Mechanistic approaches to palladium-catalyzed alkene difunctionalization reactions

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Alkene difunctionalization, the addition of two functional groups across a double bond, exemplifies a class of reactions with significant synthetic potential. This emerging area examines recent developments of palladium-catalyzed difunctionalization reactions, with a focus on mechanistic strategies that allow for functionalization of a common palladium alkyl intermediate.

Introduction

The Sharpless asymmetric dihydroxylation (eqn (1)) is the quintessential alkene difunctionalization reaction.[1] An argument can be made that this transformation and related variants are the only direct enantioselective alkene difunctionalization reactions currently used extensively in synthesis. Considering the accessibility of alkenes and their robust nature, there is clearly a need to develop new catalytic difunctionalization reactions that add two functional groups across alkenes in a regio- and stereocontrolled manner beyond that of the asymmetric dihydroxylation. This emerging area describes recent contributions to this important class of reactions. Due to the diverse mechanistic manifolds at play and the recent activity in the field, Pd-catalyzed reactions will be highlighted. It should be noted that only reactions that add two functional groups across alkenes will be described and the focus will be on selected contributions of the last several years. Therefore, a significant body of work in hydrofunctionalization (only one functional group) and alkoxycarbonylation reactions (developed over the last several decades mainly by Semmelhack) will be excluded.

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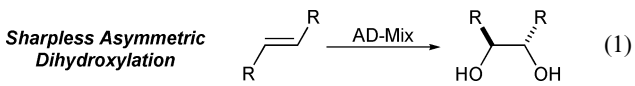

(1)

A reason to use Pd in alkene difunctionalization reactions is the ease with which Pd(II) facilitates the addition of nucleophiles to alkenes (Fig. 1). However, the main issue arises in the formation of the resultant Pd alkyl, which generally undergoes rapid β-hydride elimination to yield Wacker-type products. While these processes are clearly useful, they generally only lead to functionalization at one of the two alkene carbons. Therefore, to pursue alkene difunctionalization, the key question is how does one modify the system to allow for an increased rate of Pd alkyl functionalization as compared to the rate of β-hydride elimination? This can be accomplished by using substrates containing a functional group

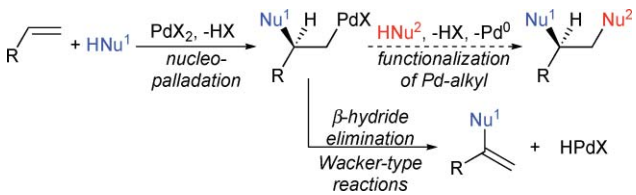

Fig. 1 Mechanistic possibilities for Pd-alkyl intermediates.

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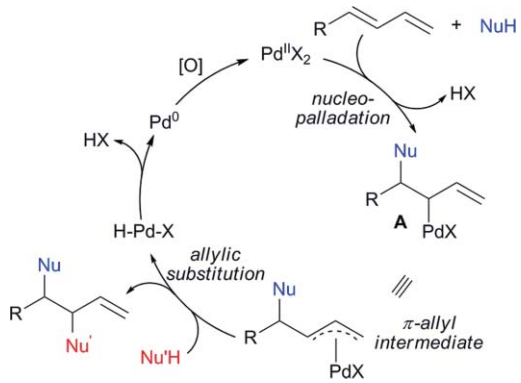
to stabilize the Pd alkyl, or by promoting a rapid step to transform the Pd alkyl into an intermediate that can be functionalized.

Nucleopalladation of dienes

The classic approach to Pd-catalyzed difunctionalization reactions of alkenes, developed by Bäckvall, is to use dienes as substrates.[2] In this case, the Pd alkyl formed upon initial nucleopalladation contains an adjacent alkene, and thus can form a π-allyl intermediate (**A**, Scheme 1). The π–allyl interaction stabilizes the intermediate and slows β-hydride elimination, while increasing the electrophilicity of the complex, allowing for attack by a second nucleophile. Examples of this approach are vast and include diacetoxylation, amino-acetoxylation, and amino-halogenation reactions.[2]



Scheme 1 Proposed mechanism for Pd-catalyzed diene difunctionalization.

