Highly Stereospecific Cyclizations of Homoallylic Silanols

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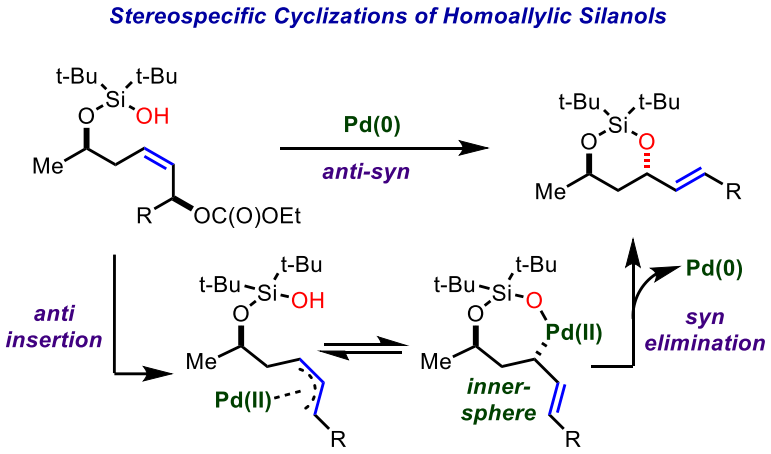
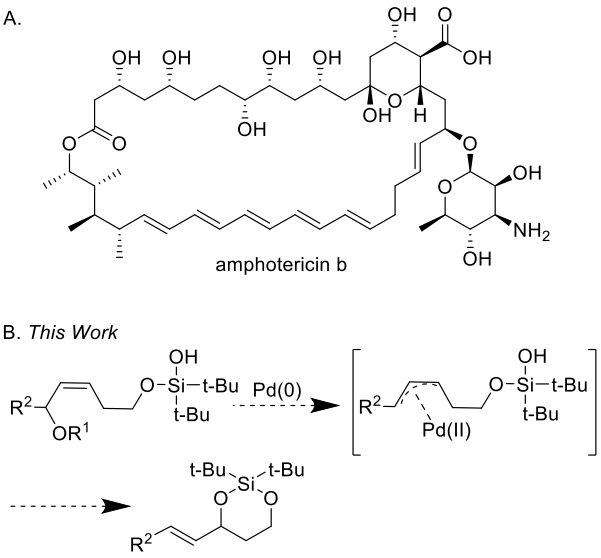


ABSTRACT We demonstrate that di-*tert*-butylsilanols are competent nucleophiles for the intramolecular interception of palladium π-allyl species. In these reactions, allyl ethyl carbonates are the best precursors for the formation of palladium π-allyl intermediates, and [(Cinnamyl)PdCl]$_2$/BINAP is superior to other Pd salt/ligand framework combinations. Our optimized protocol is compatible with a variety of silanol substrates. Importantly, the cyclization is perfectly stereospecific, proceeding *via* an *anti-syn* mechanism, which stands in contrast to reported analogous reactions of alcohols and phenols, which proceed via an *anti-anti* mechanism. The alkenes in the product dioxasilinanes serve as blank slates for further functionalization.

The invention of highly regioselective and stereoselective methods for the installation of carbon-heteroatom linkages remains a very active area of research.[1-4] The interception of palladium π-allyl complexes with carbon nucleophiles is a well-established method for the construction of C–C bonds,[5-12] but many opportunities remain for the analogous construction of C–O bonds.[13-19] Our laboratory has a programmatic focus on the development of the di-*tert*-butyl-silanol auxiliary for alkene manipulation reactions.[20-25] We envisioned a new method for the construction of C–O bonds *via* the intramolecular interception of a palladium π-allyl species with a pendant di-*tert*-butylsilanol functional group (**Scheme 1**). Based on our previous work as well as that of others,[26-31] we expected such a reaction to be highly chemo-, regio-, and diastereoselective. This would be an important addition to existing technology for the synthesis of complex polyhydroxylated molecules (**Scheme 1**).[32]

Scheme 1. (A) Many biologically active molecules are polyhydroxylated and stereochemically complex. (B) A potentially mild and highly selective method for protected 1,3-diol formation.



