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Synthetic and Mechanistic Studies of the Cycloisomerization and Cyclization/Hydrosilylation of Functionalized Dienes Catalyzed by Cationic Palladium(II) Complexes

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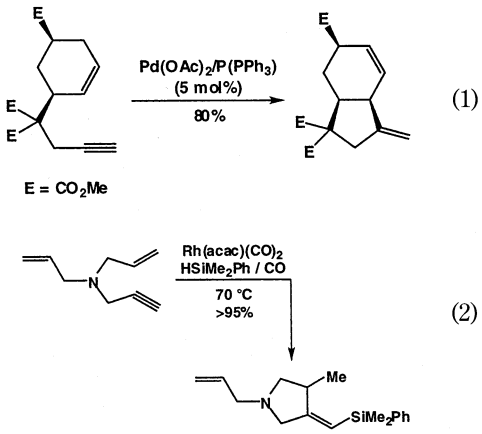
ABSTRACT

This Account describes the development and mechanistic study of the cycloisomerization and cyclization/hydrosilylation of functionalized dienes catalyzed by cationic palladium(II) complexes. These transformations are characterized by good functional group compatibility, high regio- and stereoselectivity, and low air- and moisture-sensitivity. Mechanistic studies of palladium phenanthroline-catalyzed diene cycloisomerization and cyclization/hydrosilylation established mechanisms involving C−C bond formation via intramolecular carbometalation of an alkyl olefin chelate complex, which was directly observed in the context of cyclization/hydrosilylation.

Introduction

Background. Substituted carbocycles represent a common structural component of naturally occurring and biologically active molecules, including pharmaceuticals. Because pharmaceutical design and development requires ready access to a broad spectrum of molecular structure, the discovery of new and efficient methods for the formation of a diverse range of carbocycles represents a constant challenge in organic synthesis. In this area, catalytic methods employing soluble transition metal complexes have demonstrated considerable utility due to the ability of transition metal complexes to facilitate transformations not possible using traditional approaches and due to the high levels of selectivity, efficiency, and atom-economy often realized by transition metal-catalyzed processes.[1,2] Two transformations that exemplify the potential of transition metal catalysis in the synthesis of functionalized carbocycles are the palladium-catalyzed cycloisomerization (eq 1)[3] and the rhodium-catalyzed cyclization/hydrosilylation of functionalized 1,6-enynes (eq 2).[4]



Catalytic Diene Cyclization. Dienes are less reactive toward transition metals than are enynes, and the development of diene cyclization catalysts that display high activity coupled with good chemoselectivity represents a challenging yet important objective in homogeneous catalysis. For example, although the ring-closing metathesis (RCM) of nonconjugated dienes to form cycloalkenes has been known for over 20 years,[5] the utility of RCM was, for many years, limited by the poor functional group compatibility and excessive air- and moisture-sensitivity of the oxophilic tungsten, titanium, and later molybdenum metathesis catalysts.[6] However, the more recent development of ruthenium catalysts that display high activity coupled with excellent functional group compatibility and low air- and moisture-sensitivity has led to an explosive growth in the application of RCM to the synthesis of functionalized carbocycles.[7]

The difficulties associated with catalytic diene cyclization extend to cycloisomerization and cyclization/hydrosilylation. For example, the palladium and rhodium enyne cyclization catalysts noted above are unreactive toward dienes, and early attempts to effect diene cycloisomerization employing late transition metal catalysts required forcing conditions in an acidic medium and/or suffered from poor selectivity and generality.[8] As a result, effective diene cycloisomerization and cyclization/hydrosilylation has required employment of highly reactive d^0 scandocene[9] and yttrocene[10] catalysts, respectively (Scheme 1). Unfortunately, the excessive oxophilicity of these metallocene complexes leads to poor functional group compatibility and extreme air- and moisture-sensitivity, which together restrict the synthetic utility of these potentially useful C−C bond-forming processes.

We felt that the development of diene cycloisomerization and cyclization/hydrosilylation catalysts that displayed high activity combined with low oxophilicity would be significant. The resulting protocols would expand the scope of transition metal-catalyzed diene cyclization and would require no specialized equipment or techniques. As a result, these processes would be potentially applicable to the synthesis of complex, functionalized carbocycles. We were particularly interested in complexes that would catalyze the exo,exo cyclization of dienes. Exo,exo diene

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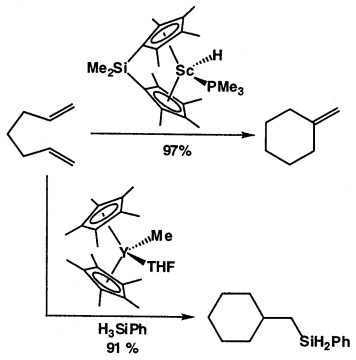
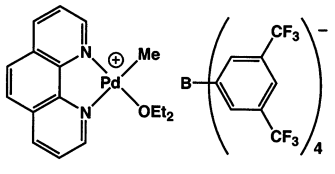
Scheme 1



cyclization would generate an additional stereocenter relative to the corresponding metallocene-catalyzed endo,exo cyclization processes and would therefore open new avenues for diastereo- and enantioselective synthesis.