Recent advances in palladium difunctionaliztion of dienes include a diamination variant reported by Lloyd-Jones and Booker-Milburn (Fig. 2).[3] The authors choose to utilize *N,N′*-diethyl urea (**1**) as a nitrogen nucleophile to attenuate the Lewis basicity of the nitrogen relative to amines, making it less likely to bind palladium and inhibit catalysis. Further, tethering the nitrogen source renders the second nucleophilic attack intramolecular. High chemoselectivity for diamination of the terminal olefin is observed.

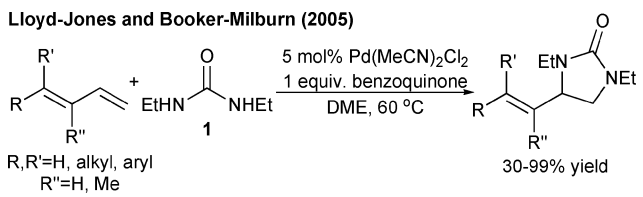
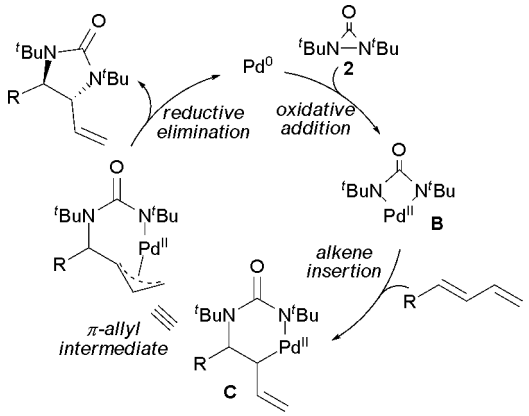


Fig. 2 Pd-catalyzed diamination of terminal dienes.

Oxidative addition–diene insertion

Another method of diene diamination has been developed by Shi and coworkers.[4] This variant is distinct from the remainder of the work discussed in this paper in that Pd^0 initiates the catalytic cycle, and the nitrogen source, di-*tert*-butyldiaziridinone (**2**), functions as the oxidant. The mechanism is believed to involve an initial oxidative addition of **2** to Pd^0, followed by alkene insertion to reach a palladium-π-allyl intermediate **C**, which proceeds similarly to other diene difunctionalization reactions (Scheme 2).



Scheme 2 Proposed mechanism for Pd-catalyzed diene difunctionalization reaction with diaziridinones.

This reaction has been successfully rendered enantioselective using chiral phosphoramidite ligands, with generally high enantioselectivity (Fig. 3, A).[5,6] An additional advancement includes the ability to expand this reaction to terminal olefins through the *in situ* formation of dienes (Fig. 3, B).[7,8] The Shi process is complementary to the Lloyd-Jones–Booker-Milburn reaction[3] in that the internal alkene is selectively diaminated.

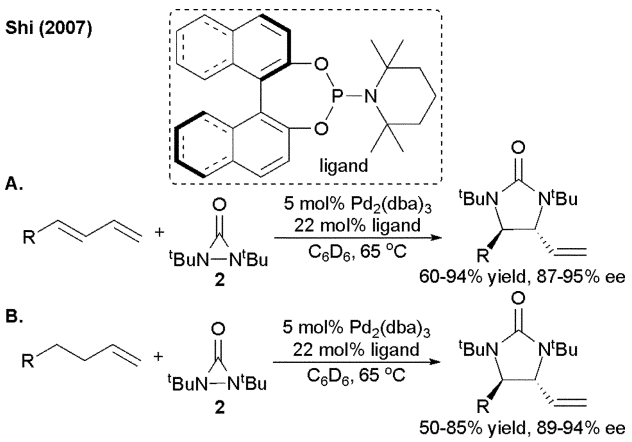
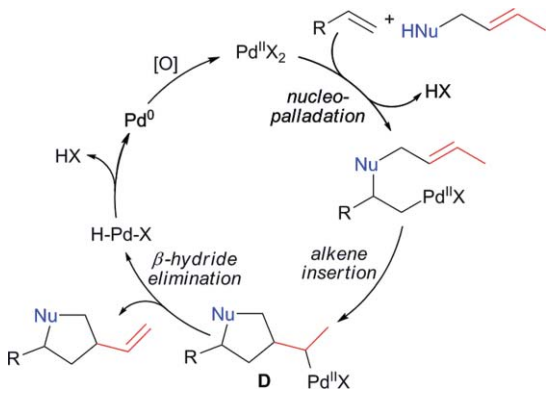


Fig. 3 Pd-catalyzed asymmetric diamination of dienes and alkenes.

