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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

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Abstract: The borylstannane [−N(Me)CH_2CH_2(Me)N−]B−$SnMe_3$ is a superior reagent capable of effecting bisfunctionalization−cyclization in several highly functionalized 1,*n*-diynes, 1,*n*-enynes, and 1,*n*-allenynes (including 1,2-dipropargylbenzenes, 2,2′-dipropargylbiphenyls, 4,5-dipropargyldioxolanes, and 1,4-dipropargyl-β-lactams) where the more well-known silylstannanes fail. Variable-temperature NMR studies showed that conformational restraints imposed by selected backbones 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 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 precipitation. For further synthetic applications, it is advantageous to convert these compounds in situ into the corresponding dioxaborolidines with either retention of the Me_3Sn group or replacement of this group via 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, can be synthesized using this chemistry.

Introduction

Cyclizations of α,ω-diynes and other similar 1,*n*-π-systems such as enynes, allenynes, and bisallenes mediated by main-group bismetallic 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 silylstannylation/cyclization of 1,6-diynes (**1**) mediated by $R_3Si-SnR'_3$ reagents (eq 1).[2] The exceptional control of regio- and stereoselectivity, 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 diyne are tolerated. A number of adducts, including **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 (^{1}H, ^{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]

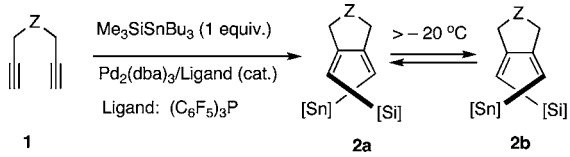
The myriad possibilities for further stereoselective functionalization of the dienes through the use of the vinyl moieties as well as the potential use of the resident axial chirality for introduction of new stereocenters provided sufficient impetus

(1) For recent reviews of multicomponent cyclizations, see: (a) Itoh, K.; Matsuda, I.; Yamamoto, K. *J. Synth. Org. Chem., Jpn.* **1999**, *57*, 912. (b) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. For other representative examples involving acetylenes, see: (c) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478. (d) Tsuda, T.; Kiyoi, T.; Miyane, T.; Saegusa, T. *J. Am. Chem. Soc.* **1988**, *110*, 8570. (e) Ojima, I.; Donovan, R. J.; Shay, W. R. *J. Am. Chem. Soc.* **1992**, *114*, 6580. (f) Chatani, N.; Fukumoto, Y.; Ida, T.; Murai, S. *J. Am. Chem. Soc.* **1993**, *115*, 11614. (g) Kondo, T.; Suzuki, N.; Okada, T.; Mitsudo, T. *J. Am. Chem. Soc.* **1997**, *119*, 6187. (h) Ojima, I.; Zhu, J.; Vidal, E. S.; Kass, D. F. *J. Am. Chem. Soc.* **1998**, *120*, 6690. (i) Madine, J. W.; Wang, X.; Widenhoefer, R. A. *Org. Lett.* **2001**, *3*, 385. (j) Doung, H. A.; Cross, M. J.; Louie, J. *J. Am. Chem. Soc.* **2004**, *126*, 11438. (k) Miura, T.; Shimada, M.; Murakami, M. *J. Am. Chem. Soc.* **2005**, *127*, 1094. (l) Brummond, K. M.; You, L. *Tetrahedron* **2005**, *61*, 6180. (m) Tsuchikama, K.; Kuwata, Y.; Shibata, T. *J. Am. Chem. Soc.* **2006**, *128*, 13686. (n) Beletskaya, I.; Moberg, C. *Chem. Rev.* **2006**, *106*, 2320. (o) Denmark, S. E.; Liu, J. H.-C. *J. Am. Chem. Soc.* **2007**, *129*, 3737.

(2) Greau, S.; Radetich, B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2000**, *122*, 8579.

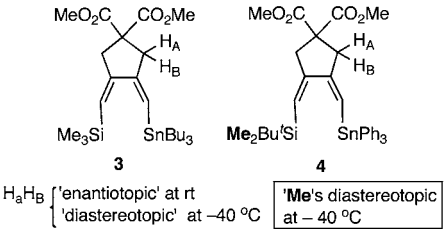
(3) Warren, S.; Chow, A.; Fraenkel, G.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2003**, *125*, 15402.

10.1021/ja105939v



(1)

	Z	[Si]	[Sn]
3	$C(CO_2Me)_2$	Me_3Si	$^nBu_3Sn$
4	$C(CO_2Me)_2$	^{t}BuSiMe$_2$	Ph_3Sn
5	$C(CO_2Me)_2$	Et_3Si	$^nBu_3Sn$
6	$CH(CO_2Me)$	^{t}BuSiMe$_2$	Ph_3Sn
7	N-Ts	^{t}BuSiMe$_2$	Ph_3Sn
8	N-C(Me)(H)Ph (*R*)	^{t}BuSiMe$_2$	Ph_3Sn



for more work in this area. However, before the contemplation of any serious synthetic applications of these and other related [X−Y]-mediated cyclizations, a number of important issues have to be addressed, among which are the following: (a) identification of the most optimal [X−Y] reagent to allow facile cyclization *and* subsequent chemistry of the installed functionality for carbon−carbon or carbon−heteroatom bond formations;

