When Is a Proton Not a Proton?**

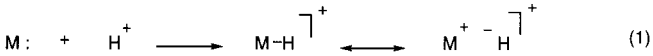
Barry M. Trost*

Abstract: The importance of transition metal catalyzed reactions stems from their ability to control subtle differences in reaction pathways, which can thus in turn be tuned for chemo-, regio-, diastereo-, and enantioselectivity. In addition, subtle differences in catalysts can have vast implications for reactivity and thereby change the nature of the reaction itself. The development of new pathways for the generation of reactive transition metal organometallic intermediates in catalytic reactions by simple additions provides a good strategy for developing atom-economic reactions. One of the simplest processes is protonation, wherein use of a low-valent metal transforms the proton into a metal hydride and therefore gives access to organometallic complexes by hydrometallation. Here I exemplify the concept with palladium as the transition metal and weak acids as the proton donors (carboxylic acids, activated methylene compounds, etc.), from which several new reactions have evolved and new strategies for the synthesis of complex organic molecules have been developed.

Keywords: catalysis · cyclizations · palladium · protonations · transition metals

Introduction

Acid–base concepts constitute an integral part of the foundation of chemistry. The original notions focused around the donation or acceptance of a proton. While we recognize certain structures as bases, like amines, alkoxides, thiolates and so on, the broad definition of bases includes any atom that has an unshared pair of electrons. Low-valent transition metals form an unusual class of bases[1] since protonation generates a metal–hydrogen bond that can function very differently from a typical conjugate acid—that is, the species containing the metal–hydrogen bond may be considered to be a hydridometal species rather than a protonated metal, as depicted in Equation (1).[2] The formation of such a metal–hydrogen bond raises the prospects of a simple, atom-economical approach for formation of organometallic intermediates in a catalytic cycle by addition to π unsaturation. Thus, the resultant carbon–metal bond can subsequently potentially participate in numerous reactions typical of that metal including but not limited to carbametalations of alkenes and alkynes, cross-coupling, carbonylation, and so forth.



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Protonation of transition metals dates back over forty years to the reported reaction of dicyclopentadienylrhenium hydride with hydrochloric acid, in which the basicity of the initial rhenium complex was likened to that of ammonia.[3] In the intervening years, protonation with relatively strong Bronsted acids of low-valent complexes of virtually every transition element has been reported.[4] However, although the estimated basicities in many cases suggest that carboxylic acids should also function, only the use of the strongest carboxylic acids, such as trifluoroacetic acid, has been explored. Switching from protonation to oxidative addition with weaker acids may also become an issue, but, for the purposes of this presentation, the net effect is considered functionally equivalent and therefore no differentiation between the two processes is made.

In spite of the large number of protonated complexes, their use in catalytic cycles has been little explored. While the use of cationic metal hydrides as catalysts for hydrogenation is well documented, the catalytic cycle normally generates this species by processes other than protonation.[5] An early example of a catalytic cycle involving a protonated transition metal complex is the synthesis of 1,4-hexadiene from 1,3-butadiene and ethylene employing a catalyst derived from a nickel(0) complex and sulfuric acid as shown in Scheme 1.[6] The reaction takes advantage of the ability of the nickel hydride to hydrometallate 1,3-butadiene, thereby generating a

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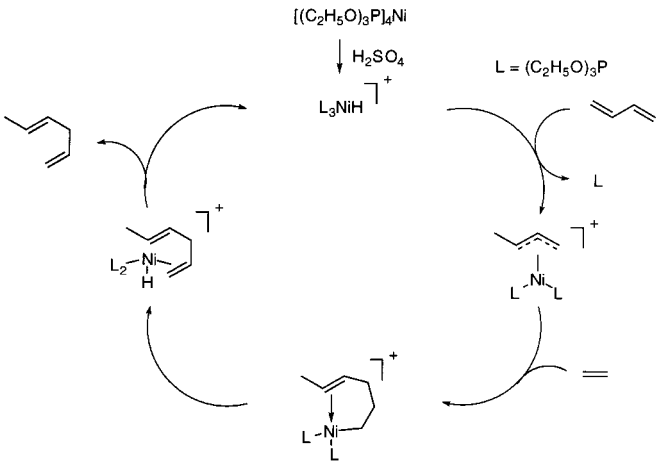
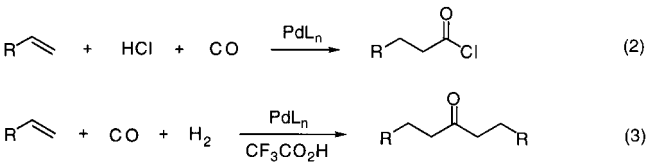
[**] Abbreviations used in this article are: dba = dibenzylideneacetone; PMB = *p*-methoxybenzyl; DMAP = 4-dimethylaminopyridine; PMHS = polymethylhydrosiloxane; DMF = dimethylformamide; TBDMS = *tert*-butyldimethylsilyl; dppb = 1,4-bis(diphenylphosphino)butane; TBDPS = *tert*-butyldiphenylsilyl; dppf = 1,1′-bis(diphenylphosphano)ferrocene; TIPS = triisopropylsilyl; dppp = 1,3-bis(diphenylphosphano)propane; TMS = trimethylsilyl.



Scheme 1. A Ni-catalyzed addition of ethylene and 1,3-butadiene.