Before undertaking reaction optimization, we first had to develop a method that would allow for facile access to the requisite starting materials (**Scheme 2**). Using our laboratory's silylation procedure,[23] 3-butyn-1-ol or 4-pentyn-2-ol could be converted into the corresponding silanol. Bis-deprotonation with two equivalents of n-BuLi enabled condensation with a variety of aldehydes. Reduction of the alkyne to a *cis*-alkene was effected using Lindar's catalyst under 1 atm of H_2 gas. Finally, the free alcohol was converted into an ethyl carbonate using ethyl chloroformate and pyridine. This procedure was remarkably modular, reproducible, and scalable. We have carried it out reliably on starting scales as large as 10 mmol, and all substrates shown in this account were prepared using this method.

Scheme 2. Typical sequence for starting material preparation.

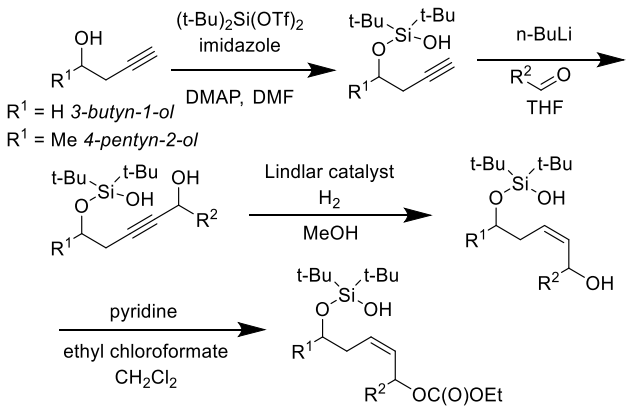
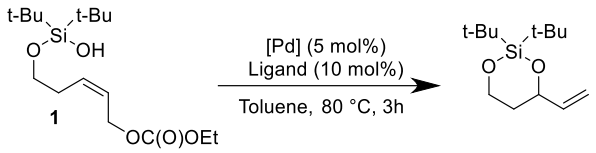


Table 1. Reaction Optimization



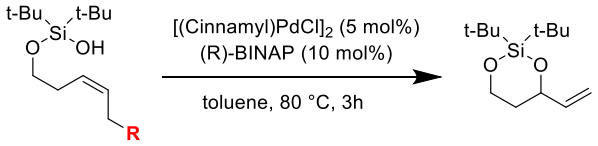
Entry	[Pd]	Additive[a]	Ligand	Yield (%)[b]
1	$Pd(PPh_3)_4$	-	(R)-BINAP[c]	35%
2	[(Cinnamyl)PdCl]$_2$	-	(R)-BINAP	62%
3	[(Cinnamyl)PdCl]$_2$	-	(R)-BINAP	28%[d] Trace[e]
4	[(Cinnamyl)PdCl]$_2$	-	(R)-DTBM-SEGPHOS	19%
5	[(Cinnamyl)PdCl]$_2$	-	Xantphos	27%
6	[(Cinnamyl)PdCl]$_2$	KO^{t}Bu	(R)-BINAP	46%
7	[(Cinnamyl)PdCl]$_2$	$NaHCO_3$	(R)-BINAP	42%
8	[(Cinnamyl)PdCl]$_2$	CH_3CO_2H	(R)-BINAP	trace
9	[(Cinnamyl)PdCl]$_2$	$PhCO_2H$	(R)-BINAP	NR

[a] 1 equiv. [b] Performed on a 0.1 mmol scale; yields are determined by ^{1}H NMR integration using methyl phenyl sulfone as an internal standard. [c] arbitrarily chosen as no enantioselectivity was observed. [d] at 110 °C. [e] at room temperature. See Supporting Information for additional conditions tested.

Treating **1** with $Pd(PPh_3)_4$ and (*R*)-BINAP gave cyclized product in 35% yield (**Table 1**, **Entry 1**). When $Pd(PPh_3)_4$ was replaced with [(Cinnamyl)PdCl]$_2$, the yield increased to 62% (**Table 1**, **Entry 2**). Maintaining the reaction temperature at 80 °C was crucial, as increasing it to 110 °C and decreasing it to 23 °C were both deleterious (**Table 1**, **Entry 3**). The reaction performance suffered when (*R*)-BINAP was replaced with either (*R*)-DTBM-SEGPHOS (**Table 1**, **Entry 4**) or Xantphos (**Table 1**, **Entry 5**). Using either base (**Table 1**, **Entries 6–7**) or acid additives (**Table 1**, **Entries 8–9**) was similarly deleterious.