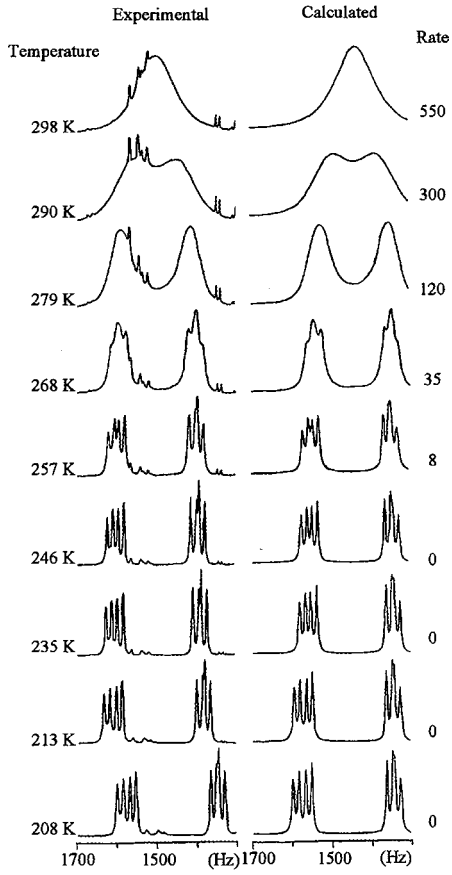
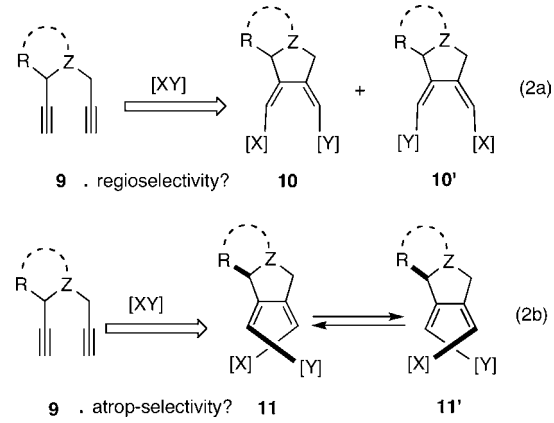


Figure 1. VT NMR behavior of (*Z*,*Z*)-1,3-diene **3** (only H_A and H_B are shown).

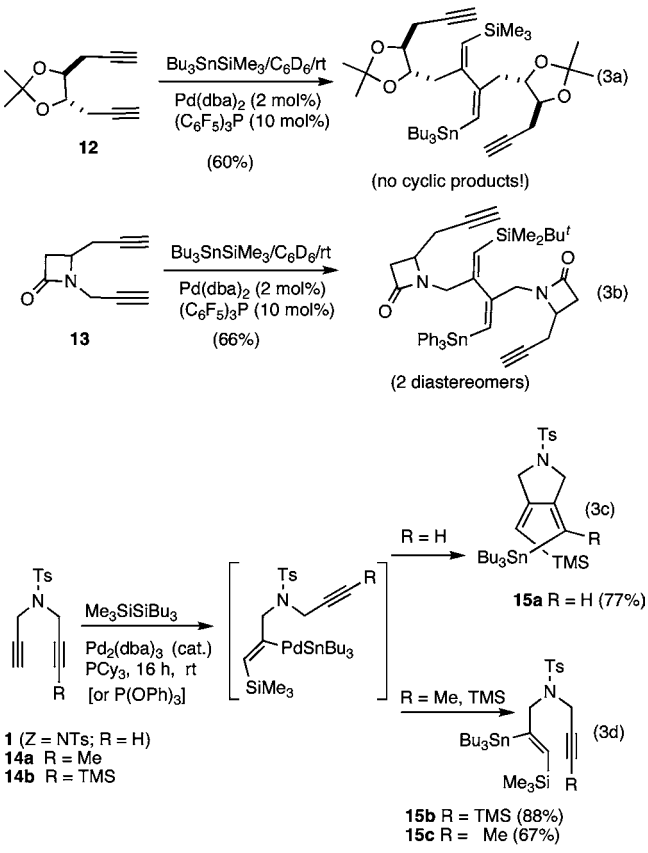
(b) how to control the regioselectivity of the [X−Y] addition in an unsymmetrical 1,*n*-diyne (see eq 2a); and (c) how to increase the activation barrier to allow the atropisomer(s) to be isolated at or near room temperature (eq 2b). For example, would substitution on the backbone (eq 2b) permit such isolation? If so, in these reactions, could we bring about atropselectivity that is dependent on the substrate (diastereoselectivity), or even better, on a metal catalyst in the reactions of a prochiral substrate (enantioselectivity)?



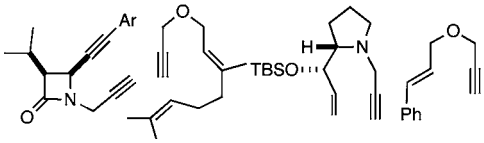
While the Pd-catalyzed silylstannylation−cyclization (eq 1) is a very useful reaction for the synthesis of highly functionalized *cyclyopentanoid* compounds from diynes,[2,3] allenynes,[4,5] and allenealdehydes,[6] its *use for the synthesis of carbocyclic and heterocyclic compounds of other ring sizes* 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,b.[8] In these cases, no cyclization products were detected under the reaction conditions. Likewise, 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 = NTs, R = H)] gave a good yield of the cyclic product **15a** (eq 3c). Several other examples of substrates for which the cyclization reactions failed when the [Si−Sn] reagent was used are listed in column 5 of Table 1. Examples of more complex substrates that highlight the limitations of the [Si−Sn] reagents can be seen in ref 7.

The challenges outlined in the previous paragraphs became immediately apparent as we sought to apply[9] these types of cyclization reactions in a general synthesis of dibenzocyclooctadienes (Figure 2 left),[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 of several of the issues raised above, including the expanded use of the

(4) Shin, S.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2001**, *123*, 8416.
(5) Kumareswaran, R.; Shin, S.; Gallou, I.; RajanBabu, T. V. *J. Org. Chem.* **2004**, *69*, 7157.
(6) (a) Kumareswaran, R.; Gallucci, J.; RajanBabu, T. V. *J. Org. Chem.* **2004**, *69*, 9151. (b) Kang, S.-K.; Ha, Y.-H.; Ko, B.-S.; Lim, Y.; Jung, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 343.
(7) Apte, S.; Radetich, B.; Shin, S.; RajanBabu, T. V. *Org. Lett.* **2004**, *6*, 4053.
(8) Gallou, I. Selective Pd- and Rh-Catalyzed Processes: I. Enantioselective Synthesis of Tetrahydroquinolines; II. The Asymmetric Hydroformylation Reaction. III. Silylstannylation of Diynes and Alleneynes. Ph.D. Thesis, The Ohio State University, Columbus, OH, 2002.
(9) Singidi, R. R.; RajanBabu, T. V. *Org. Lett.* **2008**, *10*, 3351.