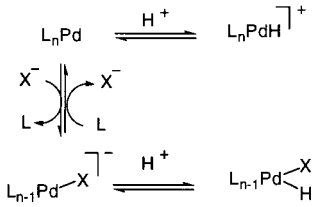
π-allylnickel complex. The presence of the positive charge also provides a kinetic advantage in coordinating with electron-rich ligands like alkenes. The validity of the initial hydrometalation step is supported by the stoichiometric formation of π-allylplatinum[7] and palladium[8] complexes by reaction of platinum and palladium(0) complexes protonated with strong acids. Telomerization of dienes like 1,3-butadiene in the presence of palladium catalysts and acids also invokes a similar sequence.[9] Hydrocarbonylations of alkenes are presumed to involve initiation by hydrometalation with a palladium(0) complex protonated by a strong acid. For example, the formation of acid chlorides according to Equation (2)[9] and of ketones according to Equation (3)[10] has been proposed to proceed by hydropalladation via a



(2)

(3)

protonated palladium(0) complex as the initiation step. Thus, an opportunity to devise catalytic processes invoking the protonation of a low-valent metal as an initiation step appears to hold promise for the development of addition reactions under very mild conditions if the protonation could occur with weak acids. The acidity required obviously depends upon the basicity of the metal, and the basicity of the metal can be tuned by the nature of the ligands—more electron-rich ligands would increase the basicity, allowing even weaker acids to be employed. Enhancing basicity (increasing ligand donor ability) by replacing a neutral ligand with an anionically charged one [Eq. (4)] represents a second strategy to adjust

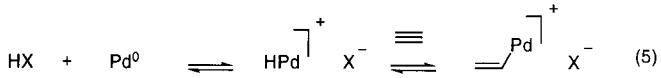


(4)

the metal basicity. The development of addition reactions that can be initiated under such mild conditions is very attractive, since synthetic efficiency would be increased by reactions that can be simultaneously selective as well as atom-economical.

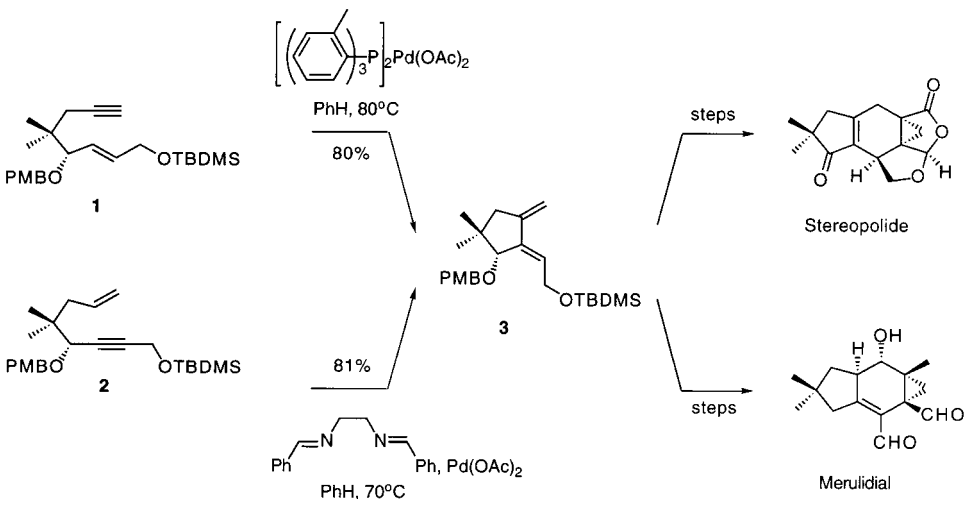
Discussion

Cycloisomerization and cycloreduction: The possibility of formation of a metal–hydrogen bond by simple protonation leads us to consider transition metal catalyzed additions to alkynes. The excellent coordinating properties of the alkyne to a transition metal suggests that an equilibrium as shown in Equation (5) may provide a very mild approach for the



(5)

formation of vinylpalladium intermediates. Indeed, such an equilibrium was originally conjectured as one of the possible pathways to explain the cycloisomerization of 1,6- and 1,7-enynes catalyzed by palladium acetate, as shown in Equation (6).[11–14] Thus, either enyne **1**[13] or enyne **2**[14] cycloisomerizes with a ligated palladium acetate to the same 1,3-diene **3**, which proved to be a pivotal intermediate to the isolactarane cytotoxic antibiotics merulidial and stereopolide. While one mechanistic consideration focused upon a palladacycle intermediate,[15] an alternative catalytic cycle summarized in Scheme 2 considered an equilibrium depicted in Equation (5) wherein acetic acid and palladium(0) are formed