Nucleopalladation–alkene insertion

If the substrate is not a diene, and thus does not have the enhanced electrophilicity of a palladium-π-allyl, the Pd alkyl intermediate must be intercepted in some other fashion. One approach is *via* insertion of a second alkene into the Pd–C bond (intermediate **D**). Following alkene insertion, β-hydride elimination occurs to release the product (Scheme 3). Such a sequence results in an overall oxygen/carbon or nitrogen/carbon alkene difunctionalization.

An example of an intramolecular version of oxypalladation–alkene insertion was developed by Sasai and coworkers, producing bicyclic ether **4** in one step from **3** (Fig. 4).[9] Moreover, the use of a chiral bis(isoxazoline) ligand **5** renders the reaction asymmetric, providing the product in 89% enantiomeric excess. A similar



Scheme 3 Proposed mechanism for Pd-catalyzed difunctionalization reactions involving nucleopalladation–alkene insertion.

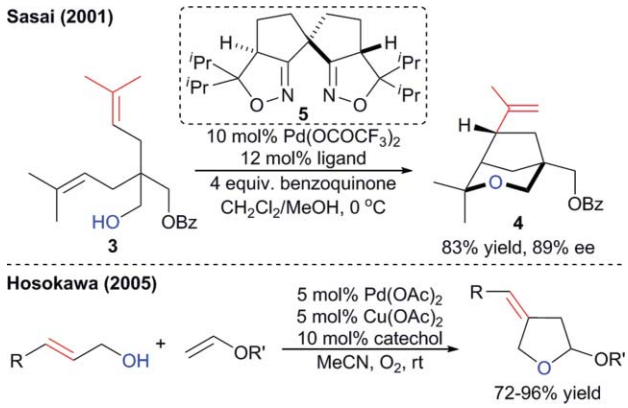


Fig. 4 Pd-catalyzed difunctionalizations involving oxypalladation–alkene insertion.

reaction involving an initial intermolecular oxypalladation of an enol ether, followed by alkene insertion and β-hydride elimination, was reported by Hosokawa and coworkers (Fig. 4).[10,11] Allylic alcohols provide both the oxygen and carbon nucleophiles in these reactions.

Yang and coworkers reported an intramolecular carbon/nitrogen alkene difunctionalization (Fig. 5), likely occuring through the above mentioned mechanism.[12] Substrates of type **6** include mono-, di-, or trisubstituted alkenes. Using (–)-sparteine (**8**) as a chiral ligand, an enantioselective variant was developed, with ee's as high as 91%. Stahl and Scarborough reported the intermolecular carboamination of vinyl ethers and styrenes.[13] Mono-, di-, and trisubstituted allylic tosylamides of type **9** are used as substrates that include both the nitrogen and carbon nucleophiles. The diastereoselectivity of the reaction ranges from 1.3 : 1 to 2.4 : 1.

Nucleopalladation of *ortho*-vinyl phenols

The palladium-catalyzed dioxygenation of *ortho*-vinyl phenols was reported by Le Bras, Muzart,[14] and coworkers, and shortly thereafter by Sigman and Schultz (Fig. 6).[15] While the two reports differ in reaction conditions and product, both result in the addition of two oxygen nucleophiles across an alkene, and both require the *ortho*-phenol functionality.