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



[B−Sn] reagent **16** (Figure 2 right).[11,12] We found that this reagent has several advantages in comparison with the [Si−Sn] 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]

Results and Discussion

Our initial studies started with an examination of the cyclization of 2,2′-di-2-propynyl-1,1′-biphenyl (**17**), as shown in Scheme 1. The choice of the biphenyl scaffold was based on two premises besides the obvious similarity to the backbone of the dibenzocyclooctadienes (Figure 2a), the key targets in our synthesis efforts. From our dynamic NMR studies,[3] we had

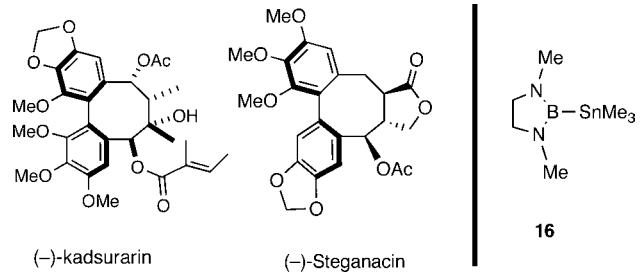
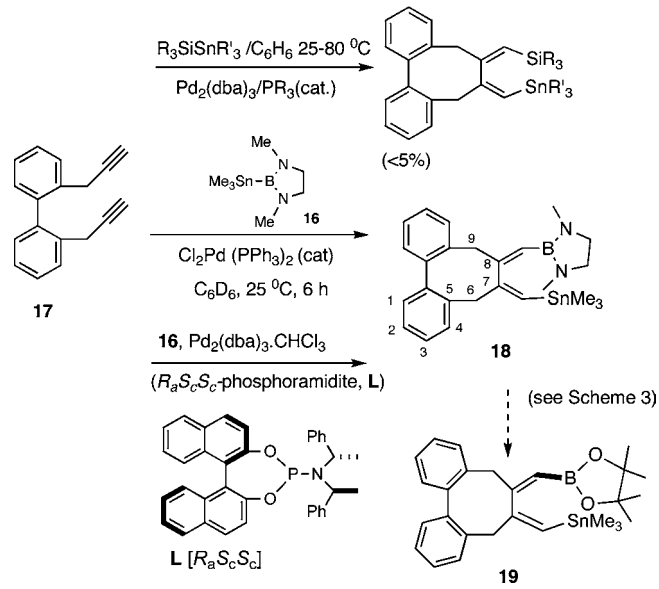


Figure 2. (left) Examples of biologically active dibenzocyclooctadienes. (right) Stannylborane reagent **16**.

Scheme 1. Relative Reactivities of [Si−Sn] and [B−Sn] Reagents



surmised that the backbone of a 1,2-bis(alkylidene)cycloalkane (eqs 1 and 2b) significantly influences the rate of the helical isomerization process, indicating that it should be possible to increase the free energy of activation ($\Delta G^{\ddagger}$) 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 nonplanar diene, i.e., a preference to form one of the diastereomers (R_a^*,R_a^*) or (R_a^*,S_a^*).

In the event, the exploratory studies of the Pd-catalyzed silylstannylation of **17** under a variety of conditions [$Pd_2(dba)_3$, THF, 80 °C; $Pd_2(dba)_3/P(C_6F_5)_3$, room temperature (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, proceeded in very good yield under two different sets of conditions, giving exclusively the product **18** as a single diastereomer in >75% yield. The reaction could be carried out using $PdCl_2\cdot(PPh_3)_2$ or $Pd_2(dba)_3\cdot$

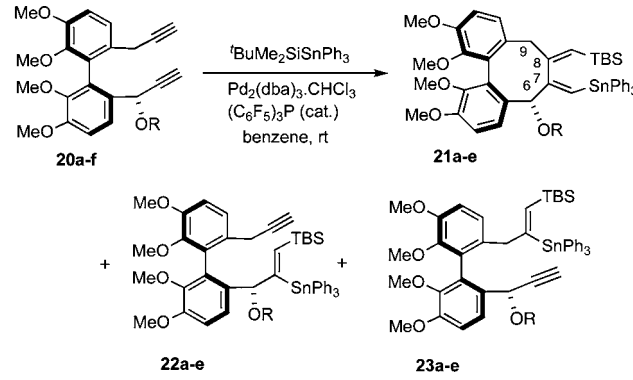
(10) For representative references on the isolation and biological activities of these classes of compounds, see: (a) Chang, J.; Reiner, J.; Xie, J. *Chem. Rev.* **2005**, *105*, 4581. (b) Li, H.; Wang, L.; Yang, Z.; Kitanaka, S. *J. Nat. Prod.* **2007**, *70*, 1999. (c) Chen, D.-F.; Zhang, S.-X.; Kozuka, M.; Sun, Q.-Z.; Feng, J.; Wang, Q.; Mukainaka, T.; Nobukuni, Y.; Tokuda, H.; Nishino, H.; Wang, H.-K.; Morris-Natschke, S. L.; Lee, K.-H. *J. Nat. Prod.* **2002**, *65*, 1242. (d) Chen, D.-F.; Zhang, S.-X.; Xie, L.; Xie, J.-X.; Chen, K.; Kashiwada, Y.; Zhou, B.-N.; Wang, P.; Cosentino, L. M.; Lee, K.-H. *Bioorg. Med. Chem.* **1997**, *5*, 1715. (e) Kuo, Y.-H.; Wu, M.-D.; Hung, C.-C.; Huang, R.-L.; Kuo, L.-M. Y.; Shen, Y.-C.; Ong, C.-W. *Bioorg. Med. Chem.* **2005**, *13*, 1555. (f) Chen, D.-F.; Zhang, S.-X.; Chen, K.; Zhou, B.-N.; Wang, P.; Cosentino, L. M.; Lee, K.-H. *J. Nat. Prod.* **1996**, *59*, 1066. (g) Tan, R.; Li, L. N.; Fang, Q. *Planta Med.* **1984**, *50*, 414. (h) Ikeya, Y.; Taguchi, H.; Yosioka, I. *Chem. Pharm. Bull.* **1982**, *30*, 3207. (i) Ikeya, Y.; Taguchi, H.; Yosioka, I.; Kobayashi, H. *Chem. Pharm. Bull.* **1979**, *27*, 2695.
(11) Niedenzu, K.; Rothgery, E. F. *Synth. React. Inorg. Met.-Org. Chem.* **1972**, *2*, 1.
(12) Onozawa, S.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389.
(13) Singidi, R. R.; RajanBabu, T. V. *Org. Lett.* **2010**, *12*, 2622.