Approach and Catalyst Identification. We reasoned that the goals outlined in the preceding paragraph could be achieved through employment of late transition metal complexes as diene cyclization catalysts. As was demonstrated in the context of ring-closing metathesis (RCM), late transition metal complexes are less oxophilic than are early transition metal complexes, and therefore they display greater functional group compatibility and diminished air- and moisture-sensitivity. In addition, late transition metal-catalyzed cyclization of enynes and related substrates leads consistently to formation of the exo,exo isomer (eqs 1 and 2), suggesting that a late transition metal complex would also catalyze the exo,exo cyclization of dienes. The primary challenge in realizing our objective was overcoming the inherent low reactivity of late transition metal complexes toward dienes.

The high reactivity of d^0 metallocene complexes toward diene cycloisomerization and cyclization/hydrosilylation stems from the electropositivity of the metal and the presence of an available coordination site. These features together facilitate olefin β-migratory insertion, the key C−C bond-forming process in these transformations, and Si−H bond cleavage via a low-energy σ-bond metathesis pathway. We reasoned that an electrophilic late transition metal complex that possessed an available coordination site should also be reactive with respect to β-migratory insertion and Si−H bond cleavage and should therefore catalyze the cycloisomerization and cyclization/hydrosilylation of functionalized dienes. Specifically, the cationic palladium(II) phenanthroline complex $[(phen)Pd(Me)(OEt)]^+[BAr_4]^-$ [Ar = 3,5-$C_6H_3(CF_3)_2$] (**1a**) is highly elec-

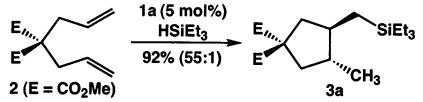


1a

trophilic and possesses an available coordination site but is neither oxophilic nor acidic.[11−13] As a result, **1a** is reactive with respect to both olefin β-migratory insertion and Si−H bond cleavage but displays good functional group compatibility along with low air- and moisture-sensitivity.[11−13] For these reasons, we targeted **1a** and related palladium complexes as catalysts for diene cycloisomerization and cyclization/hydrosilylation, and here we provide an account of our efforts in this area.

Diene Cyclization/Hydrosilylation

Cationic palladium phenanthroline complex **1a** was an active catalyst for the exo,exo cyclization/hydrosilylation of functionalized 1,6-dienes to form silylated cyclopentanes. For example, reaction of dimethyl diallylmalonate (**2**) and $HSiEt_3$ catalyzed by **1a** (5 mol %) at 0 °C was complete within 5 min to form carbocycle **3a** in 92% isolated yield with ≥98% trans selectivity (eq 3).[14] Conver-

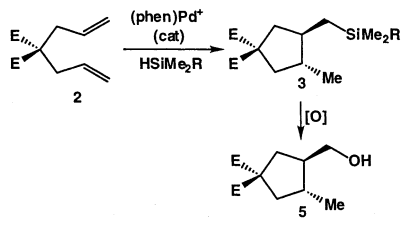


(3)

sion of **2** to **3a** represents a substantial increase in molecular complexity with the formation of a C−C bond, a ring, a C−Si bond, and two adjacent stereocenters. Although highly active, cationic complex **1a** and its precursors were thermally sensitive, and for this reason, the active cationic complex was more conveniently generated in situ via halide abstraction from (phen)Pd(Me)Cl (**4**) with $NaBAr_4$. In accord with our initial expectations, the presence of air or water led to no deterioration in the rate, yield, or selectivity of diene cyclization/hydrosilylation catalyzed by **4**/$NaBAr_4$.[15]

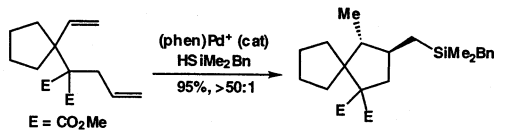
Silane Oxidation. A silyl group that bears one or more functional group can be oxidized under mild conditions to form a hydroxyl group, and this relationship constitutes an important strategy in the synthesis of complex alcohols and polyols.[16] Similarly, the synthetic utility of palladium-catalyzed diene cyclization/hydrosilylation rests on the efficient oxidation of the silyl group to unmask the latent hydroxyl group. Although the triethylsilyl group of **3a** bears no functional group and is therefore inert toward oxidation, a number of functionalized silanes including dimethylphenylsilane,[15] pentamethyldisiloxane,[17] and benzhydryldimethylsilane[18] reacted efficiently with diene **2** under palladium catalysis to form silylated carbocycles **3b**−**d**, respectively (Scheme 2). Carbocycles **3b**−**d** were each oxidized under mild conditions to form alcohol **5** in good yield.