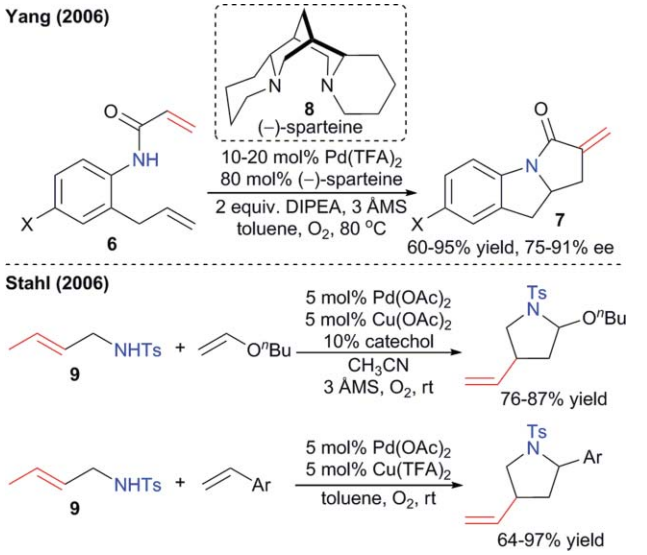


Fig. 5 Pd-catalyzed difunctionalization reactions involving aminopalladation–alkene insertion.

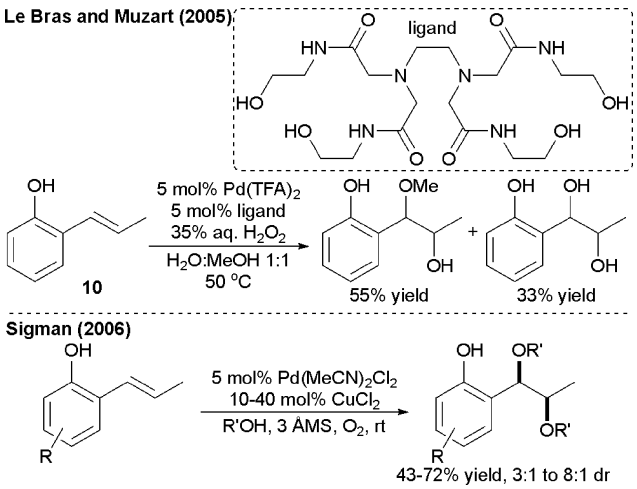
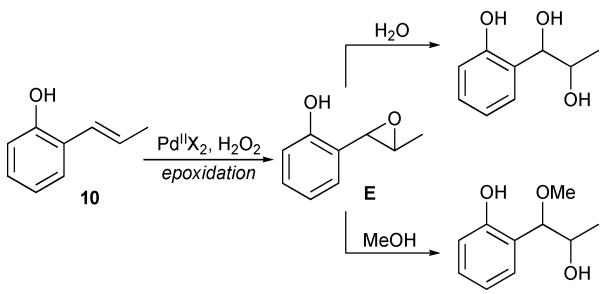


Fig. 6 Pd-catalyzed dioxygenation of *o*-vinylphenols.

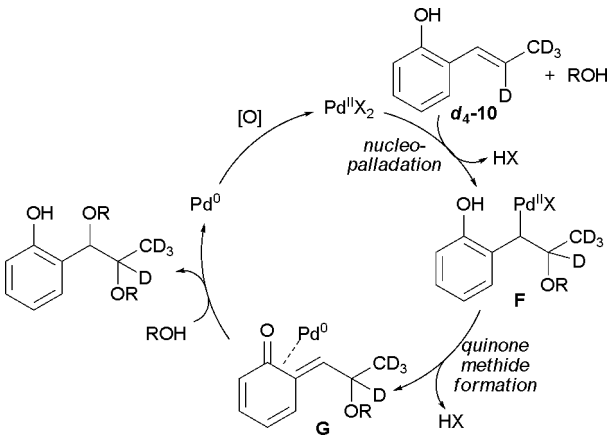
Le Bras, Muzart, and coworkers propose that this reaction occurs through initial Pd-catalyzed epoxidation of propenyl phenol (**10**) with H_2O_2, followed by attack of intermediate **E** at the benzylic position by either water or methanol (Scheme 4).[16] In support of this mechanism, the authors observed by mass



Scheme 4 Proposed mechanism for Pd-catalyzed dihydroxylation or hydroxyalkoxylation of *o*-vinyl phenols.

spectrometry a complex corresponding to palladium–ligand–epoxide. Furthermore, they submitted the Bn-phenoxide protected epoxide to the reaction conditions and observed a similar ratio of dihydroxylation and hydroxyalkoxylation products. It should be noted that the reaction is observed in the absence of palladium, albeit in lower yield.

