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Stereoselective Cyclization of Functionalized 1,n-Diynes Mediated by [X-Y]- Reagents [X-Y = R₃Si-SnR'₃ or (R₂N)₂B-SnR'₃]. Synthesis and Properties of Atropisomeric 1,3-Dienes

Ramakrishna Reddy Singidi, Amanda M. Kutney, Judith C. Gallucci, T. V. RajanBabu*

Department of Chemistry, The Ohio State University, 100 W 18th Avenue, Columbus, OH 4321.

rajanbabu.1@osu.edu

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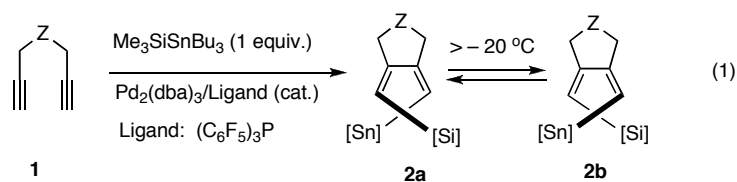
ABSTRACT Borylstannane [-N(Me)CH₂CH₂(Me)N-]B-SnMe₃ (**16**) is a superior reagent capable of effecting bis-functionalization-cyclization in several highly functionalized 1,n-diynes, 1,n-eneynes and 1,n-allenynes where the more well-known silylstannanes fail. These include 1,2-dipropargylbenzenes, 2,2'-dipropargylbiphenyls, 4,5-dipropargyldioxolanes and 1,4-dipropargyl-β-lactams. Variable temperature NMR studies show that conformational restraints imposed by selected back-bones increase the activation barrier for the helical isomerization in (Z,Z)-dienes that are generated in the cyclization of the diynes. In the biphenyl and the dioxolane systems, the reactions proceed with surprisingly good regio- and stereoselectivity. The resulting diazaborolidine derivatives are hydrolytically unstable, but can be isolated by recrystallization or reprecipitation. For further synthetic applications, it is

advantageous to convert these compounds in situ into the corresponding dioxaborolidines with the retention of either the Me_3Sn group or with replacement of this group via a halodestannylation. The configurations of the vinyl moieties are preserved in these reactions. Highly functionalized dibenzocyclooctadienes, which adorn the carbon frames of several important cytotoxic natural products, may be synthesized using this chemistry.

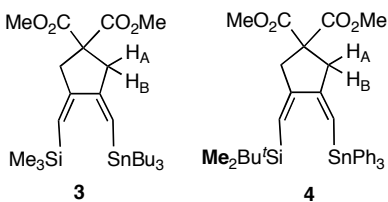
Introduction

Cyclizations of α,ω -diynes and other similar $1,n-\pi$ -systems such as enynes, allenynes and bis-allenes mediated by main-group bimetallic reagents have attracted considerable attention because of the ease with which highly functionalized products with versatile latent functionalities are generated from relatively simple substrates.¹ In initial work in the area, we reported a facile synthesis of a new class of 1,4-disubstituted (*Z,Z*)-1,3-dienes (**2**) via Pd(0)-catalyzed silyl-stannylation/cyclization of 1,6-diynes (**1**) mediated by $\text{R}_3\text{SiSnR}'_3$ reagents (eq 1).² The exceptional control of regio- and stereo-selectivity, a necessary consequence of the mechanisms of the various organometallic steps involved, results in the placement of the Si and Sn substituents in an “inside” orientation, thus creating a helical motif. In these reactions, only *Z,Z*-dienes are formed, and common functional groups such as silyl and alkyl ethers, esters, amides, nitriles, chlorides and even free amines and alcohols in the starting diynes are tolerated. A number of adducts, among them, **3-8** (eq 1), were synthesized in good to excellent yields. The structures and configurations of the (*Z,Z*)-diene adducts have been rigorously established by multinuclear (^1H , ^{13}C , ^{119}Sn) NMR methods, and in one case, by X-ray crystallographic analysis of a solid derivative. We expected the rate of the helical isomerization process in these systems (eq 1) to depend on the size of the groups on Si and Sn, and the substitution pattern around the ring. In solution, this process is surprisingly facile in monocyclic systems, and the two isomers are in rapid equilibrium, a process that can be monitored by variable temperature (VT) NMR spectroscopy (Figure 1). The diastereotopic methylene protons (H_A and H_B) in **3**, which appear as a broad singlet above 298 K, but as

two AB quartets below 257 K, were used to accurately measure the kinetic parameters for the enantiomerization by line shape analysis.³



	Z	[Si]	[Sn]
3	C(CO ₂ Me) ₂	Me ₃ Si	ⁿ Bu ₃ Sn
4	C(CO ₂ Me) ₂	^t BuSiMe ₂	Ph ₃ Sn
5	C(CO ₂ Me) ₂	Et ₃ Si	ⁿ Bu ₃ Sn
6	CH(CO ₂ Me)	^t BuSiMe ₂	Ph ₃ Sn
7	N-Ts	^t BuSiMe ₂	Ph ₃ Sn
8	N-C(Me)(H)Ph (<i>R</i>)	^t BuSiMe ₂	Ph ₃ Sn



$H_a H_b$ { 'enantiotopic' at rt
 { 'diastereotopic' at -40 °C

'Me's diastereotopic at -40 °C

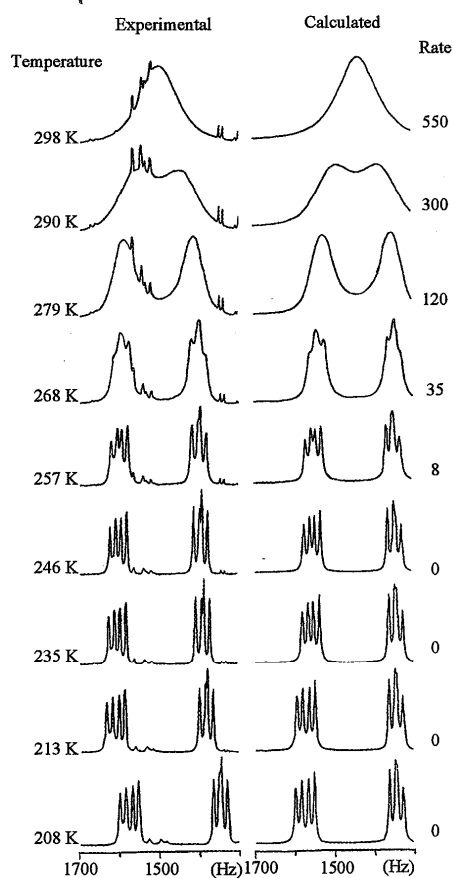
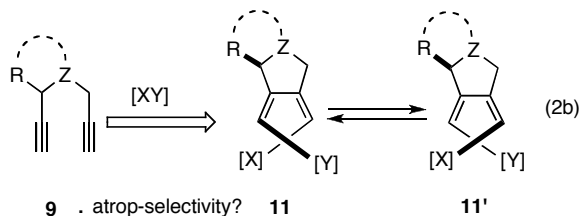
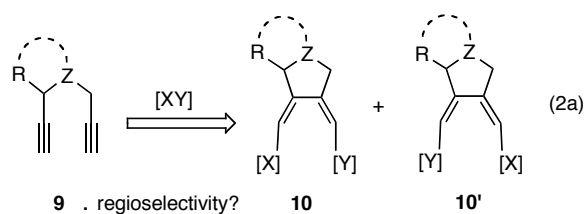