Scheme 2



R	carbocycle	[O]	yield (%) 2→3	3→5
Ph	3b	$Hg(OAc)_2$/AcOOH	93	74
$OSiMe_3$	3c	KF/AcOOH	98	92
$CHPh_2$	3d	TBAF/H_2O_2	99	80

Scope and Limitations. The synthetic utility of any transformation is ultimately determined by its generality, and we have probed the scope of palladium-catalyzed cyclization/hydrosilylation with respect to substitution, ring size, and functional group compatibility. Although transition metal-based procedures involving olefins are often sensitive to substitution on or near the olefinic groups, palladium-catalyzed cyclization/hydrosilylation of 1,6-dienes tolerated allylic and/or terminal olefinic substitution, with exclusive delivery of the silyl group to the less hindered olefin (eqs 4−6).[14,15,19] Six-membered carbocycles are the most stable and most common ring size found in naturally occurring compounds. Likewise, nitrogen heterocycles are a common component of naturally occurring compounds, with a proclivity toward biologically activity. It was therefore significant that palladium-catalyzed cyclization/hydrosilylation was applicable to the synthesis of both functionalized cyclohexanes (eq 7) and pyrrolidine derivatives (eq 8), although these transformations were typically slower and less tolerant of substitution than was the cyclization/hydrosilylation of 1,6-dienes.[17,20]



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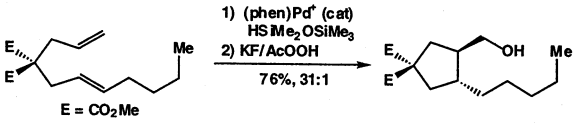

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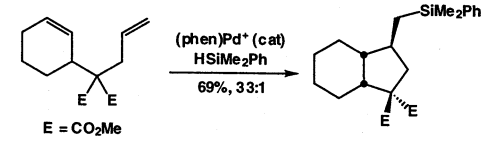

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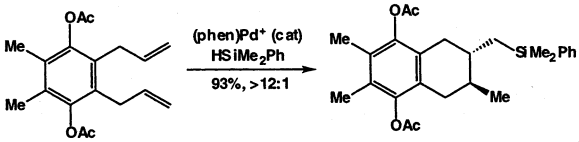

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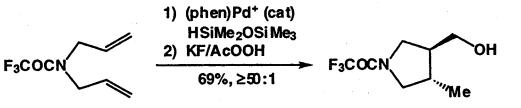
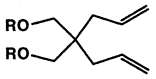
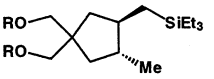
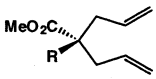
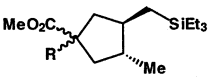
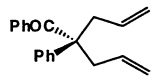
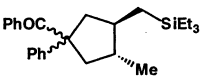


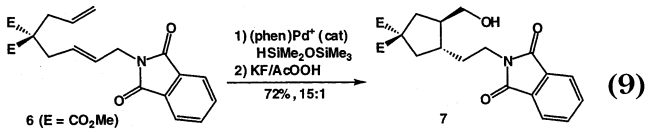
(8)

The transformations depicted in Scheme 2 and eqs 3−8 establish the compatibility of palladium-catalyzed cyclization/hydrosilylation with a number of polar functional groups, all of which are incompatible with metallocene-catalyzed processes. Cyclization/hydrosilylation also tolerated pivaloyl, sulfonyl, carbamoyl, acyl, cyano, and alkoxy- and phenoxymethyl groups at the homoallylic position of a 1,6-diene (Table 1).[15] In the course of probing the effect of diene homoallylic substitution on cyclization/hydrosilylation, we discovered that efficient cyclization/hydrosilylation was restricted to dienes that possessed an ester, ketone, or ether group in proximity to the olefinic groups. This behavior is not unusual, as proximal oxygen functionality has been shown to affect the rate and/or selectivity of many transition metal-catalyzed processes.[21] The mechanism by which the oxygenated functionality facilitates diene cyclization/hydrosilylation remains unclear but appears neither steric (Thorpe−Ingold effect) nor electronic in nature.[15]

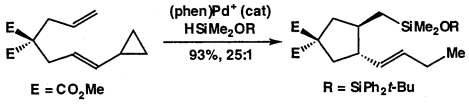
Table 1. Effect of Homoallylic Substitution on Cyclization/Hydrosilylation of 1,6-Dienes with $HSiEt_3$ Catalyzed by $4/NaBAr_4$

substrate	carbocycle yield (isomer ratio)
	
R = Ac	99% (30:1)
R = Piv	85% (>50:1)
R = Bn	99% (>50:1)
R = Me	92% (>50:1)
	
R = COMe	78% (1.5:1)
R = $CONMe_2$	99% (5:1)
R = SO_2Me	88% (2:1)
R = CN	60% (2:1)
	
	96% (1:1)

The compatibility of palladium-catalyzed cyclization/hydrosilylation with both terminal olefinic substitution and a range of functional groups allowed the synthesis of a number of vicinal difunctionalized cyclopentanes. For example, cyclization/hydrosilylation of the phthalimidomethyl-substituted diene **6** followed by oxidation gave cyclopentane **7** in 72% overall yield (eq 9).[17] Although olefins are a particularly versatile functional group, attempted synthesis of functionalized alkenylcyclopentanes via cyclization/hydrosilylation of 1,2,7-octatrienes or 1,3,8-nonatrienes was unsuccessful. However, alkenylcyclopentanes were formed in good yield with high *E*-selectivity via ring-opening cyclization/hydrosilylation of 1-cyclopropyl-1,6-dienes (eq 10).[22]