$CHCl_3$/Feringa phosphoramidite (**L**)[14] as a catalyst. The latter conditions generally gave a cleaner reaction, even though the product formed was nearly racemic. VT NMR spectroscopy showed that this molecule (**18**) or a pinacolboronate derivative prepared from this molecule (**19**) does not undergo helical isomerization up to 55 °C. This aspect will be discussed in greater detail later.

We[2−5] and others[1b,n,12,15] have invested considerable effort in optimizing the metal/ligand combination for these multicomponent 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, the scouting experiments for these reactions are remarkably easy to run, since doing so often involves no more than simply mixing the substrate with the appropriate reagent in near-stoichiometric amounts in a neutral solvent such as C_6D_6 and then following the reaction by NMR spectroscopy 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 upon which to rely. In the silylstannylation−cyclization of 1,6-diynes and allenynes, our early studies[2−4] indicated that the use of a combination of Pd(0) (usually in the form of Pd_2dba_3) and $P(C_6F_5)_3$ as the catalyst is the most suitable when the reaction is carried in a nonpolar solvent such as benzene. Chelating ligands have generally been found to be less effective, possibly because the key oxidative addition of the [X−Y] reagent to these complexes is known to be slow.[15c,e] For the borylstannylation−cyclization, we have most often used the Tanaka conditions[12] [$PdCl_2$•$(PPh_3)_2$, 1−5 mol %, C_6H_6, rt], even though the most recent studies seem to suggest that Pd_2dba_3/ phosphoramidites give cleaner products at shorter reaction times. The generality of this observation has yet to be confirmed.

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 a simple unsubstituted biphenyl backbone, such as **17**, have 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 that of 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 fall in the 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 would be the configuration of the newly created, axially chiral diene). In order to separate these two factors, we chose to restrict the conformational mobility of the biphenyl unit by introducing two methoxy substituents at the 6 and 6′ positions. A propargylic substituent (OR in structures **20a**−**f** in Scheme 2) was introduced by acetylide addition to the corresponding biaryl-derived aldehyde.[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, giving **22a** and **22c**,

Scheme 2. Silylstannylation−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_2OBn)	36	51	12
20f (R = Benzoyl)	multiple products		

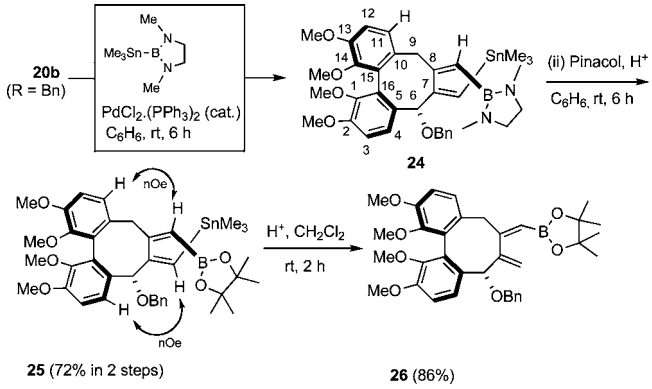
[a] estimated by ^1H NMR

(14) Arnold, L. A.; Imbos, R.; Mandoli, A.; de Vries, A. H. M.; Naasz, R.; Feringa, B. *Tetrahedron* **2000**, *56*, 2865.

(15) For key references dealing with the use of different types of ligands for palladium in multicomponent additions and cyclizations, see: Reviews: (a) Burks, H. E.; Morken, J. P. *Chem. Commun.* **2007**, 4717. (b) Ohmura, T.; Suginome, M. *Bull. Chem. Soc. Jpn.* **2009**, *82*, 29. A theoretical study of [Si−Sn] additions to alkynes: (c) Hada, M.; Tanaka, Y.; Ito, M.; Murakami, M.; Amii, H.; Ito, Y.; Nakatsuji, H. *J. Am. Chem. Soc.* **1994**, *116*, 8754. Some representative examples of unique ligand effects in [X−Y]-mediated addition and cyclization reactions: (d) Use of an isonitrile complex: Suginome, M.; Nakamura, H.; Ito, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 2777. (e) Ligand effects on oxidative addition of [B−Sn] reagents to Pd(0): Onozawa, S.-y.; Hatanaka, Y.; Sakakura, T.; Shimada, S.; Tanaka, M. *Organometallics* **1996**, *15*, 5450. Also see: Onozawa, S.; Hatanaka, Y.; Tanaka, M. *Chem. Commun.* **1997**, 1229. (f) Ligand/metal effects on [B−Si] additions: Suginome, M.; Matsuda, T.; Nakamura, H.; Ito, Y. *Tetrahedron* **1999**, *55*, 8787. (g) Ligand effects on [Si−Sn]-mediated enyne cyclization: Mori, M.; Hirose, T.; Wakamatsu, H.; Imakuni, N.; Sata, Y. *Organometallics* **2001**, *20*, 1907. Lautens, M.; Mancuso, J. *Synlett* **2002**, 394. (h) Use of an N-heterocyclic carbene ligand for enyne cyclization: Sato, Y.; Imakuni, N.; Mori, M. *Adv. Synth. Catal.* **2003**, *345*, 488. Also see: Sato, J.; Imakuni, N.; Hirose, T.; Wakamatsu, H.; Mori, M. *J. Organomet. Chem.* **2003**, *687*, 392. (i) Ligand-free Pd(0) for silylstannylation of allenes: Jeganmohan, M.; Shanmugasundaram, M.; Chang, K. J.; Cheng, C. H. *Chem. Commun.* **2002**, 2552. (j) A more effective Pd source for [B−Si] additions: Suginome, M.; Ohmura, T.; Miyake, Y.; Mitani, S.; Ito, Y.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 11174. (k) Use of a $(EtO)_3P$ ligand: Nakano, T.; Miyamoto, T.; Endoh, T.; Shimotani, M.; Ashida, N.; Morioka, T.; Takahashi, Y. *Appl. Organomet. Chem.* **2004**, *18*, 65. (l) Metal/ligand effects on [B−CN] addition to alkynes: Suginome, M.; Yamamoto, A.; Murakami, M. *J. Am. Chem. Soc.* **2003**, *125*, 6358. (m) Electronic effect on regioselectivity of [B−B] addition: Iwadate, N.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 2548.