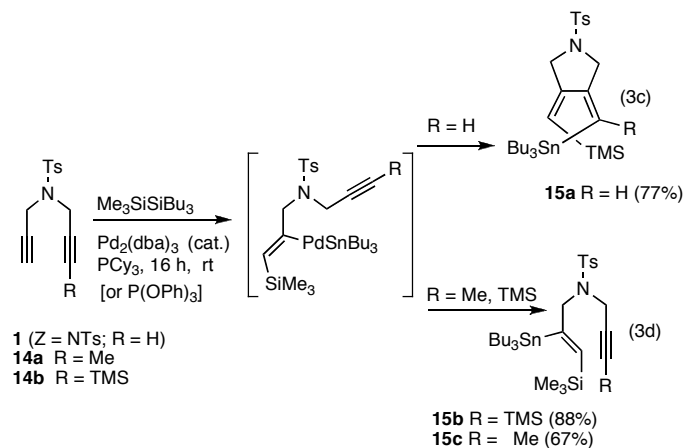
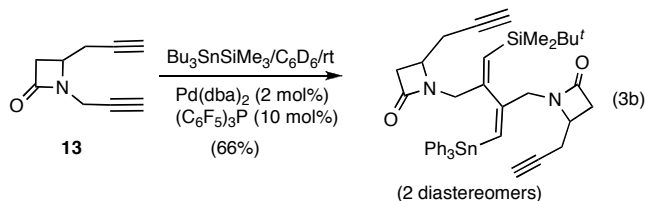
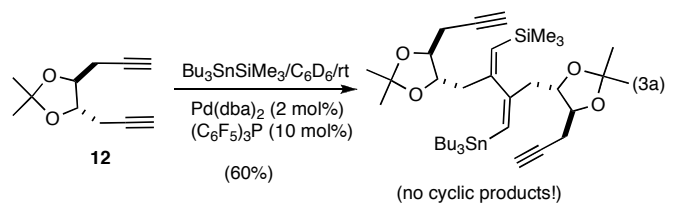
Figure 1. Variable temperature NMR behavior of (Z,Z)-1,3-diene **3** (only H_A/H_B shown)

The myriad of possibilities for further stereoselective functionalization of the dienes through the use of the vinyl moieties, and the potential use of the resident axial chirality for introduction of new stereocenters provided sufficient impetus for more work in this area. However, before contemplating any serious synthetic applications of these and other related [X-Y]-mediated cyclizations, a number of important issues have to be addressed. Among them: (a) identification of the most optimal [X-Y] reagent that would allow facile cyclization *and* subsequent chemistry of the installed functionality for carbon-carbon or carbon-heteroatom bond formations; (b) how to control the regioselectivity of the [X-Y] addition in an unsymmetrical 1,*n*-diyne (see eq 2a); (c) how to increase the activation barrier so that the atropisomer(s) can be isolated at or near room temperature (eq 2b). For example, would substitution on the backbone (eq 2b) permit such isolation, and if so, in these reactions, can we bring about

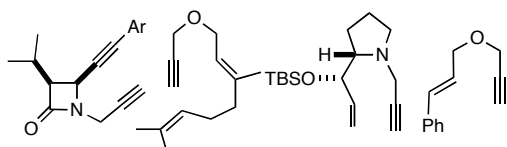
atropselectivity that is dependent on the substrate (diastereoselectivity), or even better, on a metal-catalyst, in the reactions of a pro-chiral substrate (enantioselectivity)?



While the Pd-catalyzed silyl-stannylation-cyclization (eq 1) is a very useful reaction for the synthesis of highly functionalized *cyclopentanoid* compounds from diynes,^{2,3} allenyne^{4,5} and allene-aldehydes,⁶ its use for the synthesis of carbocyclic and heterocyclic compounds of other ring sizes is severely limited. Kinetically unfavorable cyclization reactions are hampered by the formation of acyclic products via simple 1,2-additions,⁷ and, in several substrates carrying a coordinating propargylic or homopropargylic substituent, dimerization of the starting material. Two examples of this dimerization are shown in eq 3a and 3b.⁸ In these cases no cyclization products were detected under the reaction conditions. Like wise, when an internal alkyne is involved, as shown in eq 3d, only acyclic products (**15b** and **15c**) are formed. In sharp contrast, the corresponding 1,6-diyne with two terminal alkynes [**1** (Z = N-Ts, R = H)] gave good yield of the cyclic product **15a** (eq 3c). Several other examples of substrates where the cyclization reactions failed when the [SiSn]-reagent was used are listed in column 5 of Table 1. Examples of more complex substrates that highlight the limitations of the [SiSn] reagents can be seen in ref. 7.



Also failed to cyclize with [SiSn] reagents (ref. 7)



The challenges outlined in the previous paragraphs became immediately apparent as we sought to apply⁹ these types of cyclization reactions for a general synthesis of dibenzocyclooctadienes (Figure 2a),¹⁰ a class of compounds with wide-ranging biological activities. In this paper we report the results of our investigations that led to satisfactory resolutions to several issues raised above, including the expanded use of a [B-Sn] reagent **16** (Figure 2b).^{11,12} We find that this reagent has several advantages compared to the [SiSn] reagents including increased reactivity, better chemo- and regioselectivity in the reactions of several key substrates, and broad utility in the use of the adducts in complex molecule synthesis.¹³

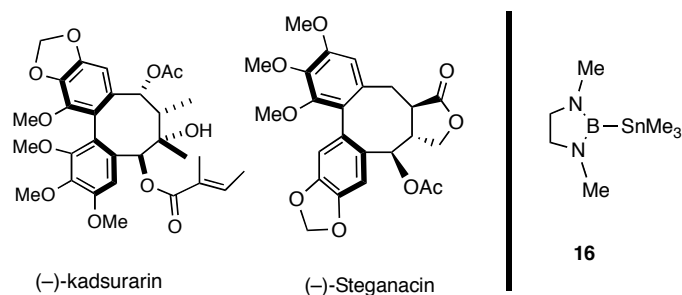
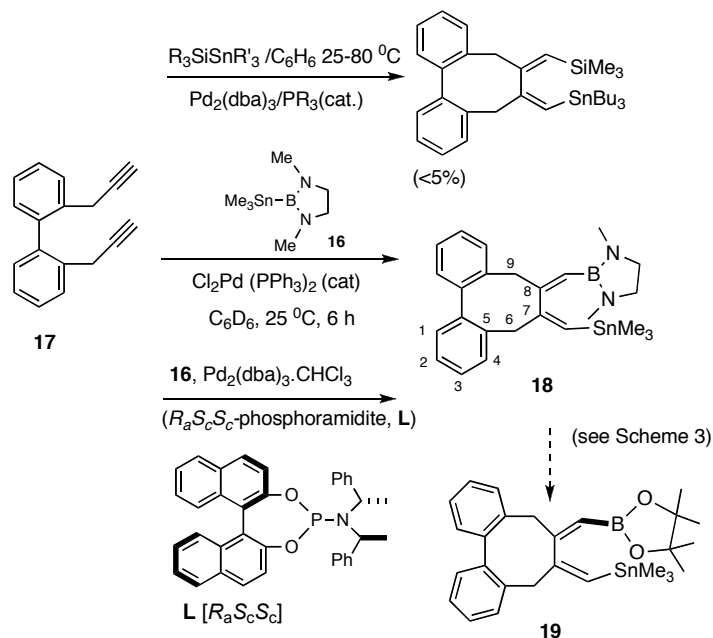


Figure 2a. Examples of biologically active dibenzocyclooctadienes. **2b.** A stannylborane Reagent

Results and Discussion. Our initial studies started with an examination of the cyclization of 2,2'-di-(2-propynyl)-1,1'-biphenyl shown in Scheme 1. The choice of the biphenyl scaffolding is based on two premises besides the obvious similarity to the backbone of the dibenzocyclooctadienes (Figure 2a), key targets in our synthesis efforts. From our dynamic NMR studies³ we had surmised that the backbone of a 1,2-bisalkylidene cycloalkanes (eq 1 and 2b) significantly influence the rate of the helical isomerization process, and thus it should be possible to increase the ΔG^\ddagger for this process by restricting the conformational mobility of this unit. In addition, this system would permit examination of hitherto unexplored aspects of stereocontrol via chirality transfer (axial to axial) from the biphenyl system to a newly created helical moiety. Since the cyclized product (Scheme 1) has two elements of axial chirality, it is conceivable that there is some atropselectivity in the formation of the non-planar diene, i. e., a preference for the formation one of the diastereomers (R_a^*, R_a^* or R_a^*, S_a^*).