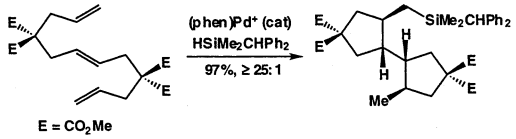
(9)



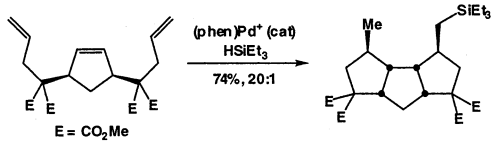
(10)

Cascade Cyclization/Hydrosilylation. Because polycyclic compounds represent an important subset of the naturally occurring carbocycles, palladium-catalyzed cyclization/hydrosilylation was applied to the synthesis of a number of silylated bicyclic compounds starting from the corresponding monocyclic dienes (eqs 4, 6, and 7).

However, a more desirable approach to the synthesis of polycyclic compounds that has been employed to good effect under both biological and laboratory conditions is through the multiple (cascade) cyclization of a suitably designed polyene.[23] For this reason, we have also explored the synthesis of polycyclic compounds via palladium-catalyzed cascade cyclization/hydrosilylation. To this end, both tethered bicyclopentanes (eq 11) and linear triquinanes (eq 12) were synthesized in a single step via cascade cyclization/hydrosilylation of the corresponding triene. These cascade cyclizations are significant both because they form compounds not otherwise accessible via cyclization/hydrosilylation and because they form multiple, contiguous stereocenters with high diastereoselectivity.[19]



(11)



(12)

Asymmetric Cyclization/Hydrosilylation

Due to the tendency of biological systems to form chiral compounds as a single enantiomer and to interact differently with the two enantiomers of a racemic mixture, stringent requirements exist regarding the enantiomeric purity of pharmaceuticals. For this reason, there is an intense current interest in the development of new, highly enantioselective organic transformations.[24] Transition metal catalysis has proven particularly well-suited to asymmetric synthesis due to the high levels of chemo- and enantioselectivity often realized via transition metal-based approaches and because catalysis obviates the need for both a stoichiometric amount of the enantiomerically pure reagent and the separation of enantiomers via resolution or chiral chromatography.[24] However, C−C bond-forming processes represent a small subset of catalytic asymmetric transformations, and processes that form both a C−C bond and a ring remain acutely limited.[24] For this reason, we devoted considerable effort to the development of an effective asymmetric diene cyclization/hydrosilylation procedure.

The high diastereoselectivity of cyclization/hydrosilylation catalyzed by palladium phenanthroline complexes pointed to an ordered transition state for ring closure (see below), which suggested the feasibility of asymmetric cyclization/hydrosilylation. A number of palladium complexes that contained enantiomerically pure bidentate nitrogen ligands were screened as catalysts for asymmetric cyclization/hydrosilylation, and from this group, pyridine-oxazoline complex **8** emerged as an effective and highly selective catalyst (Scheme 3).[25−27] The effectiveness of complex **8** as a catalyst for asymmetric cyclization/hydrosilylation was somewhat unusual, given the low, C_1-symmetry of the pyridine-oxazoline ligand, as opposed to the more desirable C_2-symmetry.[24] Nevertheless, reaction of diene **9** and benzhydryldimethylsilane catalyzed by **8**/$NaBAr_4$ led to isolation of carbocycle **10** in 98% yield as a single diastereomer with 95% enantiomeric excess (ee), which was subsequently oxidized to give alcohol **11** in 87% yield (Scheme 3).[18] Asymmetric cyclization/hydrosilylation/oxidation tolerated a number of functional groups and both allylic and terminal olefinic substitution (Table 2).[18]

Scheme 3

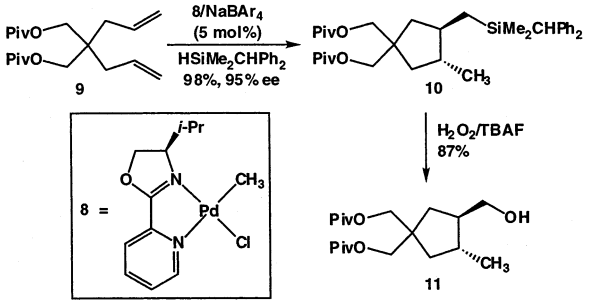
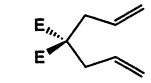
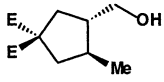
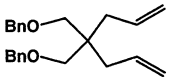
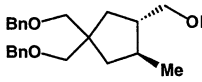
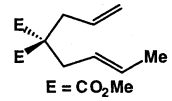
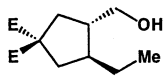
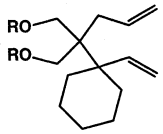
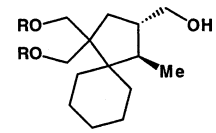
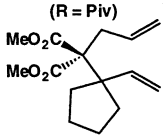
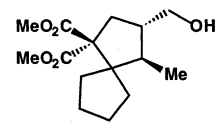


