

The Formation of Functionalized Carbocycles by Tandem Cyclization/Hydrosilylation Reactions of Dienes

Jeffrey B. Johnson

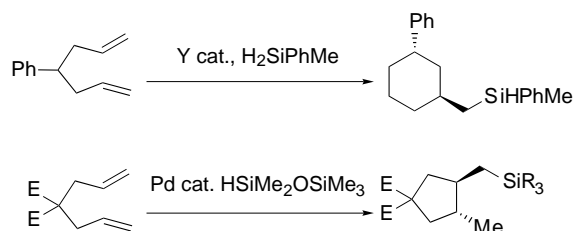
University of Wisconsin-Madison, Department of Chemistry

Madison, WI 53706

jjohnson@chem.wisc.edu

Received Date (will be automatically inserted after manuscript is accepted)

ABSTRACT



Palladium and yttrium catalyzed cyclization/hydrosilylation cascade reactions provide an efficient and selective route to silylated carbocycles from dienes. These transition metal catalysts display complementary reactivity in product regiochemistry and functional group compatibility. Extension of these methods to hindered olefins and the use of asymmetric catalysts readily provide complex silylated carbocycles. Recently developed oxidation procedures offer efficient transformation of these carbocycles to a diverse range of synthetically versatile carbocyclic alcohols.

Substituted carbocycles represent one of the most common subunits of biologically active and naturally occurring molecules, and the development of efficient routes to these structures is an issue of central importance in synthetic organic chemistry.¹ Metal catalyzed cyclization/hydrosilylation reactions of dienes provide versatile entry into these functionalized carbocycles from readily available starting materials. The utility of this tandem sequence as a route to a diverse range of synthetic building blocks has improved with the recent development

of reliable methods to oxidize silylated carbocycles to the more synthetically versatile carbocyclic alcohols.²

Many processes have been developed to catalyze the cyclization/hydrosilylation of diynes and enynes.^{3,4} The analogous process for dienes has proven to be more difficult. Among those that have been successful,⁵

¹ Hudlicky, T.; Price, J. D. *Chem. Rev.* **1989**, *89*, 1467. Trost, B. M. *Chem. Soc. Rev.* **1982**, *11*, 141.

² a) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044. b) Peng, Z. H.; Woerpel, K. A. *Org. Lett.* **2000**, *2*, 1379.

³ Molander, G. A.; Romero, J. A. C. *Chem. Rev.* **2002**, *102*, 2161 and references therein.

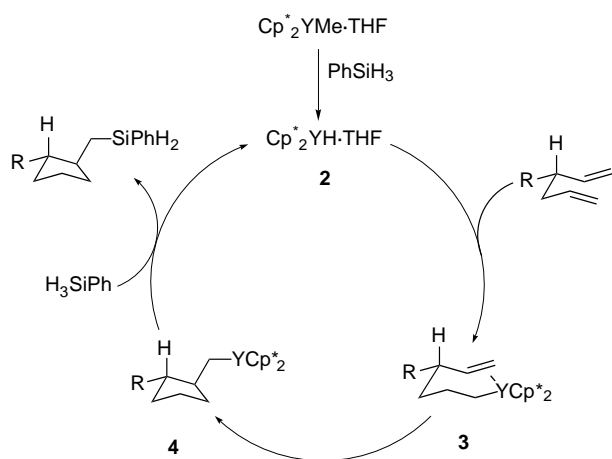
⁴ Ojima, I.; Maralee, A. C.; Cassar, V. C. *Top. Catal.* **2002**, *19*, 89 and references therein.

⁵ Radicals: a) Kraus, G. A.; Lira, S. *Tetrahedron Lett.* **1990**, *31*, 5265. b) Kopping, B.; Chatgililoglu, C.; Sehnder, M.; Griese, B. *J. Org. Chem.* **1992**, *57*, 3994. Zr: c) Molander, G. A.; Corrette, C. P. *Tetrahedron Lett.*

organoyttrium⁶ and organopalladium⁷ catalysts demonstrate considerable ability in promoting these reactions with high levels of specificity, efficiency and atom economy. These systems have proven to be effective in preparing cyclized organosilanes from acyclic diene or triene materials while displaying regio- and diastereoselectivity common to homogeneous transition metal catalysis.