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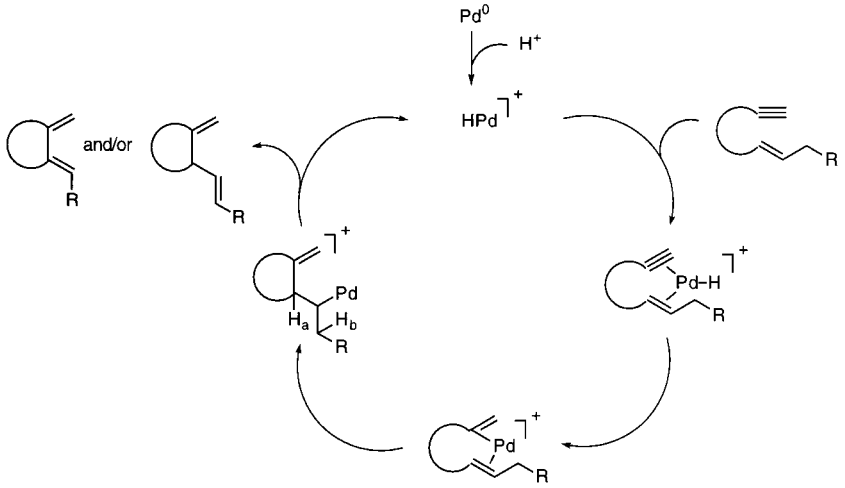
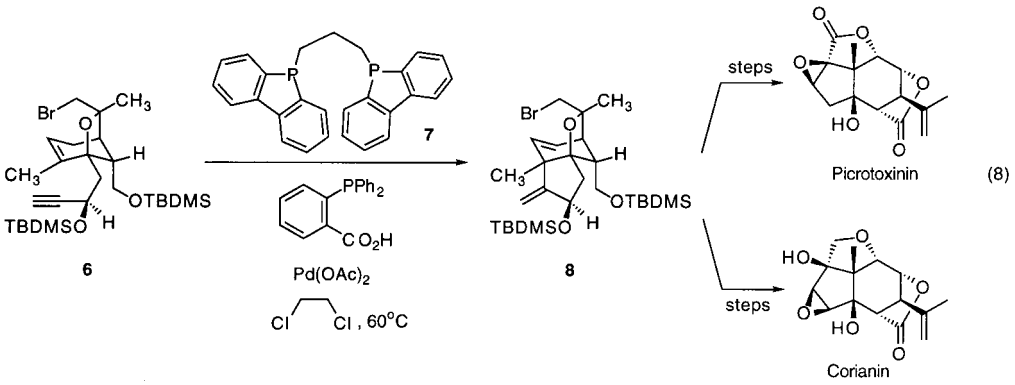


Scheme 2. Cycloisomerization of 1,6- and 1,7-enynes in a cycle involving HPd^+.

in situ from palladium acetate as a precatalyst. The cycloisomerization cycle is terminated by a β-hydrogen elimination to form the final product and reform the active catalyst. Since the β-hydrogen elimination could involve either H_a or H_b, in principle, two regioisomeric products are possible—a 1,3- or a 1,4-diene. Whereas, in the case of substrate **2**, only the 1,3-diene can be formed, substrate **1** could have produced either product, although only the conjugated isomer is observed in this case.

In accord with the feasibility of the mechanism in Scheme 2, use of Pd^0 and acetic acid does indeed catalyze the cycloisomerization.[16] One example is shown in Equation (7) in which a 1,4-diene, involving net migration of H_a, rather than a 1,3-diene, involving net migration of H_c, is formed.[17] Since hydrometalation of the alkyne initiates the cyclization, the proton from the acetic acid is delivered β to the carbonyl group in this example—a type of reactivity more in accord with the metal hydride descriptor as suggested by the resonance form depicted in Equation (1). In short, an umpolung of the hydrogen occurs by transferring it from acetate anion as base to the low-valent metal as base. The regioselectivity of the β-hydrogen elimination of H_a over H_b to give the triene **5** is also quite noteworthy. This remarkable regioselectivity complements what is normally observed in analogous thermal reactions whereby H_b rather than H_a migrates. The stereoelectronic requirement for a *cis*–syn relationship of the palladium and hydrogen in the β-hydrogen elimination and the conformational restrictions imposed by the organopalladium intermediate may account for this regioselectivity. This triene serves as a pivotal intermediate to a number of members of the chokol family of antifungal agents. Whereas 1,4-dienes can arise through a thermal Alder ene process, the palladium-catalyzed version clearly provides exquisite control of regioselectivity that simply is not possible thermally whereby both 1,3- as well as 1,4-dienes are accessed regioselectively, as illustrated in Equations (6) and (7).

Tethering the acid to the phosphorus ligand may have a beneficial effect with particularly sluggish substrates. In a synthesis of the picrotoxanes, GABA antagonists, the cycloisomerization of enyne **6** was examined [Eq. (8)].[18] While the reaction failed under the standard conditions, use of 2-diphenylphosphinobenzoic acid instead of acetic acid effected cyclizations, albeit in only 20–37% yield, depending upon ligand. On the other hand, decreasing the steric bulk of the auxiliary ligand as in **7** in conjunction with the use of 2-diphenylphosphinobenzoic acid saw the yield of **8** increase to 70%. This intermediate serves as a precursor to a number of picrotoxanes including picrotoxinin and corianin. A bridged bicyclic intermediate towards the antiviral and cytotoxic agent aphidicolin was easily available by this cycloisomerization [Eq. (9)].[19]



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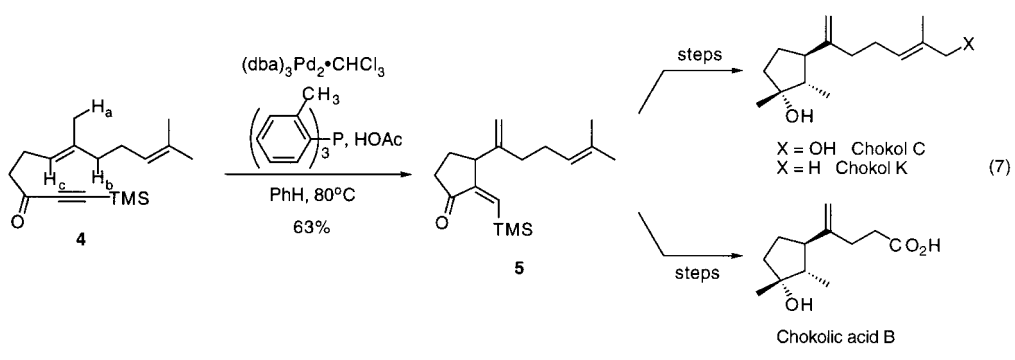

