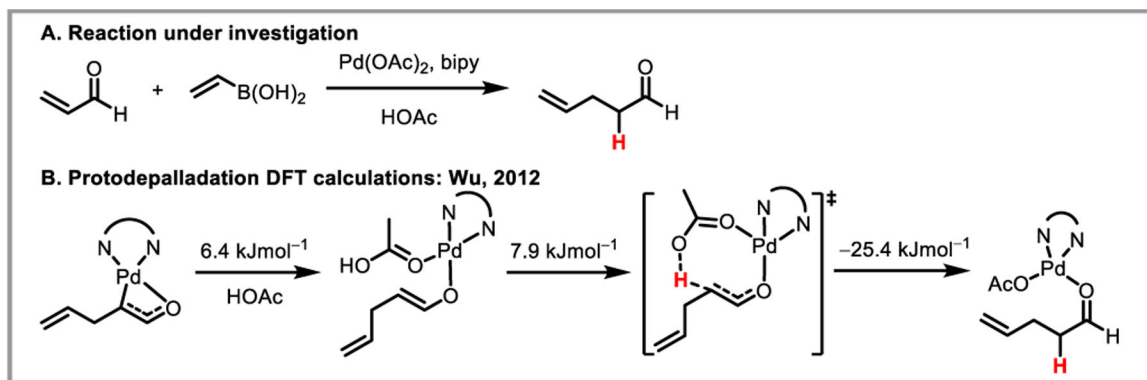**Scheme 35.**
Possible mechanisms of protodepalladation.
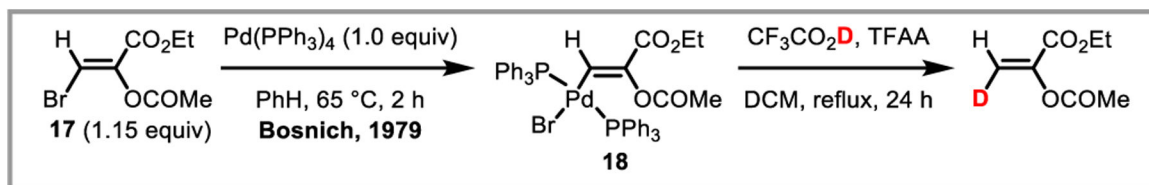
Scheme 36.
Stoichiometric, Pd-mediated deuteration of vinyl bromide **17**.
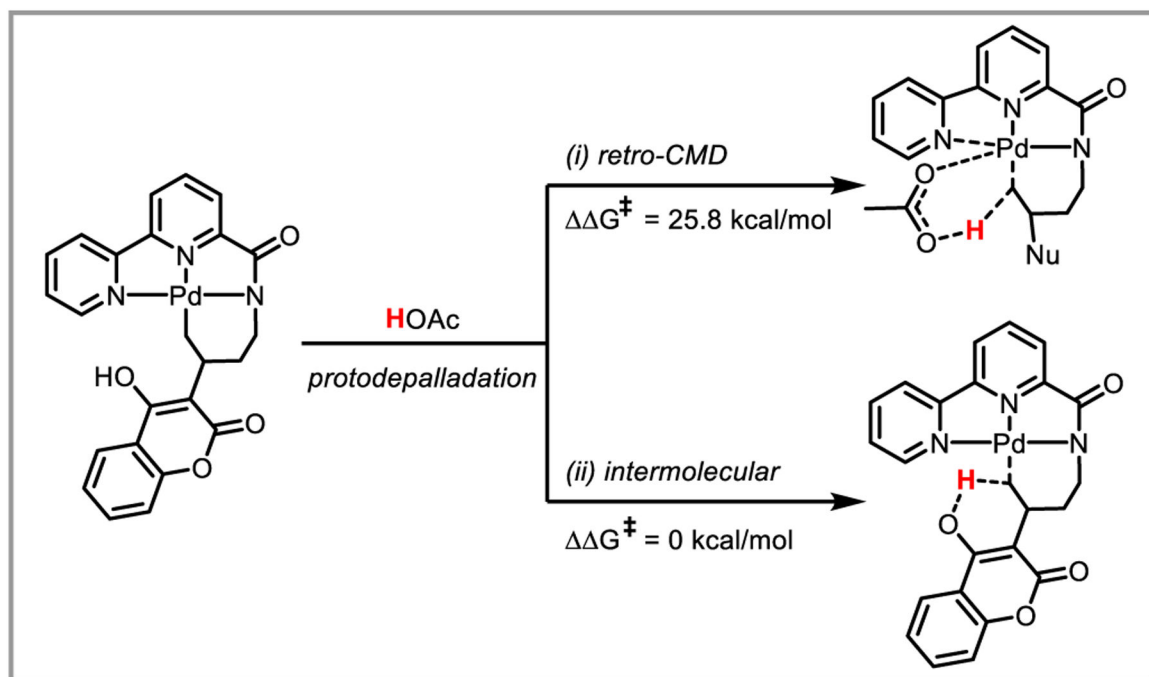
Scheme 37.
Prododepalladation via (i) palladium hydride vs. (ii) protonation by external acid.

Scheme 38.
Protodepalladation of palladium enolate complexes in methanol.

Scheme 39.
Protodepalladation of palladium enolate complexes in acetic acid.

Scheme 40.
DFT calculations: protodepalladation with tridentate directing groups.