(16) Details of the substrate syntheses can be found in the Supporting Information.

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



respectively, as the major uncyclized addition products. In these instances, the putative Pd−C(sp^2) 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-silylstannane. In sharp contrast, the reactions initiated at the unsubstitued alkynes in **20b**, **20d**, and **20e** lead to substantial cyclization (giving **21b**, **21d**, and **21e**, respectively).

While screening other similar [X−Y] reagents for the cyclization of diyne **20b**, we again found that it undergoes highly regio- and stereoselective (atropselective) cyclization upon reaction with $Me_3Sn-B[-N(Me)CH_2CH_2(Me)N-]$ (**16**) in the presence of $PdCl_2\cdot(PPh_3)_2$ to give a single product, **24** (Scheme 3).[9] The 1,3-bisazaborolidine **24** is moisture- and air-sensitive, and in the past, isolation of these compounds has limited the utility of this otherwise powerful reaction.[12,17] We found that the bis(aza)borolidine 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] The 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]

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** → **25**) using pinacol is generally applicable to most such adducts, especially those carrying Lewis basic groups. Formation of the pinacolate from the diazaborolidine allows purification and isolation of the corresponding 1-boryl-methylidene-2-stannylmethylidenecycloalkanes from a variety of diynes, including several instances where the corresponding silylstannylation−cyclization reactions fail (Table 1). With this isolation protocol, the functional-group compatibility of the [B−Sn]-mediated cyclization and its relative advantages in comparison with the corresponding [Si−Sn]-mediated reaction can be ascertained.

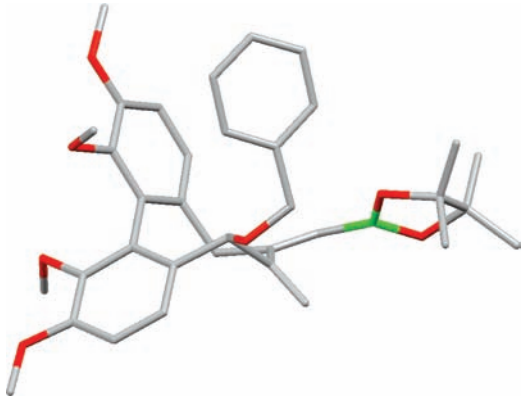


Figure 3. Solid-state structure of **26** based on X-ray crystallographic analysis (hydrogens have been omitted for clarity).

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

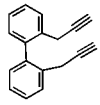
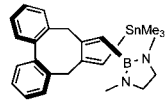
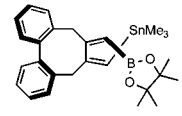
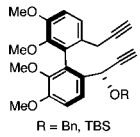
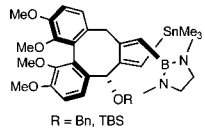
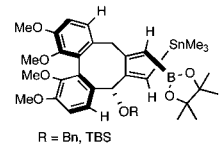
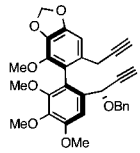
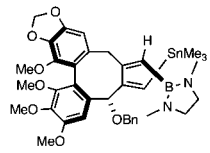
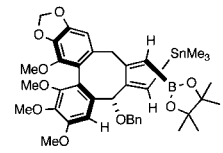
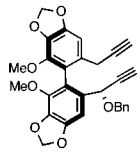
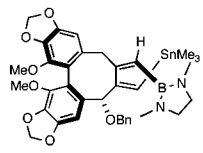
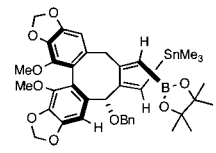
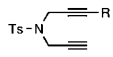
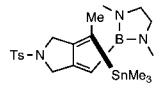
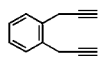
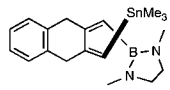
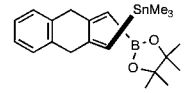
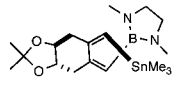
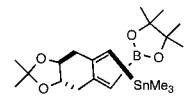
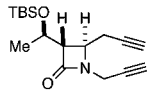
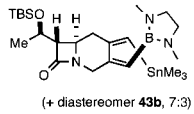
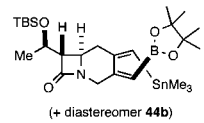
These cyclizations and the derivatization protocols are more broadly applicable. While the dipropargyl-*N*-tosylamine **33** (R = H) (Table 1, entry 5) undergoes efficient cyclization with both [Si−Sn] and [B−Sn] reagents,[2,12] the [B−Sn] reagent is clearly superior for the corresponding 1-methylalkyne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

A different mode of chirality transfer was explored with the cyclization of the C_2-symmetric dipropargyl dioxolane **12** derived from (*R*,*R*)-tartaric acid. As mentioned above, this substrate does not undergo the [Si−Sn]-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 ^{13}C NMR spectra. The configuration of the nonplanar 1,3-diene has not been established. However, the corresponding pinacolboronate **41** showed no tendency to undergo atrop-epimerization, as judged by VT ^1H NMR in toluene-d_8 (see below).

Finally, additional functional-group compatibility of the [B−Sn]-mediated cyclization was explored with diyne **42** containing a sensitive β-lactam (Scheme 4 and Table 1, entry 8). This substrate is easily assembled from commercially available β-lactam **45** (Scheme 4).[20] In the cyclization of **42**, a mixture of diastereomeric B/Sn adducts (7:3) were obtained. The major product (**43a**) is highly crystalline, and its solid-state structure was 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 pinacolboronate it appears to be a regioisomer. Treatment of the mixture of **43a** and **43b** gave the corresponding pinacolboronates **44a** and **44b**, whose structures were rigorously

(17) Weber, L.; Wartig, H. B.; Stammler, H. G.; Stammler, A.; Neumann, B. *Organometallics* **2000**, *19*, 2891.
(18) Biffar, W.; Nöth, H.; Schwerthöffer, R. *Liebigs Ann. Chem.* **1981**, 2067.
(19) Suginome, M.; Yamamoto, A.; Murakami, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2380.
(20) Jiang, B.; Tian, H. *Tetrahedron Lett.* **2007**, *48*, 7942.