Based upon previous studies in which organoyttrium complexes catalyze cyclooligomerization and hydrosilylation in independent reactions, Molander and coworkers developed a one-pot procedure combining these two reactions.⁸ In the presence of $\text{Cp}^*_2\text{YCH}_3\cdot\text{THF}$ (**1**) and phenylsilane, 1,5- and 1,6-dienes undergo tandem cyclization/hydrosilylation to form phenylsilyl-substituted carbocycles in good yields and moderate diastereoselectivity (Table 1). In each case, the product is primarily a single regioisomer. Despite the extreme Lewis acidity of the yttrium metal center, functional groups such as ethers, thioacetals and tertiary amines are tolerated, but reactivity is limited to unsubstituted olefins.

Scheme 1



The regio- and stereoselectivity of this transformation can be explained through discussion of the proposed mechanism (Scheme 1). The active species, $\text{Cp}^*_2\text{YH}\cdot\text{THF}$ (**2**) is formed via σ -bond metathesis of the catalyst precursor with phenylsilane. The least hindered olefin of the substrate inserts into the yttrium hydride bond, forming terminal organometallic species **3**. The remaining olefin undergoes an intramolecular insertion through a stereoselective chair-like transition state and forms yttrium alkyl species **4**. The cycle is completed with a σ -bond metathesis reaction to regenerate the active yttrium hydride.

1998, 39, 5011. Nd: d) Onozawa, S.; Sakakura, T.; Tanaka, M. *Tetrahedron Lett.* **1994**, 35, 8177. Sm: e) Fu, P.-F.; Brard, L.; Li, Y.; Marks, T. J. *J. Am. Chem. Soc.* **1995**, 117, 7157.

⁶ Molander, G. A. *Chemtracts* **1998**, 11, 237 and references therein.

⁷ Widenhoefer, R. A. *Acct. Chem. Res.* **2002**, 35, 905 and references therein.

⁸ Molander, G. A.; Nichols, P. J. *J. Am. Chem. Soc.* **1995**, 117, 4415.

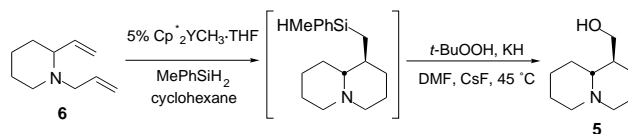
Table 1. Cyclization/hydrosilylation reaction of dienes catalyzed by **Y** precatalysts **1** and **7**.

Entry	Substrate	Product	Yield (%)
1			74 ^a
		9:1 dr, 1 h	
2			97 ^{a,d}
		2 h	
3			95 ^b
		>50:1 dr, 14 h	
4			92 ^b
		>50:1 dr, 12 h	
5			63 ^c
		3 h	
6			85 ^c
		49:1 dr, 12 h	

^a Reactions performed with 5 mol% **1** using phenylsilane at room temperature. ^b Reactions performed using 4.5 mol% **7** with phenylsilane at 90 °C. ^c Reactions performed using 4.5 mol% **7** with phenylsilane at room temperature. ^d Used methylphenylsilane.

To demonstrate the utility of this reaction, Molander and coworkers completed the total synthesis of the naturally occurring alkaloid (\pm)-epilupinine (**5**) using cyclization/hydrosilylation as the key step in determining diastereoselectivity (Scheme 2).⁹ From diene **6**,

Scheme 2



⁹ Molander, G. A.; Nichols, P. J. *J. Org. Chem.* **1996**, 61, 6040.

cyclization/hydrosilylation followed by oxidation of the resulting silane produced (\pm)-epilupinine as a single diastereomer in 62% yield.

The development of the modified organoyttrium catalyst $[(Cp^{TMS})_2YMe]_2$ (**7**) allows the transformation of more sterically hindered 1,1-disubstituted olefins.¹⁰ With the use of these more complex substrates, bicyclic, spirocyclic and propellane silylated products can be efficiently prepared (Table 1, entries 3, 5, 6). A notable reactivity trend of the more active catalyst **7** is demonstrated with a substrate containing a vinylic aryl moiety. The resulting products show different regioselectivity than products obtained using **1** or saturated cyclic substrates. With vinylic aryl substrates, the yttrium hydride formed from **7** preferentially reacts with the vinyl olefin, producing a secondary organometallic intermediate adjacent to the aryl substitution before undergoing cyclization (Table 1, entry 6).¹¹ The extended reactivity of **7** is further displayed by using a 1,1-disubstituted olefin to construct a quaternary center in the newly formed carbocycle (Table 1, entries 4 and 5)¹⁰.