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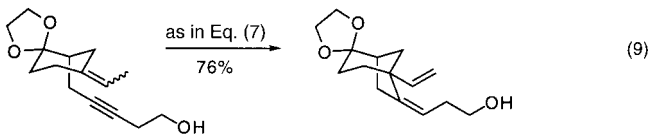
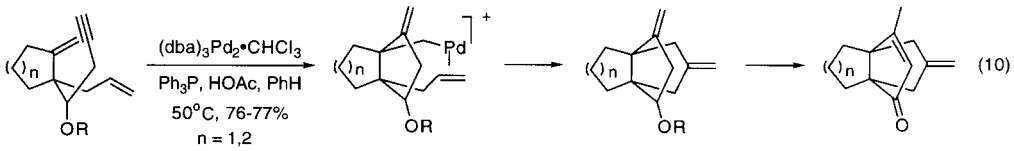


(9)

Support for the mechanistic rationale depicted in Scheme 2 is derived from interception of the proposed σ-palladium intermediate. If β-hydrogen elimination is precluded and additional π unsaturation exists, further carbametalations creating more rings may occur. Depending upon the juxtaposition of the unsaturation, a number of polycyclic skeletons can be created, including fused, bridged, spiro, and propeller. For example, [4.3.3] and [3.3.3] propellanes are readily accessed as in Equation (10) and a spiro ring system containing up to seven rings as in Equation (11) is created in one step.[20] Ligand tuning as a function of substrate may be required; thus, in the latter case involving a disubstituted alkyne initiator, the more weakly donating triphenylstibane rather than a phosphane ligand is preferred. Enediynes also undergo polycyclization in which the initial product derived from β-hydrogen elimination undergoes disrotatory cyclization to provide a tricycle with excellent remote diastereoselectivity [Eq. (12)].[21] This example is noteworthy because of the compatibility of the allyl acetate, a functionality that can react with a Pd^0 catalyst. Thus, protonation of the Pd^0 complex and hydropalladation is kinetically faster than ionization of the allyl ester.

An alternative interception mode for the proposed σ-palladium intermediate in Scheme 2 is by hydride to give a net reductive cyclization [Eq. (13)]. In this case, the acid must also be employed stoichiometrically. A facile synthesis of the antitumor agent phyllanthocin employs the cycloreduction as a key step [Eq. (14)] wherein polymethylhydrosiloxane (PMHS) was used as the silane source.[23]

Application of this cycloreduction to diynes produces the very useful 1,3-dienes, building blocks for further cycloadditions. Such a cycloreduction approach may have several benefits over cycloisomerization of enynes to 1,3-dienes [Eq. (8)]. First, regiochemical ambiguities are eliminated. Second, the stereoelectronic requirement for the intramolecular carbametalation of an alkene may limit the cyclization of an enyne substrate as it did for enyne **9**. The cylindrical symmetry of an alkyne acceptor for the carbametalation removes any such stereoelectronic barriers. Indeed, the cycloreduction of the diyne **10** [Eq. (15)] proceeded smoothly and rapidly even though the product is



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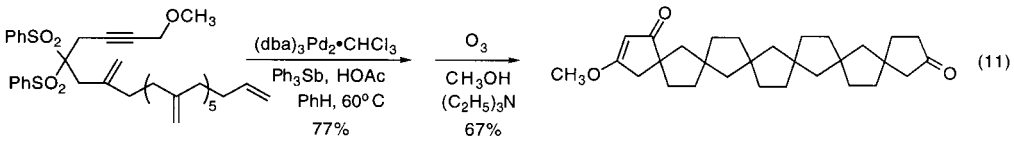

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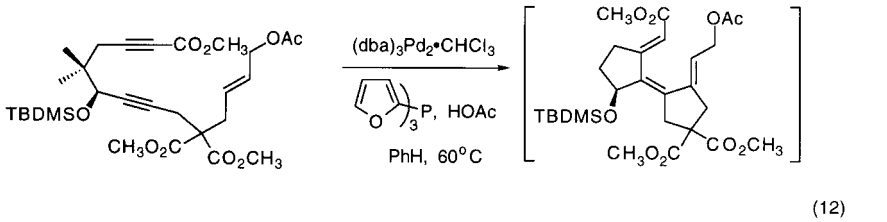

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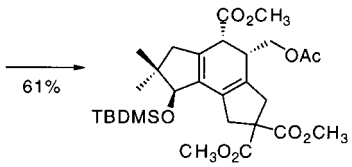

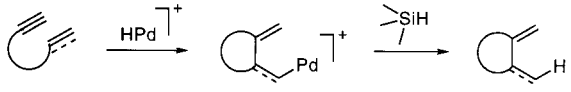

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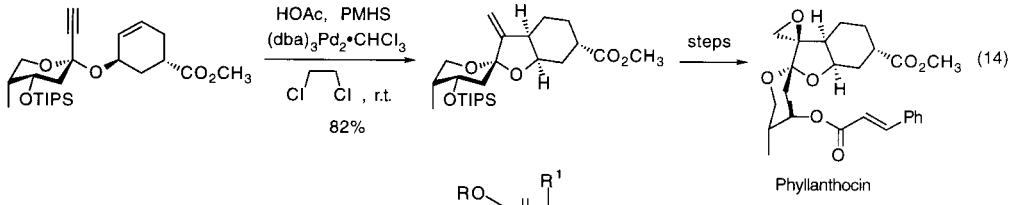