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

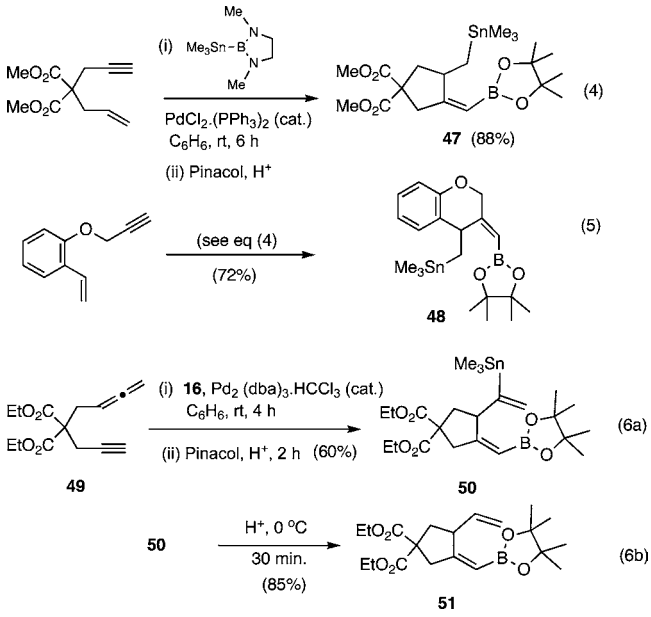
no.	diyne	diazaborolidine[a]	dioxaborolidine (yield for 2 steps, %)	[SiSn]-mediated reaction
1.	 **17**	 **18**	 **19** (78)	low yield of acyclic adducts
2.	 R = Bn, TBS **20b, 20c**	 R = Bn, TBS **24b, 24c**	 R = Bn, TBS **25b, 25c** (70, 78)	mixture of acyclic and cyclic products, see: Scheme 2
3.	 **27**	 **28**	 **29** (70)	(--)[b]
4.	 **30**	 **31**	 **32** (72)	(--)[b]
5.	 R = H **33** R = Me **34**	 **35** (73)	primary product (**35**) isolated as solid	for **34**, 67% acyclic adduct with $Me_3SiSnBu_3$[c]
6.	 **36**	 **37** (96)	 **38** (94)	acyclic adducts (**39**) major
7.	 **12**	 **40**	 **41** (83)	dimer + low yield of acyclic adducts[d]
8.	 **42**	 (+ diastereomer **43b**, 7:3) **43a** (88)	 (+ diastereomer **44b**) **44a** (79)	low yield of acyclic adducts in related β-lactam, see eq 3b

[a] Not isolated, except for **18**, **35**, **37**, and **43a**; conversions >90% as estimated by NMR spectroscopy. [b] Not attempted. [c] See ref 7. [d] See ref 8.

established by NMR methods, including extensive correlation spectroscopy (COSY) and nuclear Overhauser effect spectroscopy (NOESY) measurements (see the Supporting Information for details of the NMR analysis). Gratifyingly, the chemical shifts and coupling constants are highly diagnostic of the conformation indicated by the solid-state structure of **43a**. VT ^{1}H NMR analysis of the major product **44a** between 27 and 55 °C showed that these bicyclic compounds do not undergo helical isomerization under conditions where monocyclic adducts are known to be fluxional (see below).

As shown in eqs 4−6, this general protocol for the formation of the pinacolboronate from the corresponding diazaborolidine is also applicable to other cyclization products derived from enynes and allenynes.

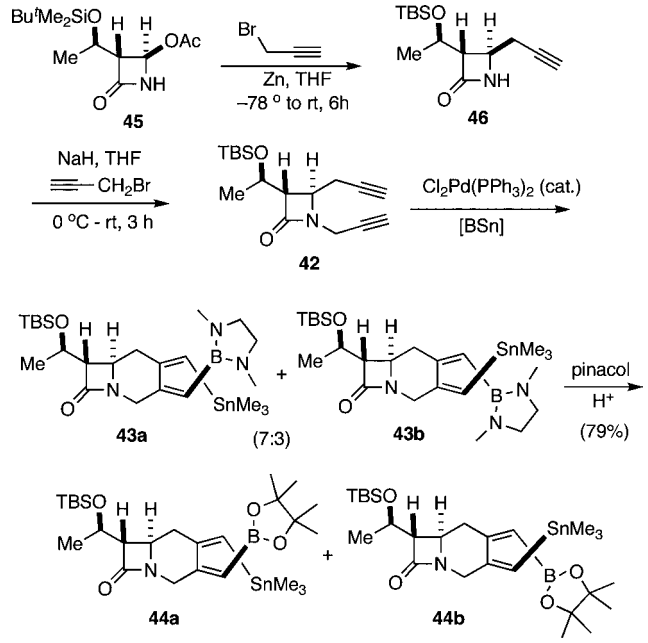
The superior reactivity of the boron−tin reagent notwithstanding, these studies indicate that further applications of this chemistry would have to depend on finding proper derivatization procedures for easy isolation of useful intermediates from the 1-borylmethylidene-2-stannylmethylidenecycloalkanes because of their hydrolytic instability. We investigated a number of these



reactions (Scheme 5) in the context of the more prototypical diene **52**,[12] which was readily prepared from 1,6-heptadiyne and **16**. Adducts with no Lewis basic groups (such as oxygen groups) on the backbone seem to be more prone to destannylation under these conditions, and significant contamination by products such as **54** was seen. For example, adduct **52** gave both stannylated and destannylated products (**53** and **54**) competitively (Scheme 5). For this substrate, even *without* the addition of the strong acid, the destannylation was competitive. Such uncatalyzed reactions generally lead to a multitude of products. Terminal vinylstannanes with more exposed vinyl moieties also appear to undergo this competitive destannylation.