Scheme 1. Relative reactivities of [SiSn] and [BSn] Reagents

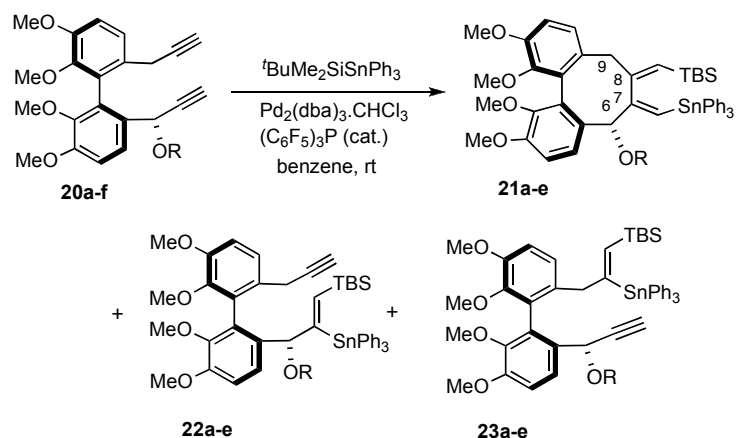


In the event, the exploratory studies of the Pd-catalyzed silylstannylation of 2,2'-dipropargyl-1,1'-biphenyl **17** under a variety of conditions [$Pd_2(dba)_3$, THF, 80 °C; $Pd_2(dba)_3/P(C_6F_5)_3$, rt to 65 °C; $Pd_2(dba)_3/P(C_6H_{12})_3$, C_6H_6 , 80 °C; $Pd_2(dba)_3/P(o\text{-tolyl})_3$, C_6H_6 , 80 °C; $Pd_2(dba)_3/P(2\text{-furyl})_3$, C_6H_6 , 80 °C; $Pd_2(dba)_3$, dppe, THF, 65 °C; $Pd_2(dba)_3/P(C_6F_5)_3$, rt to 65 °C] gave only trace amounts of the expected product (Scheme 1). The borylstannylation-cyclization, on the other hand, proceeds in very good yield under two different sets of conditions giving exclusively the product **18** as a single diastereomer in > 75% yield. The reaction can be carried out using $PdCl_2(PPh_3)_2$ or $Pd_2(dba)_3 \cdot CHCl_3$ / Feringa phosphoramidite (**L**)¹⁴ as a catalyst. The latter reaction generally gave a cleaner reaction even though the product formed is nearly racemic. Variable temperature NMR spectroscopy showed that this molecule (**18**) or a boron-pinacolate derivative prepared from this molecule (**19**) does not undergo helical isomerization up to 55 °C. This aspect will be discussed in greater detail later.

We²⁻⁵ and others^{1b,1n,12,15} have invested considerable effort in optimizing the metal/ligand combination for these multi-component reactions. However, no general trend has emerged and each situation demands scouting experiments to identify the most suitable set of conditions for a particular substrate class. Gratifyingly, in these reactions these scouting experiments are remarkably easy to run, since it often involves no more than simply mixing the substrate with the appropriate reagent in near stoichiometric amounts in a neutral solvent like C_6D_6 , and following the reaction by NMR at room temperature or slightly above that. The starting materials and products have unmistakable NMR

characteristics, and often one even has a choice of several nuclei to rely upon. In the silylstannylation/cyclization of 1,6-diynes and allenynes our early studies²⁻⁴ indicated that a combination of Pd(0) [usually in the form of Pd₂dba₃] and P(C₆F₅)₃ as the catalyst, is most suitable when the reaction is carried in a non-polar solvent like benzene. Chelating ligands have generally been found to be less effective, possibly because the key oxidative addition of the [X-Y] reagents to these complexes is known to be slow.^{15c,e} For the borylstannylation-cyclization, we have most often used the Tanaka conditions¹² [PdCl₂.(PPh₃)₂, 1-5 mol%, C₆H₆, rt], even though the most recent studies seem to suggest the Pd₂dba₃/phosphoramidites give cleaner products at shorter reaction times. The generality of this observation is yet to be confirmed.

Scheme 2. Silyl-Stannylation Cyclization of 2,2'-Dipropargylbiphenyls with Restricted Rotation



Derivative of 20	21 (%) ^a	22 (%) ^a	23 (%) ^a
20a (R = H)	29	70	0
20b (R = Benzyl)	43	46	10
20c (R = TBS)	13	87	0
20d (R = Acetyl)	54	46	0
20e (R = CH ₂ OBn)	36	51	12
20f (R = Benzoyl)	multiple products		

^a estimated by ¹H NMR

There are two factors that need to be considered in the context of the cyclization of more complex biaryl-containing alkynes, which would be needed for the projected syntheses of dibenzocyclooctadienes. (i) Diynes carrying simple unsubstituted biphenyl back-bone such as **17** has a low barrier (<5 kcal mol⁻¹) for atrop-interconversion. Generation of an additional chiral element could in principle proceed with some diastereoselectivity if this atropisomerism has a barrier lower than any of the steps involved in the cyclization process, and the products themselves are stable with respect to further equilibration. Under these conditions, the reaction could be under Curtin-Hammett regime. (ii) Additionally, if there is a chiral center present in the chain containing the diynes, such a center could impact the configuration of the newly created chiral element (in the case of a diyne cyclization, this will

be the configuration of the newly created, axially chiral diene). In order to separate these two factors, we have chosen to restrict the conformational mobility of the biphenyl unit by having two methoxy substituents at the 6 and 6'-positions. A propargylic substituent (OR, see structures **20a-f**, Scheme 2) was introduced by acetylide addition to a biaryl-derived aldehydes.¹⁶ The silylstannylation-cyclization was probed in the reactions of the diynes **20a-f**,¹⁶ and the results are shown in Scheme 2. Even though **21** is formed as a *single* regio- and stereoisomer, the reaction is complicated by significant contamination from the acyclic adducts **22** and **23**. The protecting group on the C₆-OH group has a pronounced effect on the regioselectivity of these reactions. In the cyclization product **21**, the silyl group is placed exclusively on the terminal carbon of the unsubstituted propargyl side-chain. The unprotected propargylic alcohol (**20a**) and the TBS ether (**20c**) seem to direct the addition to the proximal alkyne to give **22a** and **22c** as the major uncyclized addition products. In these instances, the putative Pd-C_{sp2} intermediates formed in the first step of the reaction are reluctant to participate in the cyclization event, leading to early reductive elimination with the formation of the 1,2-silylstanane. In sharp contrast, the reactions initiated at the unsubstituted alkynes in **20b**, **20d** and **20e** lead to substantial cyclization (giving **21b**, **21d** and **21e**).