A variety of allyl electrophiles have been used as precursors to palladium π-allyl species.[13] The ethyl carbonate and Boc moieties were chosen empirically for optimization (**Table 1** and **Scheme 3**, **Entries 1-2**). An examination of other leaving groups, including acetate (**Scheme 3**, **Entry 3**), benzoate (**Scheme 3**, **Entry 4**), and 2,2,2-trichloroethyl carbonate (**Scheme 3**, **Entry 5**), showed that none were superior to ethyl carbonate. Thus, for exploration of the substrate scope, ethyl carbonate was retained as the leaving group.

Scheme 3. Examination of leaving group effects.

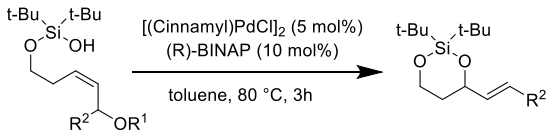


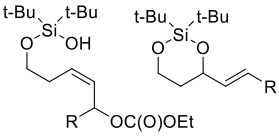
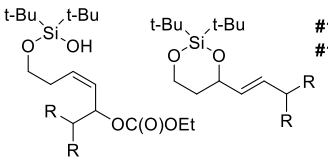
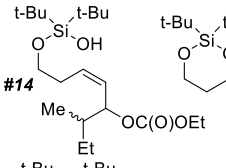
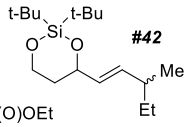
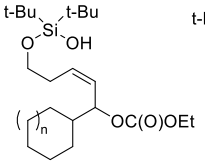
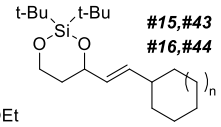
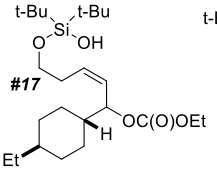
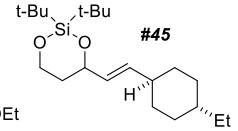
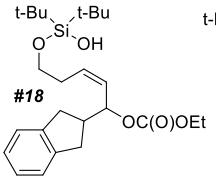
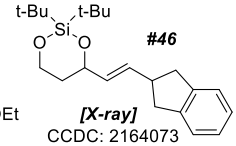
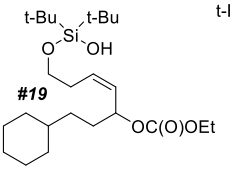
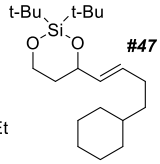
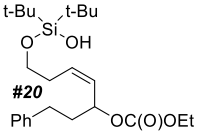
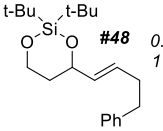
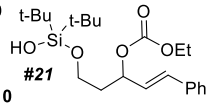
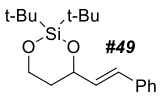
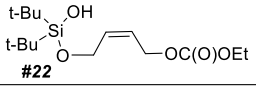
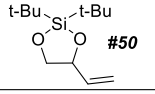
Entry	Leaving Group	Isolated Yield
1	R = OC(O)OEt	**60%**
2	R = OC(O)Ot-Bu	**43%**
3	R = OC(O)Me	**15%**
4	R = OC(O)Ph	**Trace**
5	R = OC(O)OCH$_2$CCl$_3$	**Trace**

Our optimized protocol was compatible with a variety of substrates, both with linear (**Scheme 4**, **Entry 1**) and branched alkyl chains (**Scheme 4**, **Entries 1-3**). Substrates with pendant cycloalkanes (**Scheme 4**, **Entries 4-7**), ethers (**Scheme 4**, **Entry 1**), and aromatic rings (**Scheme 4**, **Entries 1, 6, 8, and 9**) all reacted well. In general, *cis* alkene substrates were required for productive reaction; in our hands, only one *trans* alkene substrate (**Scheme 4**, **Entry 9**) cyclized as expected. In almost all reactions, starting material was consumed fully, and the remaining mass balance could be attributed to a linear diene side product arising from ionization and elimination of the allylic carbonate.[33] A crystal structure of **46** (CCDC 2164073) allowed us to unambiguously establish product identity. Most substrates were designed to form 6-membered dioxasilinane products, but a 5-membered dioxasilolane product (**Scheme 4**, **Entry 10**) could be forced to form.