Another useful derivatization protocol is the bromodestannylation reaction shown in Scheme 5 (**52** → **55** → **56**), in which the diazaborolidine−Sn adduct **52** is first treated with 1.5 equiv of *N*-bromosuccinimide in chloroform and then the acid-catalyzed pinacolboronate is formed. In case of the adduct **52**,

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



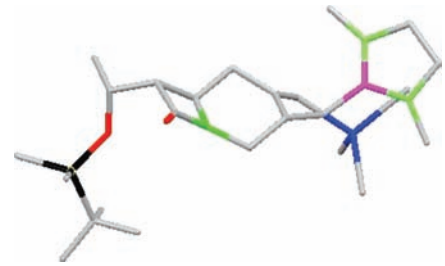
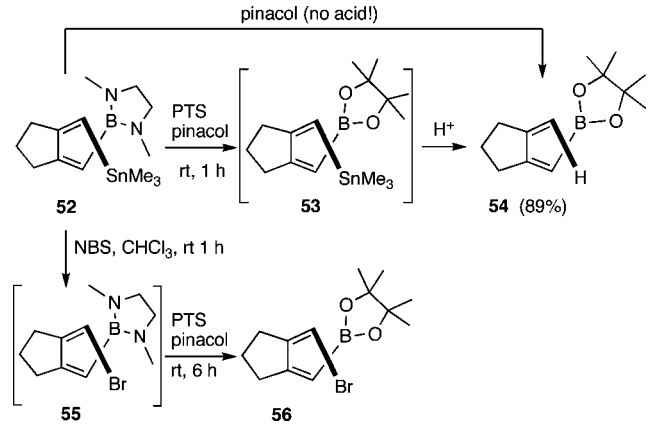


Figure 4. Solid-state structure of **43a** (hydrogens have been omitted for clarity).

Scheme 5. Derivatization Schemes for 1,3-Diazaborolidines

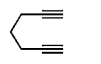
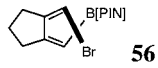
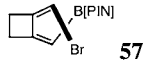
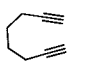
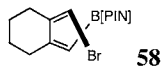
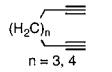
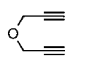
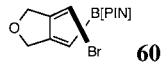
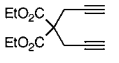
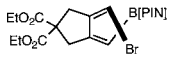
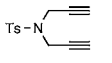
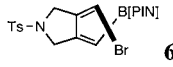
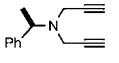
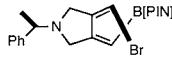
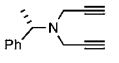
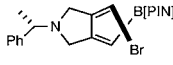
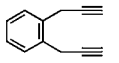
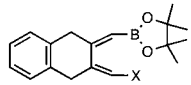
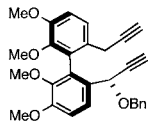
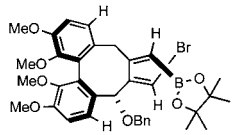


the halogen−metal exchange takes place cleanly in ∼1 h to give **55**. This resulting compound was not isolated but directly transformed into **56** by treatment with pinacol and *p*-toluenesulfonic acid (PTS). Diene 5**6**, a stable boronate, was easily isolated by column chromatography in 80% overall 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-bromomethylidenecycloalkanes, which to the best of our knowledge are new kinds of bifunctional vinyl derivatives with potential applications as linchpin reagents.[21] Several examples of the formation of these highly functionalized bisalkylidenes 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-ring compounds are readily prepared by this method. Nona-1,8-diyne and deca-1,9-diyne (entry 4) give mostly acyclic 1,2-adducts.

Atropisomerism in (*Z*,*Z*)-1,2-Bis(alkylidene)cycloalkanes. The fluxional behavior of the 1,2-bisalkylidenes containing 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 that there was little hope of increasing $\Delta G^{\ddagger}$ for the helical isomerization by simply increasing the size of the X/Y groups.[3] The kinetic parameters for the enantiomerization process were determined for the series of dienes **3**−**6** via NMR line-shape analysis, and the results are shown in Figure 5. For all of the

(21) (a) Coleman, R. S.; Lu, X.; Modolo, I. *J. Am. Chem. Soc.* **2007**, *129*, 3826. For other similar compounds, see: (b) Coleman, R. S.; Walczak, M. C. *Org. Lett.* **2005**, *7*, 2289. (c) Coleman, R. S.; Walczak, M. C.; Campbell, E. L. *J. Am. Chem. Soc.* **2005**, *127*, 16038.

Table 2. Direct Synthesis of 1-Borylmethylidene-2-bromomethylidenecycloalkanes 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.	 **8**	 **63**	65
9.	 **64**	 **65**	65
10		 **66** (X=I), **67** (X = Br)	**66** (66) **67** (70)
11.	 **20b**	 **68**	--

[a] See Scheme 5 for the procedure. [b] Mostly acyclic adducts.

molecules studied, the $\Delta G^{\ddagger}$ values were similar (52−57 kJ mol^{-1} at 300 K) and well within the range expected from the NMR spectra. Thus, *it has not been possible to synthesize monocyclic systems in which the helical isomerization is frozen on the NMR time scale at or near room temperature*.

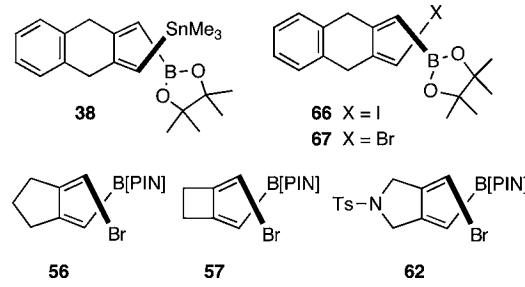
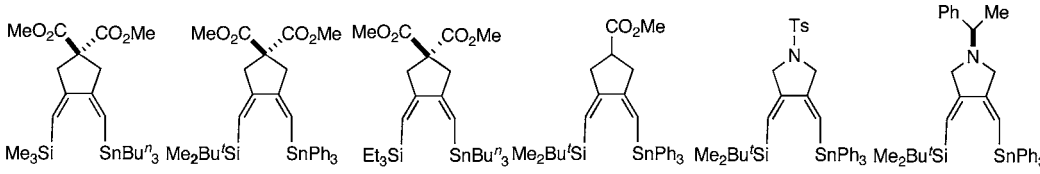


Figure 6. Some fluxional (*Z,Z*)-4-halodienyl-1-pinacolboronates.