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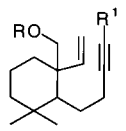

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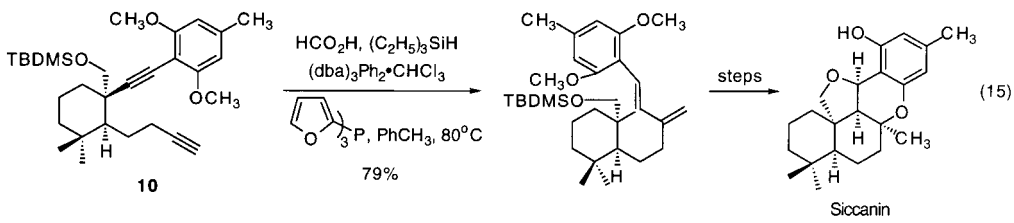

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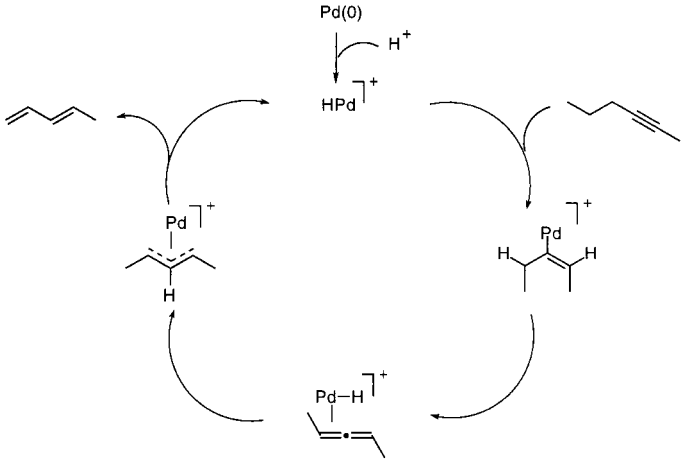
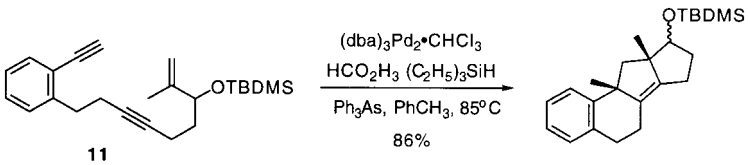
extremely hindered in this case.[24] The effectiveness of the cycloreduction permitted a 13–15 step synthesis of the clinically important antifungal agent siccanin.

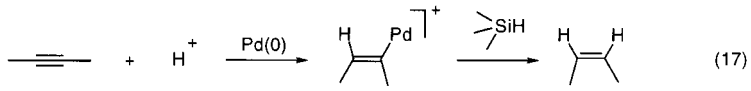
The timing of the hydride delivery by the silane can be tuned by varying the silane. When triethylsilane is used, the enediyne **11** undergoes tricyclization with none of the partially cyclized products detetcted [Eq. (16)].[25]

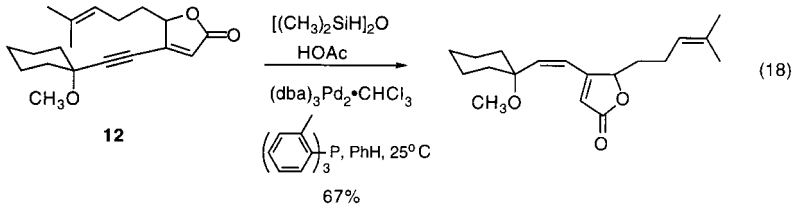
In the absence of additional unsaturation, the initial alkyne hydrometalated species, the vinylpalladium complex, would be expected to be intercepted, thereby creating a convenient and selective semihydrogenation of alkynes to *cis*-alkenes [Eq. (17)].[26] The fact that hydrometalation of a simple alkene does not occur under these conditions prevents over-reduction. The chemoselective reduction of the polyunsaturated substrate **12** [Eq. (18)] illustrates the utility of this protocol.[27]



Scheme 3. Pd-catalyzed isomerization of alkynes to dienes.





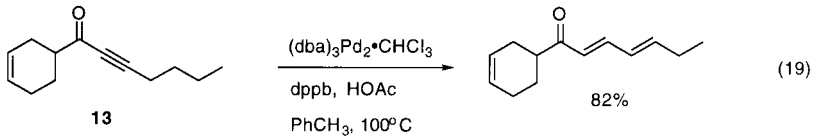


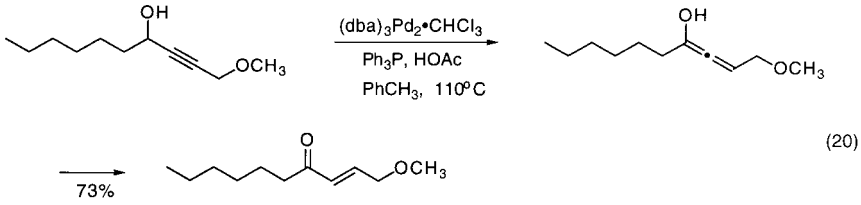
Isomerization of alkynes to 1,3-dienes: The ability to hydrometalate alkynes (but not alkenes) under these conditions raised the question of whether a β-hydrogen elimination to form an allene would occur (Scheme 3). The allene would be expected to participate equally well, if not better, in a hydrometalation to form a π-allyl species, which completes the cycle by β-hydrogen elimination to form the thermodynamically more stable 1,3-diene and regenerate the catalyst.