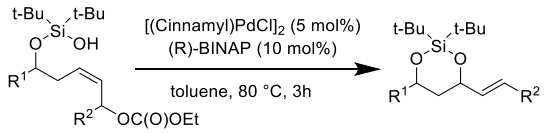
Yields were low, however, and the product was unstable for long-term storage, even in a freezer set to -20 °C.

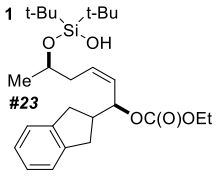
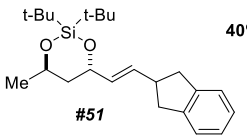
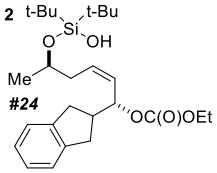
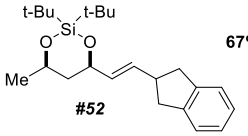
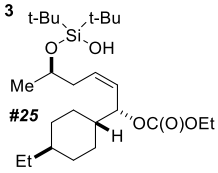
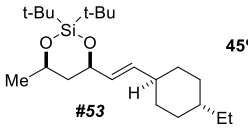
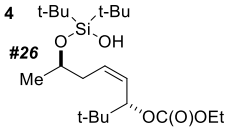
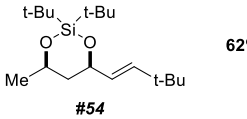
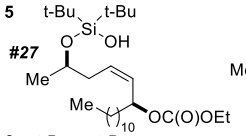
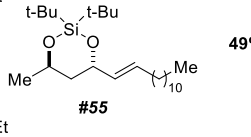
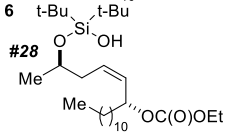
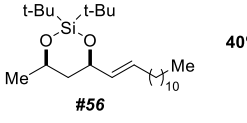
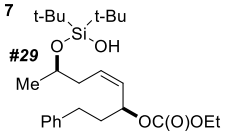
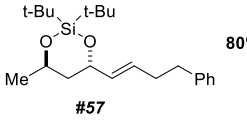
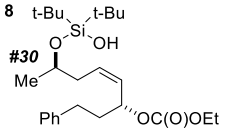
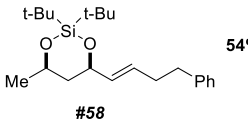
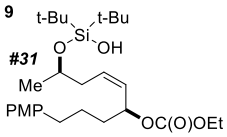
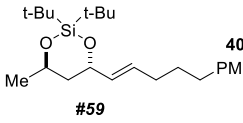
Scheme 4. Substrate scope with primary silanols.



entry	substrate	product			isolated yield
1			***#1,#33***	R = H	**60%**
			#6,#34	R = C_4H_9	**54%**
			#7,#35	R = C_6H_{13}	**55%**
			#8,#36	R = t-Bu	**62%**
			#9,#37	R = C_3H_6Ph	**51%**
			#10,#38	R = CH_2OBn	**56%**
			#11,#39	R = C_3H_6OBn	**48%**
2			***#12,#40***	R = Me	**50%**
			#13,#41	R = Et	**40%**
3			***#42***		**39%** *dr = ~1:1*
	#14				
4			***#15,#43***	n = 1	**60%**
			#16,#44	n = 3	**52%**
5			***#45***		**51%**
	#17				
6			***#46***		**49%**
	#18	***[X-ray]*** CCDC: 2164073			
7			***#47***		**46%**
	#19				
8			***#48***	*0.2 mmol*	**54%**
	#20			*1 mmol*	**52%**
9			***#49***		**54%**
	#21				
10			***#50***		**44%**
	#22				

Scheme 5. Substrate scope with secondary silanols.