For our reported dialkoxylation reaction, we have proposed a mechanism in which initial oxypalladation of the alkene results in a palladium-alkyl **F**, which is capable of forming a quinone methide intermediate **G** with subsequent reduction to Pd^0 (Scheme 5).[15] The electrophilic quinone methide is then attacked by a second equivalent of alcohol. Support of this mechanism is provided by the observation that an unprotected *ortho*-phenol is required for the dialkoxylation. Additionally, when a deuterated substrate ***d*$_4$-10** is submitted to the reaction, no washing of the deuterium labels is observed, indicating that β-hydride elimination does not occur.



Scheme 5 Proposed mechanism for Pd-catalyzed dialkoxylation of *o*-vinyl phenols.

Recently, an enantioselective variant of this reaction was reported using chiral quinoline oxazoline ligands of type **11** (Fig. 7).[17] A significant detrimental effect of added copper on enantioselectivity was found. The observation that trisubstituted alkene **12** undergoes dialkoxylation without asymmetric induction indicates that absolute configuration is most likely set in the initial β-oxypalladation, and the stereoselectivity of the second nucleophilic addition is affected by the adjacent, previously set stereocenter. If the first step were α-oxypalladation, one would expect an enantiomeric excess similar to that observed with a disubstituted alkene.

Nucleopalladation–palladium oxidation

Another strategy for interception of the Pd alkyl with a nucleophile that is receiving growing attention is to rapidly oxidize the Pd alkyl from Pd^{II} to Pd^{IV} to avoid β-hydride elimination (Scheme 6). This also significantly enhances the electrophilic nature of the Pd-alkyl **H**. Depending on the nucleophile and the substrate, the second bond-forming step is hypothesized to proceed *via* either a reductive elimination of C-Nu from Pd^{IV}, resulting in retention of stereochemistry, or by nucleophillic attack of an external nucleophile, with Pd^{II} as the leaving group, resulting in inversion of stereochemistry.

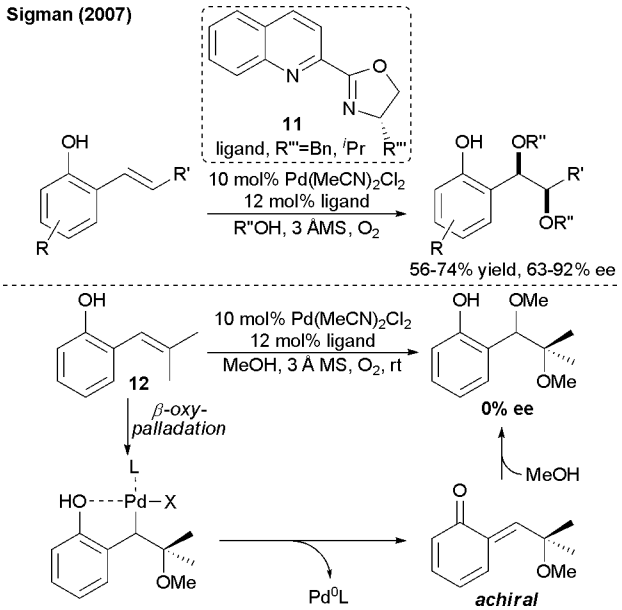
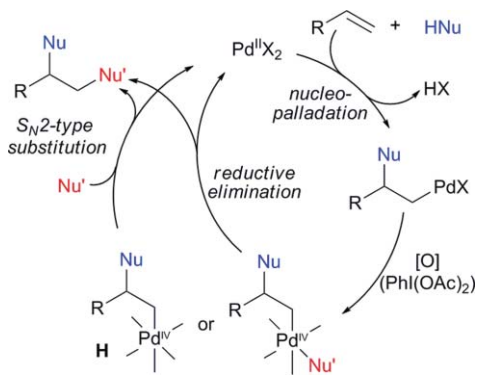


Fig. 7 Asymmetric dialkoxylation of *o*-vinyl phenols.



Scheme 6 Proposed mechanism for Pd-catalyzed difunctionalization involving Pd^{II}–Pd^{IV} oxidation.