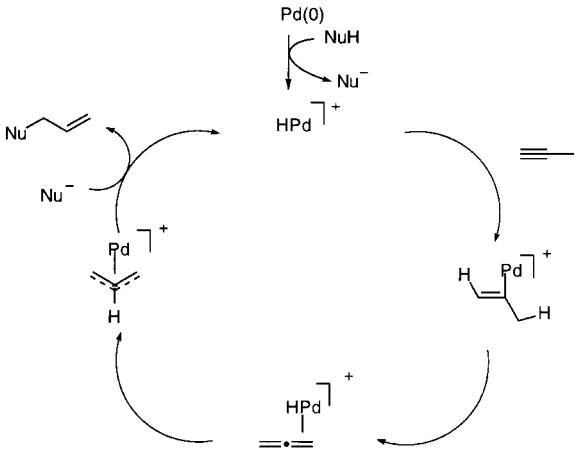
Because vinylpalladium species are generally reasonably kinetically stable towards elimination to allenes, substrates that might be activated towards this elimination, alkynes conjugated with electron-withdrawing groups, were examined. Treating the alkynone **13** with either palladium acetate/dppb (in situ generation of Pd^0 and acetic acid) or with a Pd^0 complex and acetic acid, as shown in Equation (19), provides the conjugated dienone in excellent yields.[28] The ketone is not required for the initial isomerization [Eq. (20)].[29] The initial allene, which is an enol in this case, is intercepted by tautomerization, thereby giving the α,β-unsaturated ketone. Lack of regioselectivity limits the range of alkynes that can serve as substrates in synthetically useful fashion.

Alkynes as precursors to π-allylmetal complexes: Scheme 3 suggests that π-allylpalladium intermediates may be formed by simple treatment of an alkyne with acetic acid and a Pd^0 source. Conversion of an alkyne to a π-allylrhodium complex stoichiometrically supports this interpretation.[30] The ability to intercept the π-allylpalladium intermediate suggests a novel alkylation sequence as outlined in Scheme 4. In essence, the sequence effects an internal oxidation–reduction in which the propargylic position is oxidized and the alkyne reduced. In its simplest version, the conjugate base of the acid employed would be the ultimate nucleophile. Use of a separate acid requires a pronucleophile from which the nucleophile can be generated under the acidic conditions.

The feasibility of the concept was established by the use of carboxylic acids as both acid and nucleophile. As illustrated in



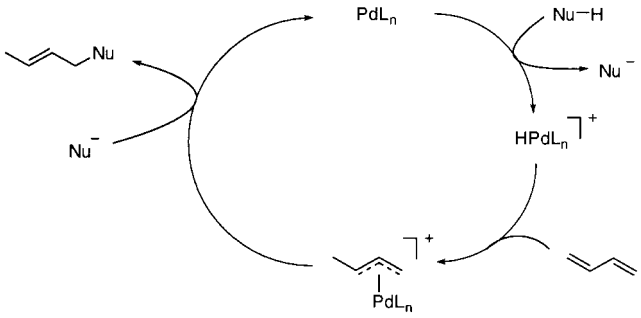




Scheme 4. Nucleophilic addition to alkynes via π-alkylpalladium intermediates.

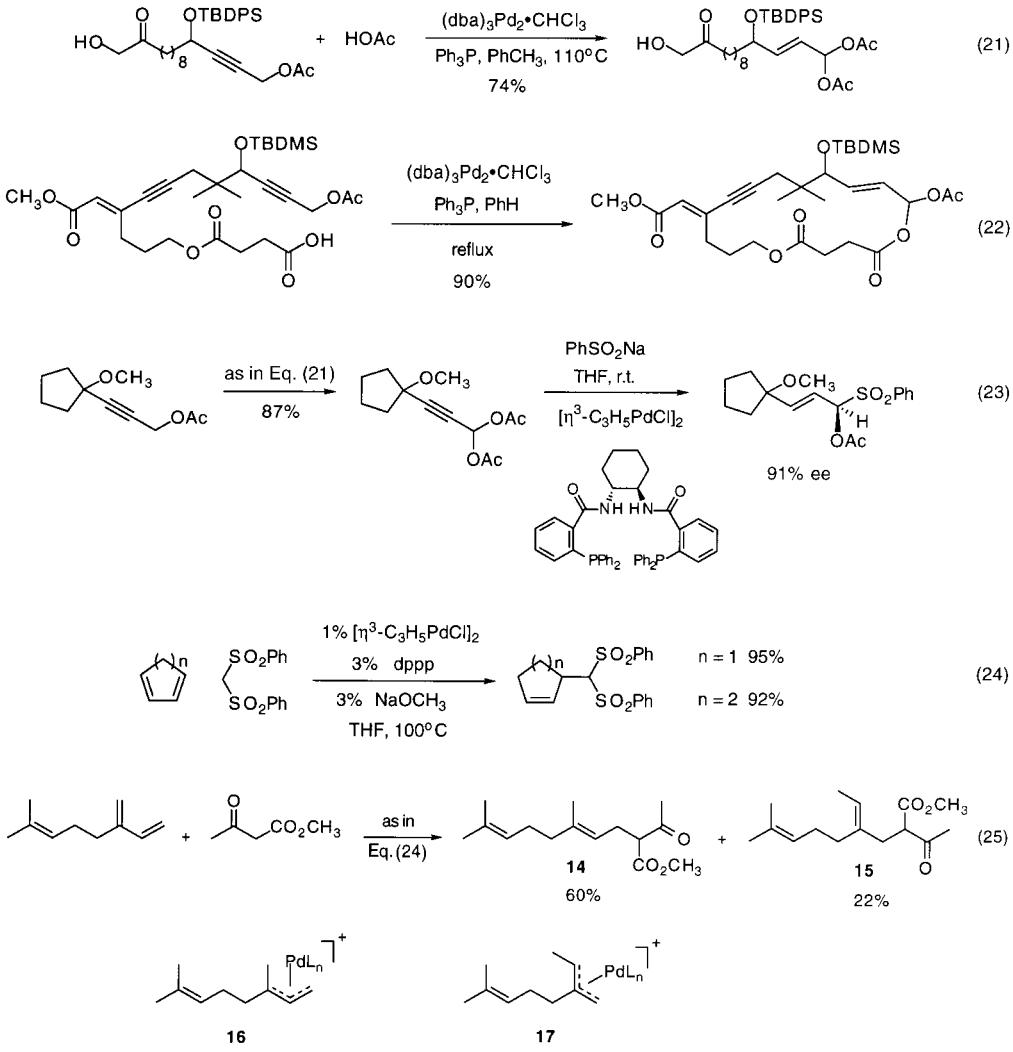
Equation (21), a highly chemoselective addition occurs.[31] An intramolecular version has led to an effective macrocyclization [Eq. (22)]. One of the uses of this methodology is the recognition that the *gem* dicarboxylate functionality can constitute enantiotopic leaving groups and lead to asymmetric substitutions as shown in Equation (23).[32] Support of the mechanism outlined in Scheme 4 derives from studies of the addition of carboxylic acids to allenes as outlined later (vide infra).