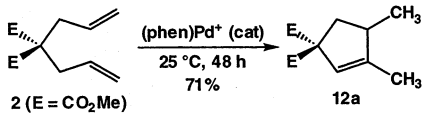
Table 2. Asymmetric Diene Cyclization/Hydrosilylation Employing Benzhydryldimethylsilane Catalyzed by 8/$NaBAr_4$ (5 Mol %) Followed by Oxidation (TBAF/H_2O_2)

diene	alcohol	overall yield (%)	ee (%)
			
E = CO_2Me		84	93
E = CO_2Bn		77	94
		65	95
		66	90
E = CO_2Me			
		58	93
(R = Piv)			
		96	88

Cycloisomerization

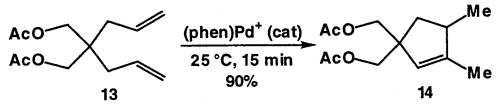
Palladium Phenanthroline Catalysts. As outlined in the Introduction, we sought to develop effective palladium-catalyzed protocols for both the cyclization/hydrosilylation and cycloisomerization of functionalized dienes. With respect to this latter goal, we have shown that cationic palladium phenanthroline complexes catalyze the selective exo,exo cycloisomerization of 1,6-dienes to form chiral cyclopentenes.[28] For example, reaction of diene **2** and a catalytic amount of **4**/$NaBAr_4$ (5 mol %) for 2 days at room

temperature formed predominantly (~90% selectivity) the chiral cyclopentene **12a**, which was isolated in 71% yield with 98% isomeric purity after chromatography (eq 13).[28] The rate of cycloisomerization depended strongly on the



(13)

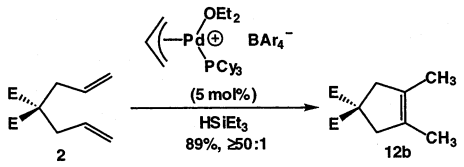
nature of the homoallylic groups of the diene, and cycloisomerization of the acetoxymethyl-substituted diene **13** was complete within 15 min at room temperature to form cyclopentene **14** in 90% isolated yield with 98% isomeric purity (eq 14).[29] Since the time we initiated our



(14)

studies in this area, a number of highly selective late transition metal-catalyzed diene cycloisomerization protocols have been reported,[30−33] including the conversion of 1,6-dienes to methylenecyclopentanes catalyzed by ruthenium[30] and nickel[31] complexes and the conversion of **2** to **12a** catalyzed by $PdCl_2(CH_3CN)_2$.[32]

(π-Allyl)Palladium Catalysts. The first general and selective procedure for the cycloisomerization of functionalized 1,6-dienes to form symmetric cyclopentenes was discovered inadvertently in an attempt to identify new catalysts for diene cyclization/hydrosilylation. Specifically, reaction of diene **2** and triethylsilane catalyzed by the cationic (π-allyl)palladium complex $[(\eta^3\text{-}C_3H_5)Pd(OEt_2)\text{-}PCy_3]^+[BAr_4]^-$ (5 mol %)[34] gave none of the expected cyclization/hydrosilylation product **3a**, but instead formed the symmetric cyclopentene **12b** in 89% isolated yield with ≥98% isomeric purity (eq 15).[35,36] Although not incorporated into the product, silane was required for both high activity and high selectivity in diene cycloisomerization and presumably served as a hydride donor to generate an active palladium hydride catalyst (see below). Silane-mediated diene cycloisomerization tolerated a number of functional groups as well as allylic and terminal olefinic substitution.[35,36]

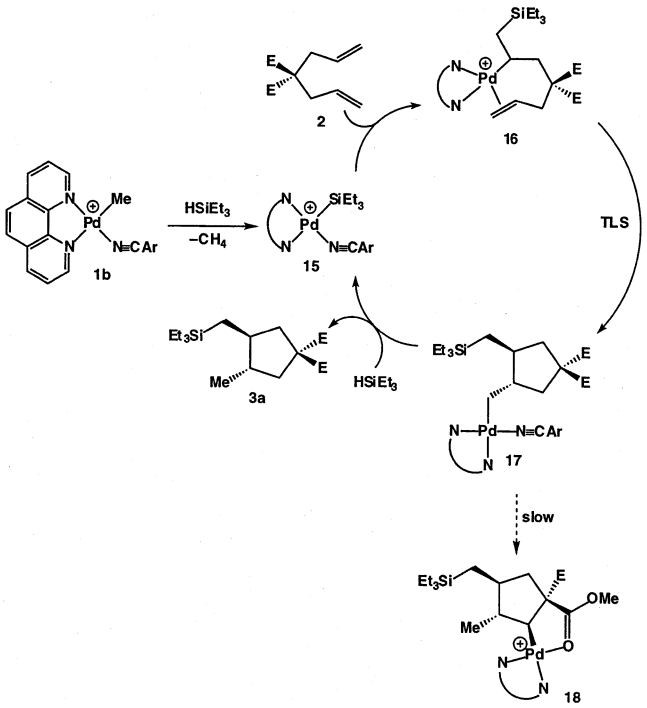


(15)