Sorensen and coworkers utilized substrates of type **13** with a tethered nitrogen nucleophile in an aminoacetoxylation reaction, with acetate as the second nucleophile (Fig. 8).[18] Shortly after,

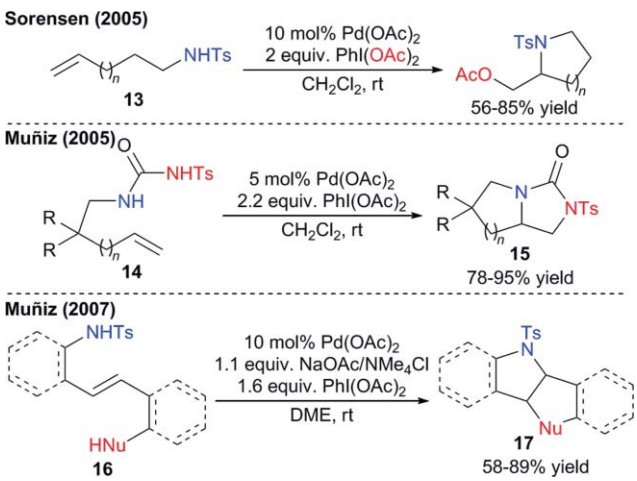


Fig. 8 Intramolecular Pd-catalyzed difunctionalization reactions.

Muñiz and coworkers published a report of alkene diamination of substrates of type **14** containing a tethered urea, which can act as a nucleophile in both steps, resulting in bicyclic products.[19] The authors have demonstrated that 5-, 6-, and 7-membered heterocycles can be successfully formed with this method. Muñiz also reported a version of this reaction in which two separate tethered nucleophiles are incorporated into substrates **16** providing fused heterocyclic products **17**.[20] In all of these cases, excess $PhI(OAc)_2$ is required as the oxidant.

More recently, mechanistic studies have led Muñiz and coworkers to propose a process in which the olefin undergoes initial *syn*-aminopalladation, followed by oxidation to Pd^{IV}, and subsequent S_N2-type attack by the tosylamide.[21] Deuterium labeled substrates were used to demonstrate that the reaction is stereospecific, with (*E*)-**18** leading to *cis*-**19** and (*Z*)-**18** leading to *trans*-**19** (Fig. 9). Furthermore, intermediates **20** and **21** where observed by ^1H NMR in the absence of $PhI(OAc)_2$, indicating that the initial step likely occurs through a *syn*-aminopalladation.

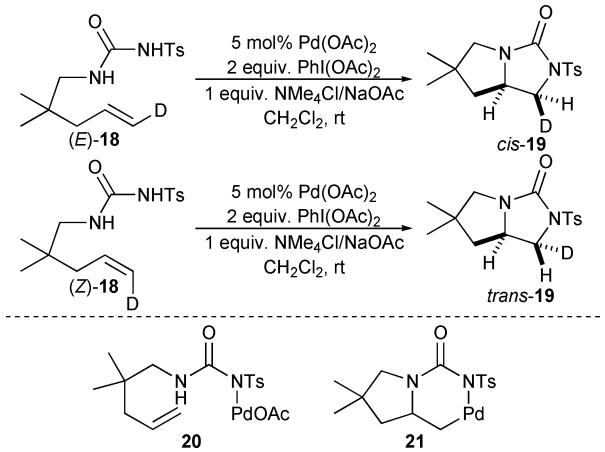


Fig. 9 Mechanistic experiments supporting *syn*-aminopalladation and S_N2-type substitution.

Stahl and Liu's report of a Pd-catalyzed aminoacetoxylation reaction represents the only example of alkene difunctionalization in which Pd^{IV} is invoked wherein both new C–heteroatom bonds arrive from exogenous nucleophiles in a regioselective manner (Fig. 10).[22] Specifically, phthalimide (**23**) is the nitrogen source, and the acetate is derived from $PhI(OAc)_2$, which also serves as the oxidant. Successful substrates of type **22** contain ether functional groups, which potentially chelate palladium, enhancing reactivity and selectivity. Allylic ethers are good substrates, with vinylic and homoallylic ethers also reacting, albeit in lower yield. The authors propose that this reaction proceeds through an initial *syn*-aminopalladation, and C–O bond formation with inversion of stereochemistry (S_N2-like). This mechanistic proposal is based on the observation of the byproduct (*Z*)-**25**, which would arrive from *syn*-aminopalladation followed by *syn*-β-hydride elimination from intermediate **I**. This indicates that the initial aminopalladation step occurs *via syn*-addition. Secondly, (*Z*)-**24**, which does not isomerize under reaction conditions, leads to *erythro*-**26**, which establishes that the acetate adds with inversion of stereochemistry.