Additions of pronucleophiles to 1,3-dienes: An alternative and attractive process invokes the direct addition of pronucleophiles to 1,3-dienes via π-allylpalladium intermediates as depicted in Scheme 5. When a strongly donating bidentate ligand, 1,2-bis (dialkylphosphino)ethane, was used, additions of 1,3-diketones and β-ketoesters to 1,3-butadiene could occur whereby simple alkylation rather than butadiene oligomerization dominated.[33] An alternative strategy using a charged ligand to enhance basicity had led to a useful addition, shown in Equation (24).[34, 35] A complication arises with unsymmetrically substituted 1,3-dienes such as myrcene, which furnish two addition products **14** and **15** [Eq. (25)]. Depending upon the regioselectivity of the hydrometalation, both regioisomeric π-allylpalladium complexes **16** and **17** may be formed. Since



Scheme 5. Addition of pronucleophiles to 1,3-dienes.

attack at either terminus of each π-allylpalladium complex is feasible, a total of four regioisomeric products could result, but only two products did actually form—a fact that indicated that good regioselectivity characterizes the nucleophilic addition step; it may be possible to tune the ligands to further improve the regioselectivity of the hydropalladation step. The adduct **14** is an important commercial intermediate in the synthesis of vitamins A and E as well as other products.[35a]



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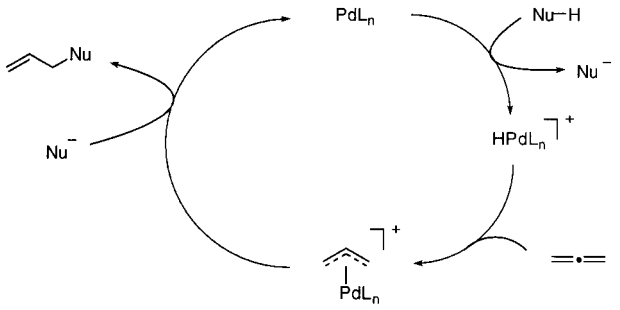
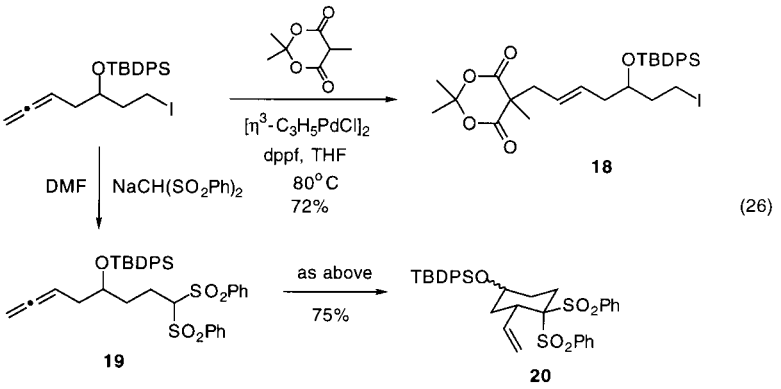
Additions of pronucleophiles to 1,2-dienes: A potential solution to the regioselectivity issue switches the substrate to a 1,2-diene (an allene) since hydrometalation of either double bond generates the same π-allylpalladium species (Scheme 6). With unsymmetrical allenes, the regioselectivity



Scheme 6. Addition of pronucleophiles to 1,2-dienes.

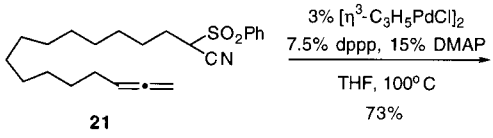
would be determined solely in the nucleophilic addition step, which has normally shown good selectivity. Equation (26) illustrates the efficacy of



(26)

the approach as well as its novel chemoselectivity, whereby addition to the allene occurs exclusively in the presence of the palladium catalyst to give the adduct **18** but only normal iodide displacement to **19** occurs when one equivalent of base is used in the absence of the palladium complex.[36, 37] The latter can now participate in an intramolecular addition of the pronucleophile to the allene catalyzed by palladium(0) to give the six-membered ring **20** exclusively. Thus, the starting allenyl iodide serves as a bis-electrophile in which either the allene or the iodide can be chosen to function as such independently by simple modification of the reaction conditions.