While screening other similar [X-Y]-reagents, for the cyclization of the diyne **20b** we again found that it underwent highly regio- and stereoselective (atropselective) cyclization upon reaction with Me₃Sn-B[N(Me)CH₂CH₂(Me)N-] (**16**) in the presence of PdCl₂(PPh₃)₂ to give a single product **24** (Scheme 3).⁹ The 1,3-bis-azaborolidine **24** is moisture and air sensitive, and in the past, isolation of these compounds have limited the utility of this otherwise powerful reaction.^{12,17} We find that the bisazaborolidine is readily converted in situ into air-stable vinylboronate **25** by treatment with pinacol in the presence of catalytic amounts of a strong acid.^{18,19} Structures of the (Z,Z)-1,2-bis-alkylidene dibenzocyclooctadienes **24** and **25** were determined by extensive NMR studies, and further confirmed by X-ray crystallography of the destannylated compound **26** (Figure 3).⁹

Scheme 3. [B-Sn]-Mediated-Cyclization of an Axially Chiral 1,9-Diyne

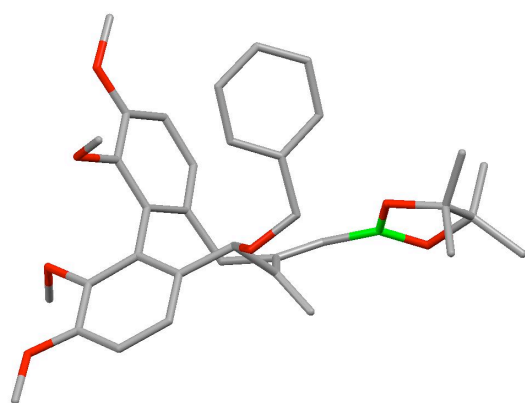
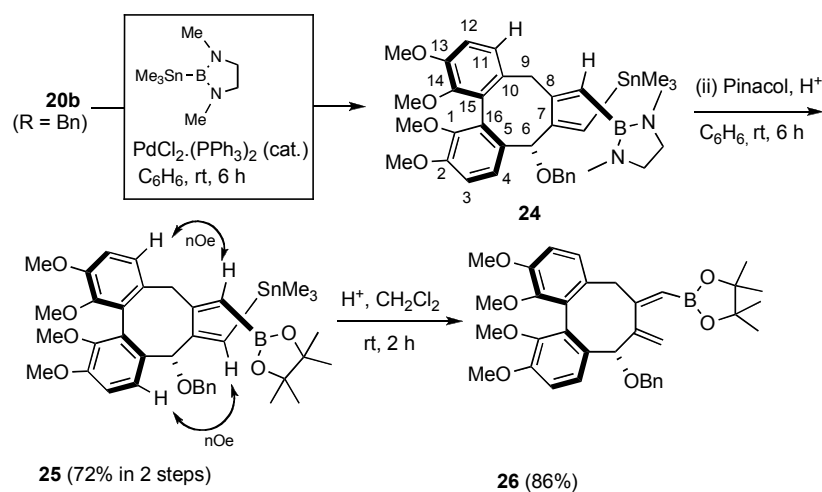


Figure 3. Solid state structure of **26** based on X-ray crystallographic analysis (hydrogens are omitted for clarity)

As documented in Scheme 3, we initially found that the H^+ -catalyzed exchange of the 1,2-diamino-ligand on boron for a 1,2-dioxa-ligand (**24** \rightarrow **25**) using pinacol is generally applicable to most such adducts, especially those carrying Lewis basic groups. The pinacolate formation from the diazaborolidine allows purification and isolation of the corresponding 1-(borylmethylidene)-2-(stannylmethylidene)cycloalkanes from a variety of diynes including several instances where the

corresponding silylstannylation-cyclization reactions fail (Table 1). Using this isolation protocol, the functional group compatibility of the [B-Sn]-mediated cyclization and its relative advantages as compared to the corresponding [SiSn]-mediated reaction can be ascertained.

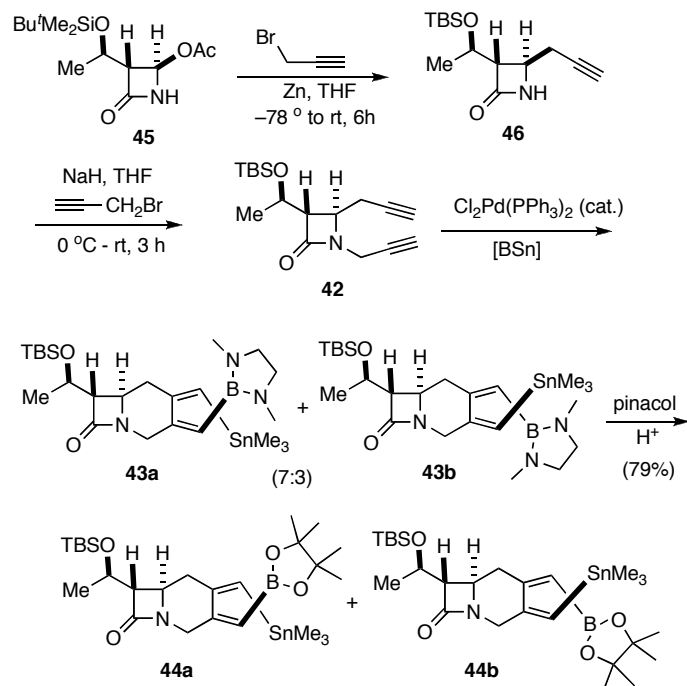
In addition to the 2,2'-dipropargylbiphenyls **17**, **20b** (Schemes 1 and 3), other related diynes **20c**, **27** and **30**, entries 2, 3 and 4, Table 1) also undergo the cyclization reaction with very high chemo-, regio- and stereoselectivity giving dibenzocyclooctadienes. The presence of the additional stereogenic center such as a benzylic ether (entries 2-4), does not erode the regio- or stereoselectivity; formation of a single isomer is observed in each case, including in the cyclizations of the enantiomerically pure substrates, **27** and **30** (entries 3 and 4). The configuration of **24b** and **25b** were determined on the basis of the solid-state structure of a destannylated compound (**26**, Scheme 3), while those of similar compounds **28-31** were deduced from the similarity in the structures of the starting diynes, and from the comparison of ¹H NMR parameters with those of the former set.

These cyclizations and the derivatization protocols are more broadly applicable. While the dipropargyl-*N*-tosylamine **33** (R = H) (entry 5, Table 1) undergoes efficient cyclization with both [SiSn]- and [B-Sn]-reagents,^{2,12} for the corresponding 1-methylalkyne **34** (R = Me), the [B-Sn]-reagent is clearly superior. The diyne **34** failed to cyclize with the [SiSn] reagents, giving instead an acyclic adduct.⁷ In sharp contrast, the [B-Sn] reagent affects efficient cyclization giving a highly crystalline adduct **35**. Likewise 1,2-dipropargylbenzene **36** undergoes borylstannylation to give **37**, which was isolated as the pinacolboronate **38** in 94% yield (entry 6).

A different mode of chirality transfer is explored with the cyclization of the C₂-symmetric dipropargyl dioxolane, **12**, derived from (*R,R*)-tartaric acid. Recall that this substrate does not undergo the [SiSn]-mediated cyclization (Eq 3a).⁸ Only one of the two possible products is formed in the generation of a new axially chiral 1,3-diene **40** as determined by ¹H and ¹³C NMR spectra. The configuration of the non-planar 1,3-diene has not been established. However, the corresponding boron-pinacolate **41** molecule showed no tendency to undergo atrop-epimerization as judged by variable temperature ¹H

NMR in toluene- d_8 (see later).