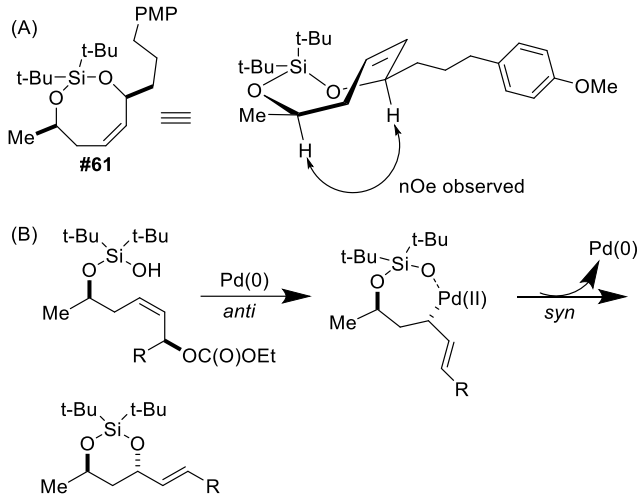


entry	substrate	product	isolated yield
1	 ***#23***	 ***#51***	**40%**
2	 ***#24***	 ***#52***	**67%**
3	 ***#25***	 ***#53***	**45%**
4	 ***#26***	 ***#54***	**62%**
5	 ***#27***	 ***#55***	**49%**
6	 ***#28***	 ***#56***	**40%**
7	 ***#29***	 ***#57***	**80%**
8	 ***#30***	 ***#58***	**54%**
9	 ***#31***	 ***#59***	**40%**
10	***#32***	***#60***	**70%**

When starting with 4-pentyn-2-ol, the aldehyde addition in **Scheme 2** furnished mixtures of diastereomers. Fortunately, in all cases, these

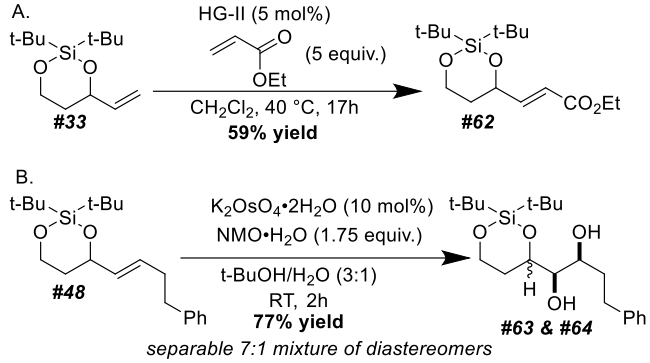
diastereomers were separable by chromatography on silica gel. We were pleased to see that the subsequent palladium catalyzed cyclization was perfectly stereospecific. The major *syn* diastereomer reliably formed *anti* product; the minor *anti* diastereomer formed *syn* product (**Scheme 5**). Determining the stereochemistry of the linear starting materials was a considerable challenge (**Scheme 6A**). After various failed crystallization attempts, we globally deprotected **31** (**Scheme 5**, see supporting information for full experimental details) and converted it into silocine **61**. Based on observed nOe correlations, the stereochemistry of **61** and, by analogy, of **31** was assigned. To explain the stereospecificity of this reaction, we propose a mechanism shown in **Scheme 6B**. Insertion of palladium occurs *anti* to the ethyl chloroformate leaving group[34] and is followed by coordination of the silanol nucleophile (inner-sphere process).[35] Subsequent *syn* reductive elimination furnishes product (**Scheme 5**). It is interesting to note that this stereoselectivity stands in contrast to related reactions where alcohols or phenols are used as nucleophiles; in these reactions, there is an overall retention of stereochemistry through an *anti-anti* mechanism.[13, 18]

Scheme 6. (A) Determining the stereochemistry of linear starting materials. (B) Mechanistic hypothesis.



The product alkenyl dioxasilinanes could be further elaborated (**Scheme 7**). Using the 2nd generation Hoveyda-Grubbs catalyst, cross metathesis of **33** with ethyl acrylate formed **62** in a 59% yield (**Scheme 7A**). Dihydroxylation of **48** formed tetrols **63** and **64** as a separable mixture of diastereomers (**Scheme 7B**).

Scheme 7. The product alkenyl dioxasilinanes are convenient synthons for many transformations including (A) cross-metathesis and (B) dihydroxylation.



separable 7:1 mixture of diastereomers

In summary, we have demonstrated that di-*tert*-butylsilanols are competent nucleophiles for the intramolecular interception of palladium π-allyl species. In these reactions, allyl ethyl carbonates were the best precursors for the formation of palladium π-allyl intermediates, and $[(Cinnamyl)PdCl]_2$/BINAP was superior to other Pd salt/ligand framework combinations. Our optimized protocol was compatible with a variety of silanol substrates. Importantly, the cyclization is perfectly stereospecific, proceeding via an *anti-syn* mechanism. The alkenes in the product dioxasilinanes serve as blank slates for further functionalization, and we expect this reaction to be a useful addition to existing technology for the assembly of poly-hydroxylated targets.

ASSOCIATED CONTENT

Supporting Information. Experimental Procedures, Reasoning for Structural Assignments, NMR Spectra, and Crystallographic Information.

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