Mechanistic Studies

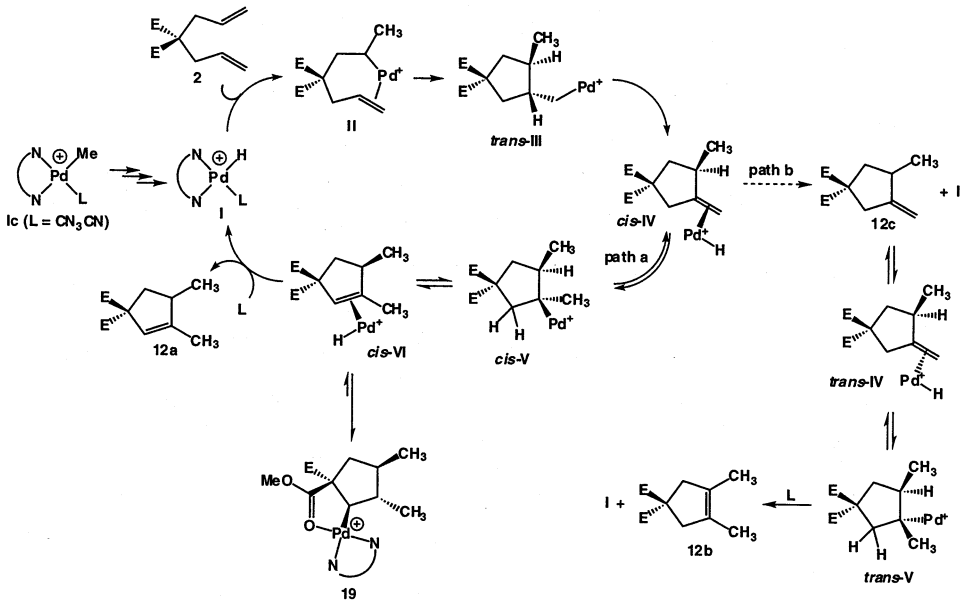
In contrast to the many advances that have been made in the development and synthetic applications of late transition metal-catalyzed annulation processes, little information regarding the mechanisms of these transformations has been forwarded.[1] Mechanisms involving the β-migratory insertion of an olefin into the M−C bond of an alkyl olefin chelate complex (intramolecular carbometalation) are often proposed for late transition metal-catalyzed cyclization processes, and the diastereoselectivities of these transformations are then rationalized in the context of chairlike intermediates and transition states for intramolecular carbometalation.[1] However, these contentions have not been confirmed. Furthermore, intramolecular carbometalation has never been directly observed, and as a result, the factors that control this process remain poorly understood. The lack of mechanistic information regarding late transition metal-catalyzed cyclization processes is unfortunate, as an understanding of these mechanisms could facilitate the development of new and more selective transition metal-catalyzed procedures. For these reasons, we have studied the mechanisms of the palladium-catalyzed cyclization processes developed in our laboratory.

Scheme 4



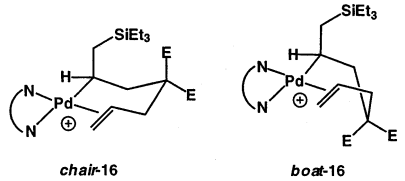
Cyclization/Hydrosilylation. We have studied the mechanism of the cyclization/hydrosilylation of dimethyl diallylmalonate (**2**) catalyzed by the cationic palladium phenanthroline complex $[(phen)Pd(Me)(NCAr)]^+[BAr_4]^-$ [Ar = 3,5-$C_6H_3(CF_3)_2$] (**1b**) to form the silylated cyclopentane **3a**.[37,38] Low-temperature NMR experiments, supported by kinetic and deuterium labeling studies, established the mechanism depicted in Scheme 4, initiated by conversion of precatalyst **1b** to the catalytically active palladium silyl complex **15** via reaction with silane.[13] Insertion of one of the olefins of diene **2** into the Pd−Si bond of **15** (silylpalladation) coupled with coordination of the pendant olefin forms the palladium alkyl olefin chelate complex **16**, which is the resting state of catalysis. Note that silylpalladation accounts for delivery of the silyl group to the less hindered olefin in the cyclization/hydrosilylation of substituted dienes (eqs 4−6). Turnover-limiting intramolecular carbometalation of **16** forms the palladium cyclopentylmethyl complex **17**, which reacts

Scheme 5



with silane to release the silylated carbocycle **3a** and regenerate the palladium silyl complex **15**. In the absence of silane, cyclopentylmethyl complex **17** undergoes slow conversion to the palladium carbonyl chelate complex **18**. Each of the complexes **15**−**18** were observed and fully characterized by NMR spectroscopy.