Scheme 4. Synthesis and Cyclization of a 1,2-Dipropargyl- β -lactam



Finally, additional functional group compatibility of the [B-Sn]-mediated cyclization is explored with the diyne **42** containing a sensitive β -lactam (Scheme 4 and entry 8, Table 1). This substrate is easily assembled from a commercially available β -lactam **45** (Scheme 4).²⁰ In the cyclization of **42**, a mixture of diastereomeric B/Sn adducts (7:3) are obtained. The major product (**43a**) is highly crystalline, and its solid-state structure has been determined by X-ray crystallographic analysis (Figure 4). The structure of the minor diastereomer has not been determined conclusively, although from NMR studies on the corresponding boron-pinacolate it appears to be a regioisomer. Treatment of the mixture **43a** and **43b** gave the corresponding boron pinacolates **44a** and **44b**, whose structures were rigorously established by NMR methods including extensive COSY and NOESY measurements (see Supporting Information for details of NMR analysis). Gratifyingly, the chemical shifts and coupling constants are highly diagnostic of a conformation indicated by the solid-state structure of **43a**. Variable temperature ^1H NMR of the major product **44a** between 27°C and 55°C show that these bicyclic compounds do not undergo helical isomerization under conditions where monocyclic adducts are known to be fluxional (see later).

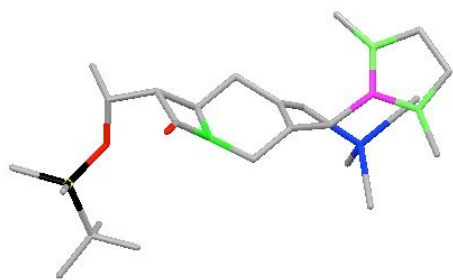
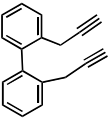
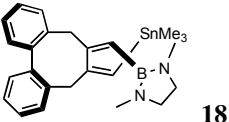
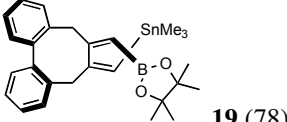
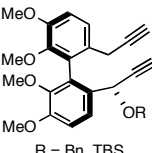
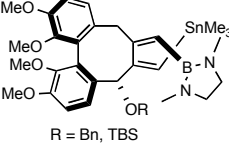
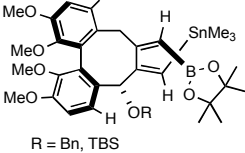
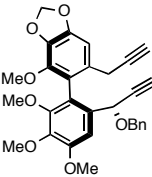
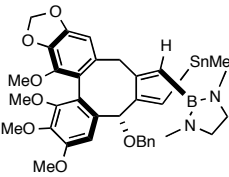
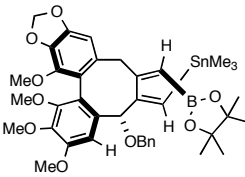
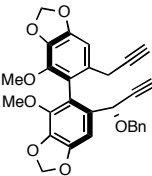
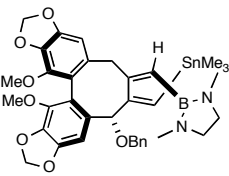
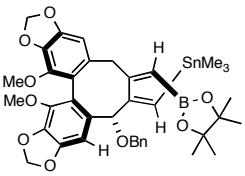
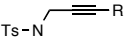
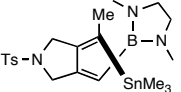
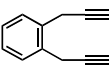
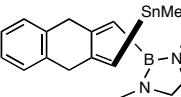
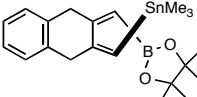
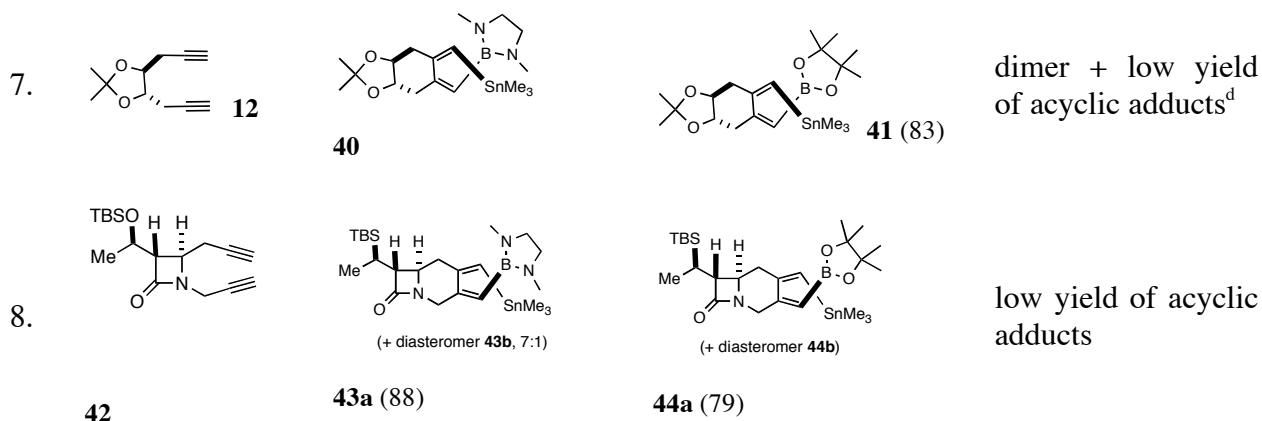


Figure 4. Solid-state structure of **43a** (hydrogens omitted for clarity)

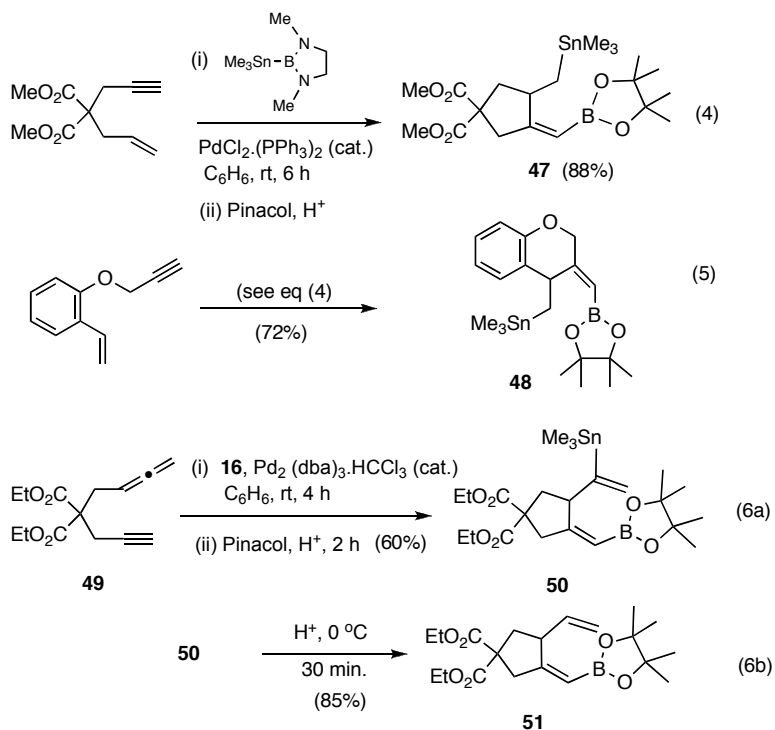
Table 1. Pd-Catalyzed Cyclizations of 1,n-Diyne Mediated by [B-Sn] and [Si-Sn] Reagents. A Comparison

no.	diyne	diazaborolidine ^a	dioxaborolidine (yield for 2 steps, %)	[SiSn]-mediated reaction
1.	 17	 18	 19 (78)	low yield of acyclic adducts
2.	 R = Bn, TBS 20b, 20c	 R = Bn, TBS 24b, 24c	 R = Bn, TBS 25b, 25c (70, 78)	mixture of acyclic and cyclic products, see: Scheme 2
3.	 27	 28	 29 (70)	(--) ^b
4.	 30	 31	 32 (72)	(--) ^b
5.	 R = H 33 R = Me 34	 35 (73)	primary product isolated as solid (35)	for 34 , 67% acyclic adduct with Me ₃ SiSnBu ₃ ^c
6.	 36	 37 (96)	 38 (94)	acyclic adducts (39) major



^a not isolated except for **18**, **35**, **37** and **43a**, conversions, >90% estimated by NMR. ^b not attempted. ^c see ref. 7. ^d ref. 8.