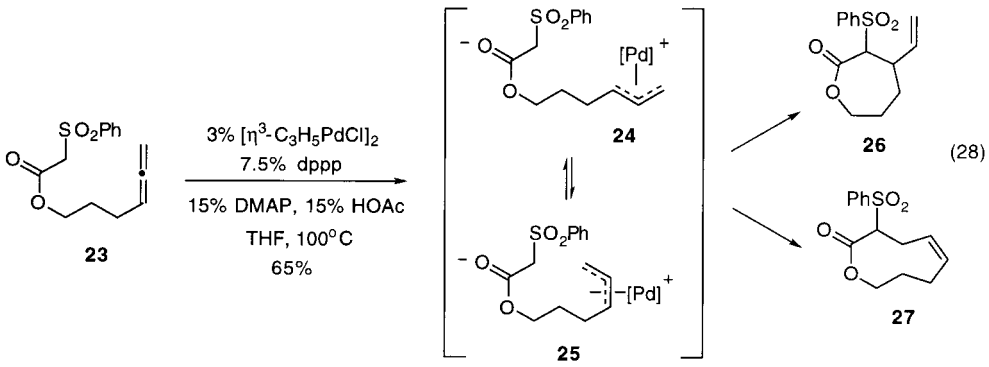
The cycloisomerization of substrates like **19** to form medium-sized and large rings required a modified catalyst system that more effectively promotes proton shuttling. Following the protocol for the synthesis of **19** from an appropriate iodoallene, the cyanosulfone **21** is easily accessed. Catalytic DMAP proves efficacious in serving as the proton shunt and effecting cyclization to the sixteen-membered carbocycle **22** possessing exclusively the *E* alkene even at 0.01M concentration of substrate [Eq. (27)]![38] Cyclization of allene **23** proves most instructive since either a seven- (i.e., **26**) or nine- (i.e., **27**) membered ring may form [Eq. (28)]. Bias for formation of the seven-membered ring arises not only from thermodynamic considerations favoring the smaller ring but also because the intermediate syn π-allylpalladium complex **24**, which should strongly favor the seven-membered ring to avoid the strain of placing a *trans* double bond in a nine-



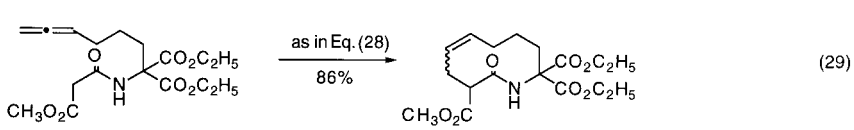
(27)

membered ring, should be more stable than the anti complex **25**, the required precursor of **27**. Nevertheless, the nine-membered macrocycle **27**, possessing only the *Z* alkene, is the exclusive product. Ten-membered rings are produced as mixtures of *E* and *Z* alkenes as shown in Equation (29)[38] wherein a macrolactam that can lead to an endopeptidase inhibitor[39] is produced.

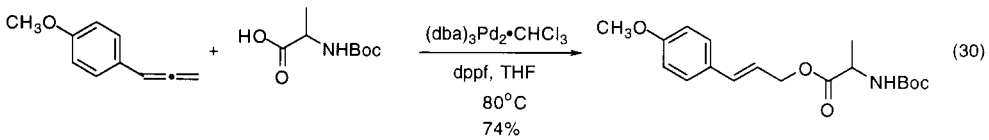
Carboxylic acids have also been reported to undergo additions to allenes that cannot isomerize to 1,3-dienes. Equation (30) illustrates an intriguing example employing an amino acid derivative.[40]



(28)



(29)



(30)

Conclusion

Transfer of a proton to a transition metal imparts chemical behavior that can range from electrophilic to nucleophilic. The resultant conjugate acid is also described as a metal hydride reflecting the diversity of properties that may be anticipated. A major aspect is the ability to effect hydrometalation of carbon–carbon unsaturation and thereby provide a convenient and atom-economical approach to organometallic intermediates in a catalytic cycle. As illustrated with palladium, a diverse range of reactions may be quasi-rationally developed. The use of carboxylic acids such as acetic acid is particularly noteworthy since, in contrast to stronger acids like hydrochloric acid or even trifluoroacetic acid where the protonated metal species can be isolated, direct observation of the palladium hydride species has failed—a fact that implies the basicity of the low-valent palladium must be several pK_b units less than that of carboxylate. Nevertheless, such a species undoubtedly is formed to some extent, albeit in an unfavorable equilibrium. When a slightly stronger carboxylic acid than acetic acid, like formic acid, is employed, the desirable aspect of maintaining a mild acid to maximize chemoselectivity is retained, but the reaction rate is increased by the shift in the acid–base equilibrium to the right. Use of excess acetic acid also may do the same thing qualitatively by mass action. While our work has so far focused on a limited range of palladium-catalyzed reactions, great opportunities exist to use this concept to generate a broad array of transition metal complexes that can be reactive intermediates for new catalytic processes. When is a proton not a proton? The simple answer derived from this discussion is when it is attached to a transition metal. It is probably more proper to say that its behavior is much more varied when the base is a transition metal. Some may argue that such a description is too simplistic; nevertheless, it has proven to be a very useful model to develop new chemistry.

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