Sanford and Desai published an aminooxygenation reaction involving homoallylic alcohols **27** as substrates and phthalimide as the nitrogen source to form substituted tetrahydrofurans **28**

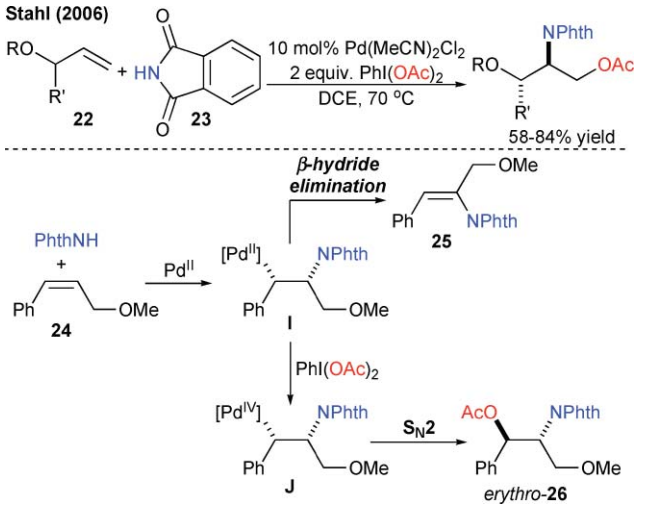


Fig. 10 Pd-catalyzed aminoacetoxylation of alkenes and mechanistic experiments.

(Fig. 11).[23] The authors evaluated mechanistic possibilities based on the stereochemical outcome with (*Z*)-**29** as the substrate. Based on the observed β-hydride elimination product **30** from intermediate **K**, *syn*-aminopalladation is assumed, and based on the *trans*-product **31**, direct reductive elimination of a Pd^{IV}–alkyl–alkoxide intermediate **L** is proposed.

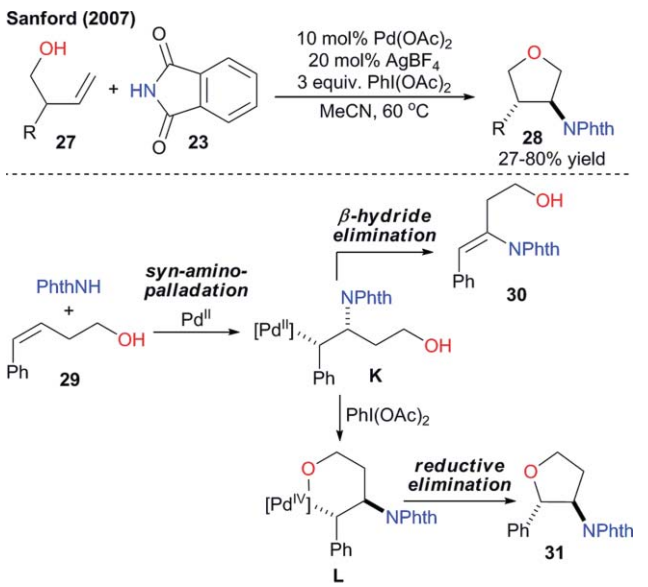


Fig. 11 Pd-catalyzed aminooxygenation of alkenes and mechanistic experiments.

A palladium-catalyzed cyclopropanation of enynes of type **32** or **33** was reported independently by Tse and coworkers[24] and by Sanford and coworkers.[25] Both groups propose a Pd^{II}–Pd^{IV} catalytic cycle. The initial nucleopalladation reaction occurs at the alkyne (intermediate **M**), which is followed by olefin insertion to obtain intermediate **N** (Fig. 12). Sanford and coworkers propose oxidation to Pd^{IV} followed by intramolecular S_N2 attack by the enol acetate, resulting in cyclopropane formation. In this case, the same carbon (originating on the alkyne) acts as the nucleophile in both steps to difunctionalize the alkene.