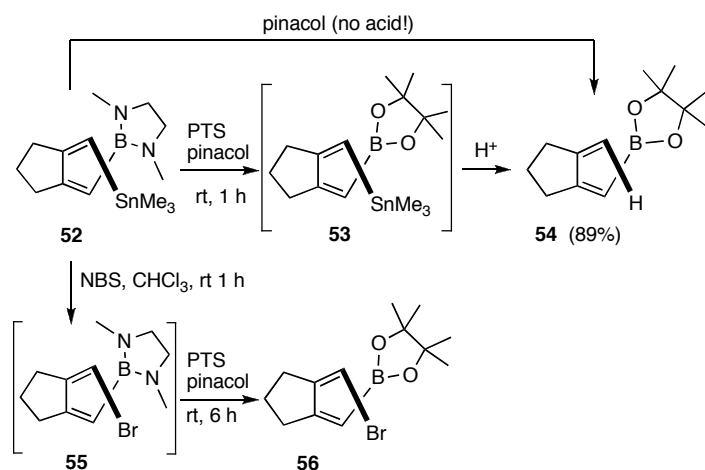
As shown in eq (4)-(6), this general protocol for the formation of the boron pinacolate from the corresponding diazaborolidine is also applicable to other cyclization products derived from enynes and allenynes.



The superior reactivity of the boron-tin reagent notwithstanding, these studies indicate that further applications of this chemistry would have to depend on finding proper derivatization procedures for

easy isolation of useful intermediates from the 1-(borylmethylidene)-2-(stannylmethylidene)-cycloalkanes because of their hydrolytic instability. We have investigated a number of these reactions (Scheme 5) in the context of a more prototypical diene **53**,¹² which is readily prepared from 1,6-heptadiyne and **16**. Adducts with no Lewis basic groups such as an oxygen groups on the backbone seem to be more prone to destannylation under these conditions, and significant contamination by the products such as **54** are seen. For example, adduct **52** gives both stannylated and destannylated products (**53** and **54**) competitively (Scheme 5). For this substrate, even *without* the addition of the strong acid, the destannylation competes. Such uncatalyzed reactions generally lead to multitude of products. Terminal vinylstannanes with more exposed vinyl moiety also appear to undergo this competitive destannylation.


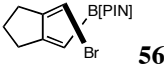

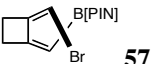

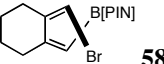


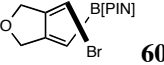
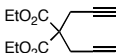
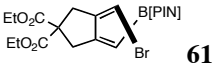
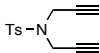
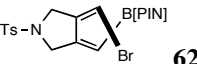
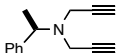
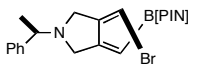
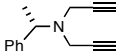
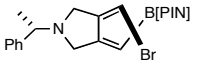
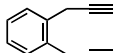
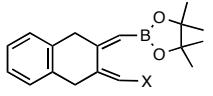
Scheme 5. Derivatization Schemes for 1,3-Diazaborolidines

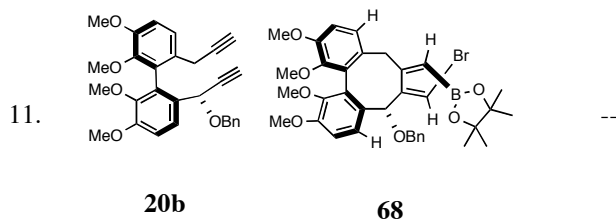


Another useful derivatization protocol is a bromodestannylation reaction shown in Scheme 5 (**52** → **55** → **56**), in which the diazaborolidine-Sn adduct **52** is first treated with 1.5 equivalents of *N*-bromosuccinimide in chloroform followed by the acid-catalyzed boron pinacolate formation. In case of the adduct **52**, the halogen-metal exchange takes place cleanly in ~ 1 h to give **55**. This resulting compound was not isolated, but transformed into **56** by treatment with pinacol and *p*-toluenesulfonic

acid. The diene **56**, a stable boronate, is easily isolated by column chromatography in 80% overall isolated yield starting from the diyne. It is clear from nOe studies that the metal-exchange takes place with complete retention of stereochemistry. This new derivatization protocol offers a route to fully substituted 1-(borylmethylidene)-2-(bromomethylidene)-cycloalkanes which are, to the best of our knowledge, new kinds of bifunctional vinyl derivatives with potential applications as linchpin reagents.²¹ Several examples these highly functionalized bis-alkylidenes from the corresponding diynes are shown in Table 2. In general good to excellent yields are obtained for the products. Four, five and six-membered compounds are readily prepared by this method. Nona-1,8-diyne and deca-1,9-diyne (entry 4) give mostly acyclic 1,2-adducts.

Table 2. Direct Synthesis of 1-(borylmethylidene)-2-(bromomethylidene)cycloalkanes from 1,n-Diynes^a

no.	diyne	product	yield(%)
1.		 56	80
2.		 57	81
3.		 58	82
4.		59^b	--
5.		 60	84
6.		 61	76
7.		 62	72
8.		 63	65
9.		 65	65
10.		 66 (66) 67 (70) 66 (X=I), 67 (X = Br)	



^a see Scheme 5 for procedure. ^b mostly acyclic adducts

Atropisomerism in (ZZ)-1,2-dialkylidenecycloalkanes. The fluxional behavior of the 1,2-bisalkylidenes containing the vinyl X and Y groups (eq 2b), while fascinating from structural and mechanistic perspectives, is a detraction if these compounds are to be used for further stereoselective synthesis. As pointed out earlier, our initial studies strongly suggested that monocyclic compounds (eq 1, Figure 1) are most likely to be fluxional and there is little hope of increasing the ΔG^\ddagger for the helical isomerization by simply increasing the size of the X/Y groups.³ The kinetic parameters for the enantiomerization process determined for the series of dienes **3-6** via NMR line-shape analysis are shown in Figure 5. For all molecules studied, the free energies of activation are similar (52-57 kJ mol⁻¹ at 300 K), well within the range expected from the NMR spectra. Thus it *has not been possible to synthesize monocyclic system where the helical isomerization is frozen on the NMR time scale at or near room temperature.*

	3	4	5	6	7	8
ΔH^\ddagger (kJ. mol ⁻¹)	54.8	55.4	63.2	48.8	--	--
ΔS^\ddagger (J. mol ⁻¹)	0.4	-4.3	21.0	-11.6	--	--
ΔG^\ddagger (J. mol ⁻¹ , 300 K)	54.7	56.7	56.9	52.2	--	--
$T_{\text{coal.}}$ (°C)	10	20	20	0	-20	-60

Figure 5. Kinetic parameters for helical isomerization and coalescence temperatures

Note that the substitution pattern of the back-bone of the precursor diyne has a strong effect on the free energy of activation. For example, the *N*-tosyl and *N*-alkyl derivatives **7** and **8** (Figure 5) have much lower coalescence temperatures compared to the corresponding geminal-bis-carbomethoxymethylene compounds **3** and **4**. The cyclic products listed in Tables 1 and 2 add to the list of these uncommon molecules. Further we find that by restricting the conformational mobility of the newly formed ring, either by having a biphenyl unit as a part of the backbone (entries 1-4, Table 1), or imposing a bicyclic motif (entries 6-8), the helical isomerization of the diene can be almost *completely* arrested at ambient temperatures.