Despite the promise of this system, there are several potential drawbacks. The considerable Lewis acidity and oxophilicity of the yttrium catalysts result in extreme air and moisture sensitivity and a lack of general functional group compatibility.¹² In addition, the desirable progression to the production of enantiomerically enriched carbocycles is a difficult challenge. To date, only one report of such a system has been published, albeit with minimal enantioselectivity.¹³

In order to circumvent the restrictions of the yttrium based catalysts, Widenhoefer and coworkers have utilized palladium complexes **8** and **9** (Figure 1) to catalyze cyclization and hydrosilylation reactions of dienes. Upon addition of $NaBAR_4$ [$Ar'=3,5-C_6H_3(CF_3)_2$], cationic complexes such as **10** are formed. These complexes are electrophilic in nature and contain an open coordination site, resulting in a propensity for β -migratory insertion as

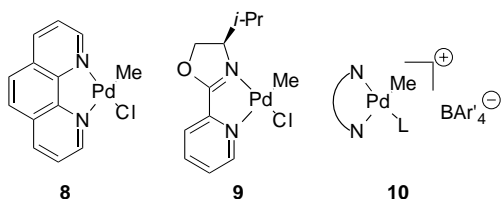


Figure 1. Palladium cyclization/hydrosilylation catalyst precursors and representative cationic complex

¹⁰ Molander, G. A.; Dowdy, E. D.; Schumann, H. J. *Org. Chem.* **1998**, *63*, 3386.

¹¹ Molander, G. A.; Schmitt, M. H. *J. Org. Chem.* **2000**, *65*, 3767.

¹² Piers, W. E.; Shapiro, P. J.; Bunel, E. E.; Bercaw, J. E. *Synlett*, **1990**, 74.

¹³ Muci, A. R.; Bercaw, J. E. *Tetrahedron Lett.* **2000**, *41*, 7609.

Table 2. Cyclization/hydrosilylation reactions catalyzed by Pd precatalyst **13** (E = CO₂Me for all substances).

Entry	Substrate	Product	Yd ^a	Yd ^b	ee ^c
			(%)	(%)	(%)
			X=SiR ₃ , X=OH		
1			87	77	94
2			87	66	90
3			67	54	20
4			98	96	88
5			97 ^d	82	66

^a Reactions performed with 5 mol% (*R*)-**13** and $NaBAR_4$ (1:1) and benzhydryldimethylsilane at -20 °C in CH_2Cl_2 . ^b Oxidation performed with excess TBAF, $KHCO_3$, and H_2O_2 in THF/MeOH/EtOAc (2/1/0.1) at room temperature. ^c Enantiomeric excess of oxidation product. ^d Used 10 mol% catalyst.

well as reaction with Si-H bonds. These characteristics result in complexes that catalyze the cyclization/hydrosilylation of dienes with high yields and excellent diastereoselectivities.

With the use of the enantiomerically pure palladium (*R*)-(+)-4-isopropyl-2-(2-pyridinyl)-2-oxazoline (**9**) precursor, $NaBAR_4$ and silane, 1,6-dienes can be transformed into the corresponding silylated 1,2-dimethylcyclopentane derivatives in excellent yields and enantioselectivities, while 1,7-dienes maintain trans selectivity but are less successful.^{14,15} Benzhydryldimethylsilane has proven to be effective in promoting high yields and enantioselectivities. In addition, benzhydryldimethylsilyl products can be readily oxidized to yield the corresponding optically active carbocyclic alcohol in high yield (Table 2).^{2b} Functional groups compatible with these robust catalyst systems include ketones, ethers, amides and sulfones; in addition,

¹⁴ a) Perch, N. S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **1999**, *121*, 6960. b) Perch, N. S.; Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2000**, *65*, 3836.

¹⁵ a) Stengone, C. N.; Widenhoefer, R. A. *Tetrahedron Lett.* **1999**, *40*, 1451. b) Widenhoefer, R. A.; Stengone, C. N. *J. Org. Chem.* **1999**, *64*, 8681.

the presence of small amounts of water or air have no detrimental effect on reaction rate, yield, or selectivity.