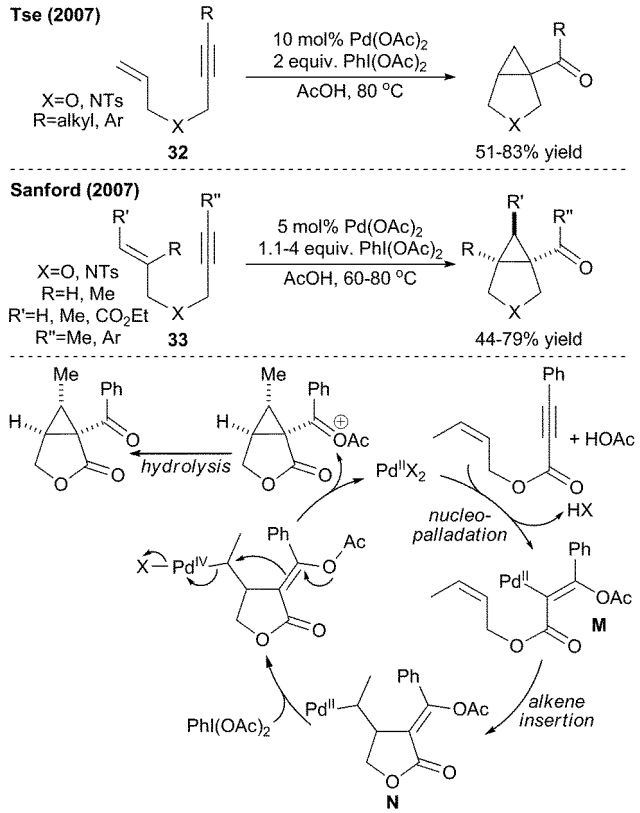


Fig. 12 Pd-catalyzed cyclopropanation of enynes.

Recently, a Pd-catalyzed alkene dioxygenation reaction was reported by Song, Dong and Li (Fig. 13).[26] Mono-, di-, and trisubstituted alkene substrates react to give *cis*-diacetates with high diastereoselectivity. Initial *anti*-oxypalladation, followed by Pd oxidation is proposed to reach intermediate **P**. Intramolecular S_N2-type reductive elimination, followed by hydrolysis of **Q** leads to a regioisomeric mixture of hydroxyacetates. Treatment of this mixture with acetic anhydride provides the diacetate products. Support for this mechanistic proposal is provided by an isotopic

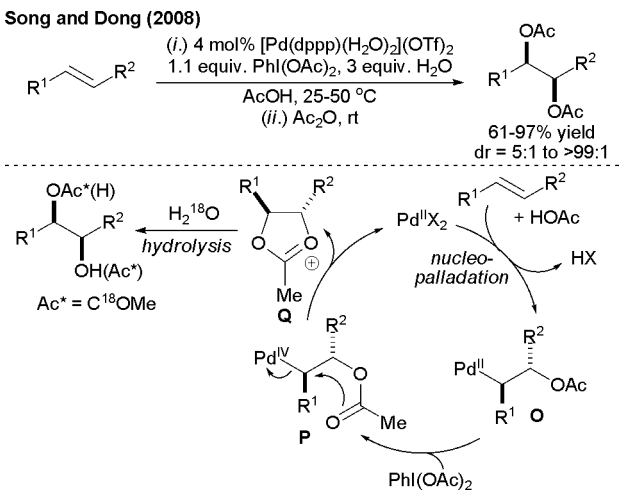


Fig. 13 Pd-catalyzed dioxygenation of alkenes.

labeling study wherein ^{18}O-enriched water was observed to be incorporated into the carbonyl of the hydroxyacetate.

Conclusions

The field of Pd-catalyzed alkene difunctionalization reactions has recently observed considerable attention. A common issue addressed by the developed reactions is the need to activate the Pd-alkyl intermediate formed following nucleopalladation. A number of solutions have been established, usually involving either the incorporation of a functional group into the starting material that can either stabilize or react with the Pd alkyl, or by oxidation of the Pd alkyl. These approaches have led to the successful development of reactions adding two new nucleophiles to an alkene, including carbon, oxygen, and nitrogen nucleophiles. Instances of chemo-, regio-, and enantioselectivity exhibit the potential synthetic utility of such endeavors.

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