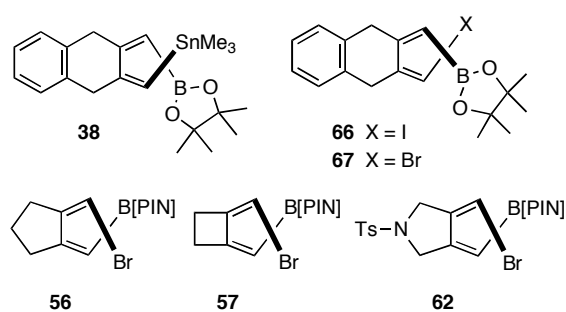


Figure 6. Some fluxional (*ZZ*)-4-halodienyl-1-boronpinacولات

A typical example of how the helical isomerization can be monitored by following the changes in the line shapes of the bis-allylic hydrogens in the adducts from symmetric diynes is shown in Figure 1 for the compound **3**. At the fast exchange regime, because of the pseudo-plane of symmetry, the allylic protons behave like two broad singlets at 279 K. When the exchange is slow on the NMR time scale, these appear as two AB quartets. In the context of the [B-Sn] adducts, these limiting cases are represented by the VT NMR spectra of the adducts **38** and the corresponding iodo- and bromo-derivatives **66** and **67**.

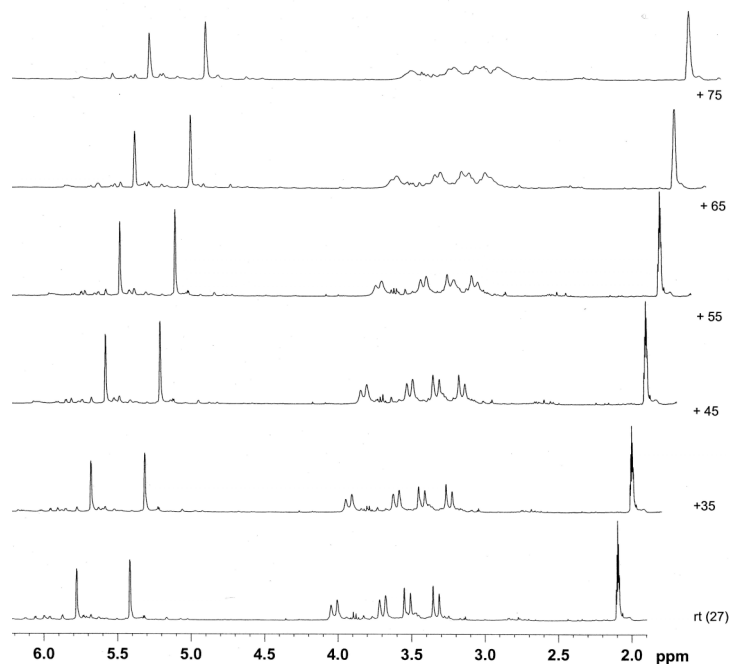


Figure 7. Temperature-dependent ^1H NMR of **38**

In compound **38** (Table 1, entry 6, column 4), the bis-allylic hydrogens appear (CDCl_3) as two distinct AB quartets centered around δ 3.806 ($\nu_A = 3.978$, $\nu_B = 3.634$, $J_{AB} = 16.8$ Hz) and 3.691 ($\nu_A = 3.814$, $\nu_B = 3.568$, $J_{AB} = 16.8$ Hz). The vinyl hydrogens in this compound appear at δ 5.328 (d, $J = 1.2$ Hz, (B)- C_{sp^2} -H) and 5.771 (t, $J = 1.2$ Hz, $J_{\text{Sn-H}} = 76$ Hz, (Sn)- C_{sp^2} -H). Upon warming a solution of this compound (27 °C to 75 °C) in toluene- d_8 very little changes occur in the ^1H NMR spectrum (Figure 7). Only above 50 °C there is some noticeable broadening in the lines due to the allylic hydrogens. Of course, the vinyl hydrogens in this compound are not expected to undergo any changes since the helical isomer is also the enantiomer of the starting material. In the corresponding iodo-derivative **66** the bis-allylic hydrogens appear as two singlets at δ 3.71 and 3.81 in CDCl_3 and at δ 3.50 and 3.57 in toluene- d_8 . As the toluene solution is cooled to -65 °C, this peak undergoes changes reminiscent of the coalescence seen in the spectrum of **3** (Figure 1),³ and, below -40 °C appears as two sets of distinct AB quartets of equal intensity (Figure 8).

Confirming the dynamic nature of the process in halo-boronates, we find that in the bromo-derivative **67**, which presumably has even a lower barrier for isomerization (due to the smaller size of Br compared

to I), the bis-allylic hydrogens appear as two sharp singlets at δ 3.41 and 3.45 at room temperature.

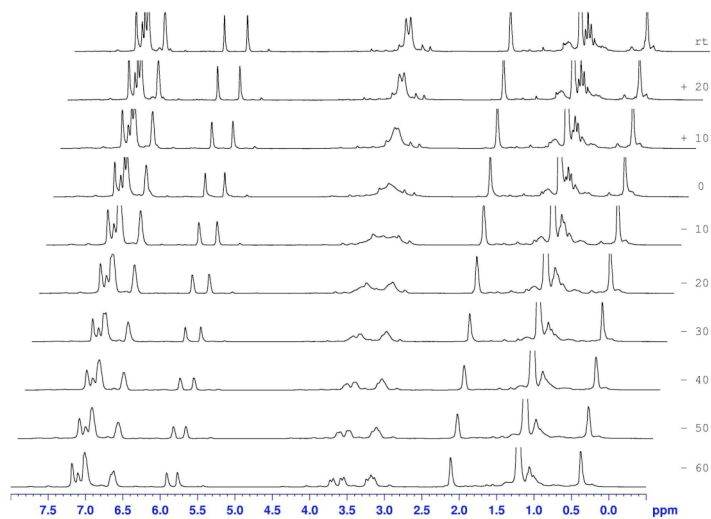


Figure 8. Temperature dependent ^1H NMR (toluene- d_8) of **66**

Temperature dependent ^1H NMR spectra of **56**, **57** and **62** (Table 2) also confirm the low barrier for the bromo-boryl derivatives.²² Between 27 °C and -70 °C there is no change in the CH_2 region except for some broadening. In none of these cases, the AB pattern characteristic of the evolving chirality as the temperature is lowered, is seen.

The biphenyl scaffoldings in diynes **17**, **20b**, **20c**, **27**, **30** (Table 1, entries 1-4) also increase the activation barrier for the helical isomerization. In each of these substrates, the only product that is formed in a highly atropselective reaction does not undergo the helical isomerization as judged by the total absence of any new peaks in the VT NMR spectra as the temperature is varied between -50 °C and 65 °C. The adduct was dissolved in toluene- d_8 and the spectra were recorded at various temperatures.²² In these cases, axial epimerization would lead to a different diastereomer and, based on a considerable body of experimental evidence,³ we should expect totally different spectra, including the appearance of new vinylic and benzylic hydrogens. Compound **18** formed from 2,2'-propargyl-1,1'-biphenyl (**17**) is

typical. It has the following characteristic peaks: δ 5.874 (s, 1 H, $J_{Sn-H} = 75$ Hz, SnCH), 5.559 (s, 1 H, BCH), 3.292 (ABq, $\nu_A = 3.386$, $\nu_B = 3.199$, $J_{AB} = 12$ Hz, 2 H, benzylic CH_2 , CH_2 C=C(H)B), 3.250-3.3580 (m, d, 2 H, benzylic CH_2 C=C(H)Sn). Variable temperature 1H NMR (toluene-d8) show that the peaks due to the C_{sp^2} -hydrogens and the benzylic hydrogens show no changes as the temperature is raised. As the solution is cooled, some line broadening is observed, which can often be ascribed to changes in viscosity of the solvent.³ VT- 1H NMR spectra of the boron-pinacolate **19** also show no evidence of isomerization.