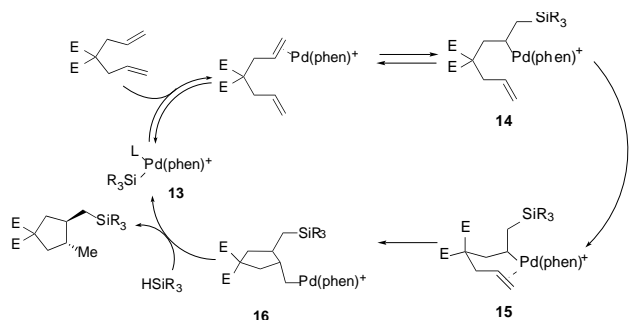
Although the cyclization/hydrosilylation reaction forms bicyclic structures when the diene contains a preexisting carbocycle, a more desirable approach to polycyclic structures entails the use of polyenes. Toward this end, the use of linear trienes have led to optically active polycyclic structures (Table 2, entry 5).¹⁶ Using the achiral catalyst precursor **8**, triene 3,5-bis(3-butenyl)cyclopentane (**11**) was transformed into the silylated linear triquinane (**12**) in 74% yield as a 20:1 ratio of isomers (Scheme 3).¹⁷ This cascade served to set four contiguous stereocenters, exemplifying the possible dramatic increase of molecular complexity in a single reaction.

Scheme 3



For their extensive mechanistic study of this tandem reaction, Widenhoefer and coworkers chose the achiral catalyst precursor (phen)PdMe(Cl) (**8**) (Scheme 4). In the presence of NaBAR₄ and triethylsilane, active Pd-Si species **13** is formed. Reversible coordination and insertion of the least substituted olefin results in a secondary palladium alkyl complex, **14**. The remaining olefin coordinates forming **15** and inserts via a chair-like transition state to form palladium-alkyl intermediate **16** with trans stereochemistry. This complex reacts with silane to regenerate the active species. Low temperature studies have allowed the observation and characterization of the intermediates **14**, **15**, and **16** by NMR spectroscopy when

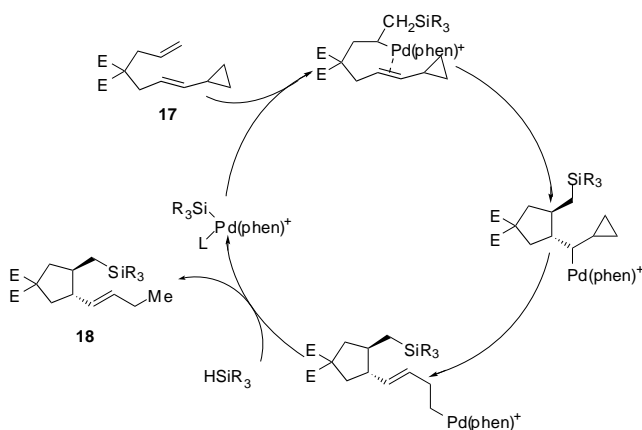
Scheme 4



using HSiEt₃, and further studies have confirmed the viability of each of these complexes as intermediates in the catalytic cycle.¹⁸

In a recent publication, Widenhoefer and coworkers presented the use of 1-cyclopropyl-1,6-heptadienes as substrates in the cyclization/hydrosilylation reaction.¹⁹ During cyclization of these dienes, insertion of the second, more hindered olefin is followed by β-alkyl elimination to open the cyclopropyl ring and selectively form the trans-substituted olefin (Scheme 5). Cyclization/hydrosilylation of 1-cyclopropyl-1,6-heptadiene **17** produced the silylated vinylcyclopentane **18** in 69% yield with an enantiomeric excess of 73%. The retention of the olefin functionality increases the versatility of the product for use in further reactions.

Scheme 5



As with the yttrium catalyzed reaction, substrate functionality is of central importance to the limitations of the palladium catalyzed cyclization/hydrosilylation. In sharp contrast to yttrium catalysis, however, the primary drawback of the palladium catalysts is the requirement of the presence of an oxygen containing functionality in the homoallylic position between the olefins, significantly limiting the range of substrates available for this transformation.

For the catalysis of tandem cyclization/hydrosilylation reactions, Y-based and Pd-based catalysts demonstrate complementary reactivity based on functional group compatibility and regioselectivity. Both have proven to efficiently provide ready entry into functionalized carbocyclic systems. Continued development of catalyst design promises the improvement of enantioselectivities and substrate compatibility of these routes to further functionalized materials.

¹⁶ Pei, T.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 7639.

¹⁷ Wang, X.; Chakrapani, H.; Stengone, C. H.; Widenhoefer, R. A. *J. Org. Chem.* **2001**, *66*, 1755.

¹⁸ Perch, N. S.; Widenhoefer, R. A. *Organometallics* **2001**, *20*, 5251.

¹⁹ Wang, X.; Stankovich, S. Z.; Widenhoefer, R. A. *Organometallics* **2002**, *21*, 901.