The conversion of alkyl olefin chelate complex **16** to the cyclopentylmethyl complex **17** represents the first direct observation of intramolecular carbometalation and provides a unique opportunity to probe the effect of chelation on olefin β-migratory insertion. Chelation appears to facilitate β-migratory insertion, as the energy barrier for the conversion of **16** to **17** is >2 kcal mol^{-1} lower than the barrier for β-migratory insertion in the analogous nonchelated complex [(phen)Pd(CH_2CH_3)-(H_2C═CH_2)]$^+$[BAr_4]$^-$.[12] As noted above, intramolecular carbometalation has been assumed to involve chairlike intermediates and transition states.[1] However, the chairlike conformation of **16** (chair-**16**) that would lead to trans cyclization would require an unfavorable pseudoaxial α-triethylsilylmethyl substituent, and for this reason, we have proposed that **16** instead adopts a boatlike conformation (boat-**16**).[37] Although the conformation of **16** could not be determined spectroscopically, DFT calculations of the hypothetical palladium hexenyl chelate complex {(NH═CHCH═NH)Pd[η^1,η^2-CH(CH_2Me)CH_2C(Me)$_2CH_2$-CH═CH_2]}$^+$ revealed that the axial boatlike conformation was ≥3 kcal mol^{-1} more stable than was the axial chairlike conformation.[37,39]



chair-16 *boat*-16

Palladium Phenanthroline-Catalyzed Cycloisomerization. The most distinctive feature of diene cycloisomerization catalyzed by palladium phenanthroline complexes was the selective formation of the chiral cyclopentene in preference to the more stable symmetric cyclopentene.[40] Also unusual was that cycloisomerization of dimethyl diallylmalonate (**2**) catalyzed by **4**/$NaBAr_4$ (eq 13) was several orders of magnitude slower than was either cycloisomerization of bis(acetoxymethyl)-substituted diene **13** (eq 14) or cyclization/hydrosilylation of **2** and $HSiEt_3$ (eq 3) under comparable conditions. Both to address these specific issues and to formulate a detailed mechanistic picture of palladium-catalyzed cycloisomerization, we have studied the mechanism of the cycloisomerization of diene **2** catalyzed by the cationic palladium phenanthroline complex [(phen)Pd(Me)($NCCH_3$)]$^+$-[BAr_4]$^-$ [Ar = 3,5-$C_6H_3(CF_3)_2$] (**1c**) to form the chiral cyclopentene **12a**.[41]

Kinetic, deuterium labeling, and in situ NMR studies of the cycloisomerization of **2** catalyzed by **1c** were in accord with the mechanism depicted in Scheme 5, initiated by conversion of precatalyst **1c** into the catalytically active palladium hydride species **I**.[41] Insertion of an olefin of **2** into the Pd−H bond of **I** (hydrometalation) coupled with coordination of the pendant olefin could form the alkyl olefin chelate complex **II**, which could undergo intramolecular carbometalation to form the palladium cyclopentylmethyl intermediate *trans*-**III**. The trans selectivity of intramolecular carbometalation was anticipated, given the trans stereochemistry of intramolecular carbometalation in the cyclization/hydrosilylation of **2** (**16** → **17**, Scheme 4), and was established independently through two key observations. First, chiral cyclopentene **12a** was formed exclusively (≥98%) as a kinetic product of cycloisomerization and not via secondary isomerization of methylenecyclopentane **12c** or any other isomer (Scheme 5, path a). Second, NMR analysis of catalytically active mixtures of **2** and **1c** established palladium carbonyl chelate complex **19** as the resting state of catalysis (Scheme 5, path a). Because neither methylenecyclopen-

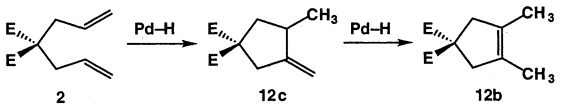
tane **12c** nor any other carbocyclic fragment dissociated from palladium prior to formation of resting state **19**, and because no mechanism exists for palladium to migrate from one face of the carbocycle to the other, the trans stereochemistry of the exocyclic methyl groups of **19** necessarily mirrors the trans stereochemistry of intramolecular carbometalation.

Isomerization of *trans*-**III** via β-hydride addition/elimination without displacement of methylenecyclopentane **12c** from intermediate *cis*-**IV** would selectively form the palladium cyclopentyl intermediate *cis*-**V** (Scheme 5, path a). Because a syn-coplanar arrangement of atoms is required for β-hydride elimination, and because the palladium atom and the tertiary β-hydrogen atom of *cis*-**V** are positioned on opposite faces of the cyclopentyl ring, elimination of the tertiary β-hydrogen atom, which would ultimately lead to formation of symmetric cyclopentene **12b**, is precluded. Conversely, β-elimination of the secondary hydrogen atom syn to the palladium atom of *cis*-**V** forms intermediate *cis*-**VI**, which undergoes turnover-limiting olefin displacement to form chiral cyclopentene **12a**, to the exclusion of **12b** (Scheme 5, path a).[41,42]