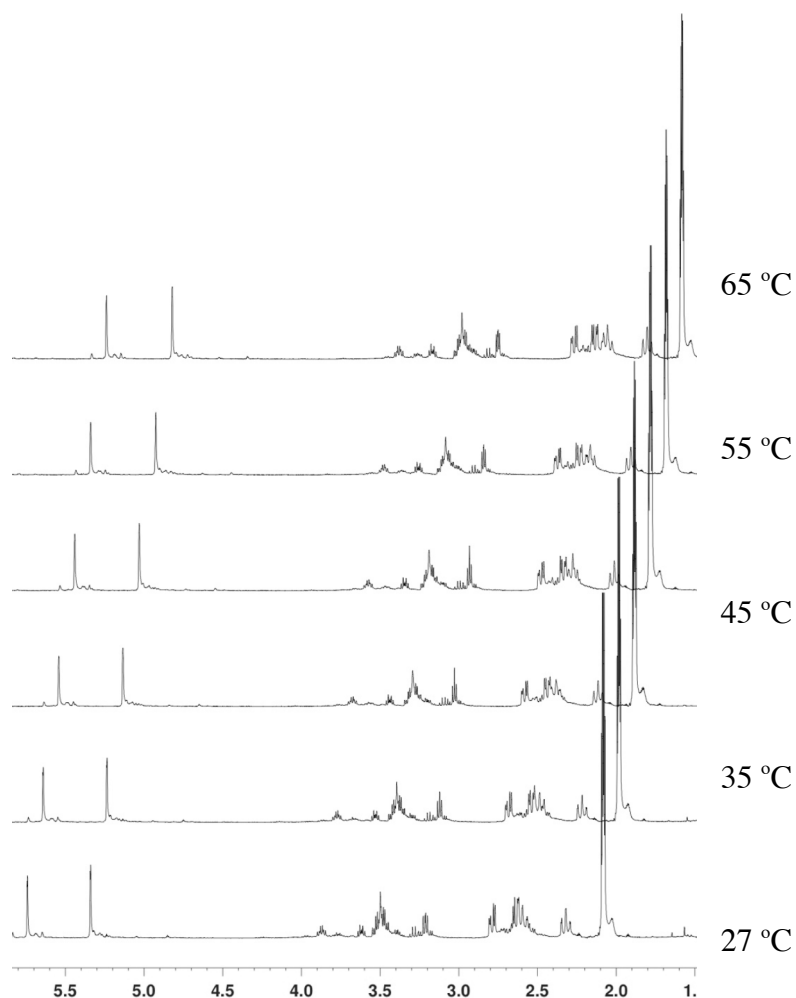


Figure 9. Temperature-dependent ^1H NMR (toluene- d_8) of **41**

Adducts from enantiopure, D-tartrate derived diyne **12** (Table 1, entry 7) represent a different class of chiral substrate (C_2 -symmetric) where, as before, the cyclization is atrop-selective, with only a *single* diastereomer formed in the reaction. The ^1H NMR shows only two vinylic hydrogens in the product **40** (and its boronate derivative **41**). The corresponding ^{13}C NMR spectra, also show only a single set of peaks. Helical isomerization would lead to a different diastereomer, and it should be possible to monitor any isomerization reaction from gross changes in the ^1H and ^{13}C NMR spectra. While the absolute configuration of the [B-Sn] adduct **40** (Table 1, entry 7) or its derivative (**41**) has not been

established, variable temperature ^1H NMR (Figure 9) clearly suggests that the coalescence temperature for the helical isomerization in this system is $>65\text{ }^\circ\text{C}$.

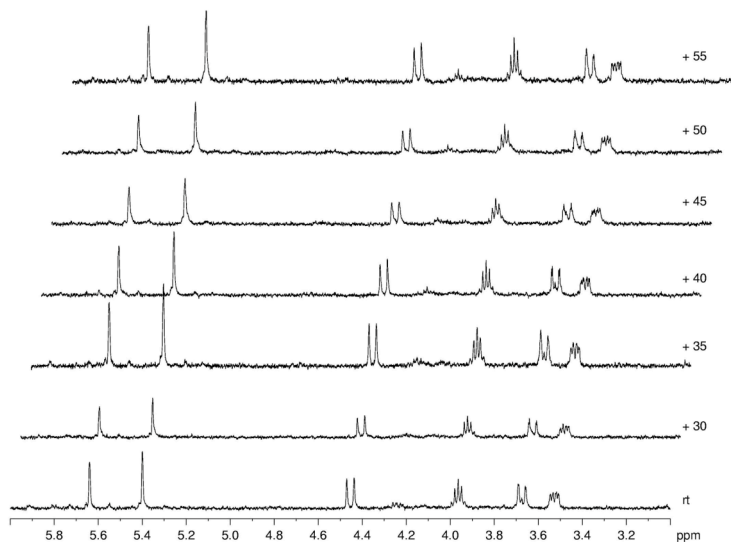


Figure 10. Temperature dependent ^1H NMR (toluene- d_8) of **44a**

The major diastereomeric adduct derived from the highly functionalized β -lactam **43a** and the corresponding boron pinacolate **44a** are also configurationally stable, as judged by variable temperature NMR studies. The major product **44a**, whose structure was determined by X-ray crystallography, was dissolved in toluene- d_8 and its ^1H NMR spectrum was monitored between rt and $55\text{ }^\circ\text{C}$. There are no apparent changes in the spectrum, confirming the high barrier for the helical isomerization (Figure 10).

Conclusions. The studies reported in this paper conclusively demonstrate that the borylstannane [$-\text{N}(\text{Me})\text{CH}_2\text{CH}_2(\text{Me})\text{N}-$] $\text{B}-\text{SnMe}_3$ (**16**) is a superior reagent capable of effecting bis-functionalization-cyclization in several 1, n -diynes where the more well-known silylstannanes fail. These include 1,2-dipropargylbenzenes, 2,2'-dipropargylbiphenyls, 4,5-dipropargyldioxolanes and 1,4-dipropargyl- β -

lactams. Conformational restraints imposed by the back-bone increases the activation barrier for the helical isomerization in (*Z,Z*)-dienes that are generated in a cyclization event. In the biphenyl and the dioxolane systems, the reactions proceed with surprisingly good regio- and stereoselectivity. The diazaborolidine derivatives are hydrolytically unstable, but can be isolated by recrystallization or reprecipitation. For further synthetic applications, it is advantageous to convert these compounds in situ into the corresponding dioxaborolidines with the retention of either the Me₃Sn group or with replacement of this group via a halodestannylation. The configurations of the vinyl moieties are preserved in these reactions, and we hope to use the resulting axially chiral compounds for further stereoselective operations. Highly functionalized dibenzocyclooctadienes, which adorn the carbon frames of several key cytotoxic natural products are logical targets of this chemistry. Studies directed at the total synthesis of these compounds will be reported in due course.

Acknowledgement. Financial assistance for this research by US National Science Foundation (CHE-0610349) is gratefully acknowledged..

Supporting Information Available: Full experimental details for the preparation of the substrates, protocols for the cyclization and subsequent derivatization reactions, ¹H and ¹³C NMR spectra of key compounds, Crystallographic Information File for **43a**. This material is available free of charge via the Internet at <http://pubs.acs.org>

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(22) See Supporting Information for the spectra and other details.

TOC Graphic

Stereoselective Cyclization of Functionalized 1,n-Diynes Mediated by [X-Y]- Reagents [X-Y = $R_3Si-SnR'_3$ or $(R_2N)_2B-SnR'_3$]. Synthesis and Properties of Atropisomeric 1,3-Dienes