As outlined in the preceding paragraph, selective formation of the chiral cyclopentene **12a** in preference to the symmetric cyclopentene **12b** in the cycloisomerization of **2** catalyzed by **1c** can be traced directly to the stereochemistry of intermediate *cis*-**V**. Selective formation of *cis*-**V**, in turn, requires both trans-selective carbometalation (**II** → *trans*-**III**) and isomerization of *trans*-**III** to *cis*-**V** without displacement of **12c** (Scheme 5, path a). If either of these conditions were not met, intermediate *trans*-**V** would form in preference to of *cis*-**V**, and cyclopentene **12b** would form in preference of **12a**. For example, cis-selective carbometalation would form *trans*-**V**, to the exclusion of *cis*-**V**. Similarly, because palladium olefin intermediate *trans*-**IV** is more stable than *cis*-**IV** due to the unfavorable steric interaction between the palladium atom and the proximal methyl group in the latter isomer, displacement of **12c** from *cis*-**IV** would lead to cis-to-trans isomerization to form *trans*-**IV**, which would subsequently isomerize to palladium cyclopentyl intermediate *trans*-**V** (Scheme 5, path b). Because the palladium atom of *trans*-**V** has a syn relationship with both the secondary and tertiary β-hydrogen atoms, β-hydride elimination could form either **12a** or **12b** and would likely favor the more stable symmetric cyclopentene **12b** (Scheme 5, path b).

Competing with turnover-limiting displacement of chiral cyclopentene **12a** from intermediate *cis*-**VI** is formation of resting state **19** via hydride addition coupled with coordination of the pendant carbonyl oxygen atom (Scheme 5, path a). Due to the high stability of five-membered palladium carbonyl chelate compounds,[11,43] formation of **19** effectively removes palladium from the catalytic cycle and significantly reduces the rate of cycloisomerization. Conversely, no stable five- or six-membered carbonyl chelate complex analogous to **19** can form during the cycloisomerization of the acetoxymethyl-substituted diene **13** (eq 14), while facile silylation of the palladium cyclopentylmethyl intermediate **17** precludes formation of carbonyl chelate complex **18** in the catalytic cyclization/hydrosilylation of **2** (Scheme 4). The formation of a stable five-membered carbonyl chelate complex in the palladium phenanthroline-catalyzed cycloisomerization of **2** but in neither the cycloisomerization of **13** nor the cyclization/hydrosilylation of **2** accounts for the significantly higher reaction rates of these latter transformations relative to the cycloisomerization of **2**.[29,41]

(π-Allyl)Palladium-Catalyzed Cycloisomerization. According to the analysis outlined above, the selective formation of chiral cyclopentene **12a** in the cycloisomerization of **2** catalyzed by palladium phenanthroline complex **1c** required both trans-selective carbometalation (**II** → *trans*-**III**) and isomerization of *trans*-**III** to *cis*-**V** without displacement of methylenecyclopentane **12c** (Scheme 5, path a). This analysis suggests that at least one of these conditions is not met in the silane-promoted, (π-allyl)-palladium-catalyzed cycloisomerization of **2**, which forms the symmetric cyclopentene **12b**, to the exclusion of the chiral cyclopentene **12a**. To test this hypothesis, we studied the mechanism of the cycloisomerization of **2** catalyzed by (η^3-C_3H_5)Pd(Cl)PCy_3/$NaBAr_4$ in the presence of $HSiEt_3$,[36] and the results of these studies were in accord with a mechanism involving C−C bond formation via intramolecular carbometalation (Scheme 5). Although we were unable to determine the stereochemistry of intramolecular carbometalation, analysis of concentration versus time plots and authentic samples of **12c** under reaction conditions established a mechanism involving initial, selective cycloisomerization of **2** to form free methylenecyclopentene **12c**, followed by secondary isomerization of **12c** to symmetric cyclopentene **12b** (eq 16).[36] Isomerization of **12c** to **12b** presumably involves sequential formation of intermediates *trans*-**IV** and *trans*-**V**, followed by selective elimination of the tertiary β-hydrogen atom of *trans*-**V** to form **12b** (Scheme 5, path b).



2 12c 12b **(16)**

Summary

The development of new catalysts that display high activity along with good selectivity and functional group compatibility remains an important challenge in homogeneous catalysis. We have addressed this problem through the employment of cationic, electrophilic palladium complexes as catalysts for diene cyclization. These efforts have produced a number of potentially useful transformations, including the selective cycloisomerization of 1,6-dienes to form either symmetric or chiral cyclopentenes, the cyclization/hydrosilylation of 1,6- and 1,7-dienes to form trans-silylated cycloalkanes, and the asymmetric cyclization/hydrosilylation of 1,6-dienes to form silylated cyclopentanes with up to 95% ee. In addition to high regio- and stereoselectivity, these palladium-catalyzed processes

displayed good functional group compatibility, low air- and moisture-sensitivity, and often high activity.

The development and the application of transition metal-catalyzed processes to complex molecule synthesis often outpaces an understanding of the mechanisms of these transformations. For this reason, we have focused our attention on both the synthetic and mechanistic aspects of palladium-catalyzed diene cyclization. Both diene cycloisomerization and cyclization/hydrosilylation catalyzed by cationic palladium phenanthroline complexes proved well-suited to mechanistic investigation, and the results of these studies established mechanisms involving C−C bond formation via trans-selective intramolecular carbometalation of an alkyl olefin chelate complex, which was directly observed in the case of cyclization/hydrosilylation. Intramolecular carbometalation was both the turnover-limiting and stereochemical-determining step of cyclization/hydrosilylation and was the product-determining step in palladium phenanthroline-catalyzed cycloisomerization, given the nondissociative nature of this transformation.

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