It should be noted that the substitution pattern of the backbone of the precursor diyne has a strong effect on $\Delta G^{\ddagger}$. For example, the *N*-tosyl derivative **7** and *N*-alkyl derivative **8** in Figure 5 have much lower coalescence temperatures than the corresponding *gem*-bis(carbomethoxy)methylene compounds **3** and **4**. The cyclic products listed in Tables 1 and 2 add to the list of these uncommon molecules. Furthermore, we found that by restricting the conformational mobility of the newly formed ring, either by having a biphenyl unit as a part of the backbone (Table 1, entries 1−4) or imposing a bicyclic motif (entries 6−8), the helical isomerization of the diene can be almost *completely* arrested at ambient temperatures.

A typical example of how the helical isomerization can be monitored by following the changes in the line shapes of the bisallylic hydrogens in the adducts from symmetric diynes is shown in Figure 1 for compound **3**. In the fast-exchange regime, because of the pseudoplane 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 adduct **38** and the corresponding iodo and bromo derivatives **66** and **67** (Figure 6).

In compound **38** (Table 1, entry 6, column 4), the bisallylic hydrogens appeared (in $CDCl_3$) as two distinct AB quartets centered around δ 3.806 ($\upsilon_A = 3.978$, $\upsilon_B = 3.634$, $J_{AB} = 16.8$ Hz) and 3.691 ($\upsilon_A = 3.814$, $\upsilon_B = 3.568$, $J_{AB} = 16.8$ Hz). The vinyl hydrogens in this compound appeared at δ 5.328 [d, $J =$ 1.2 Hz, B−C(sp^2)−H] and 5.771 [t, $J = 1.2$ Hz, $J_{Sn-H} = 76$ Hz, Sn−C(sp^2)−H]. When a solution of this compound in toluene-d_8 was warmed (27 to 75 °C), very few changes in the ^{1}H NMR spectrum occurred (Figure 7). Only above 50 °C was there some noticeable broadening in the lines due to the allylic hydrogens. Of course, the vinyl hydrogens in this compound would not be expected to undergo any changes, since the helical isomer is also the enantiomer of the starting material. In the spectrum of the corresponding iodo derivative **66**, the bisallylic hydrogens appeared 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



	3	4	5	6	7	8
$\Delta H^{\#}$ (kJ. mol^{-1})	54.8	55.4	63.2	48.8	--	--
$\Delta S^{\#}$ (J. mol^{-1})	0.4	–4.3	21.0	–11.6	--	--
$\Delta G^{\#}$ (J. mol^{-1}, 300 K)	54.7	56.7	56.9	52.2	--	--
$T_{coal.}$ (°C)	10	20	20	0	– 20	– 60

Figure 5. Kinetic parameters for helical isomerization and coalescence temperatures.

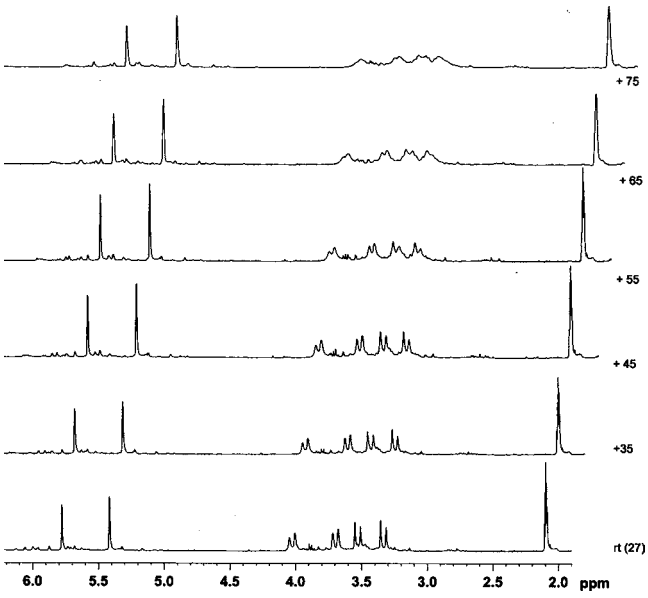


Figure 7. VT ^{1}H NMR spectra (toluene-d_8) of **38**.

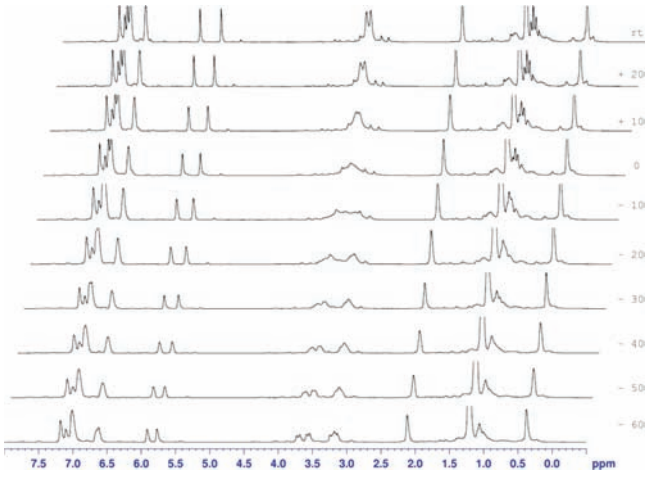


Figure 8. VT ^{1}H NMR spectra (toluene-d_8) of **66**.

was cooled to −65 °C, these peaks underwent changes reminiscent of the coalescence seen in the spectrum of **3** (Figure 1)[3] and below −40 °C appeared as two sets of distinct AB quartets of equal intensity (Figure 8).

Confirming the dynamic nature of the process in haloboronates, we found that in the bromo derivative **67**, which presumably has an even lower barrier for isomerization (because of the smaller size of Br relative to I), the bisallylic hydrogens appeared as two sharp singlets at δ 3.41 and 3.45 at room temperature.

The VT ^{1}H NMR spectra of **56**, **57**, and **62** (Figure 6, Table 2) also confirmed the low barrier for the bromoboryl derivatives.[22] Between 27 and −70 °C there was no change in the CH_2 region except for some broadening. In none of these cases did we observe the AB pattern characteristic of the evolving chirality as the temperature is lowered.

The biphenyl scaffolds in diynes **17**, **20b**, **20c**, **27**, and **30** (Table 1, entries 1−4) also increase the activation barrier for the helical isomerization. In each of these substrates, the only

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

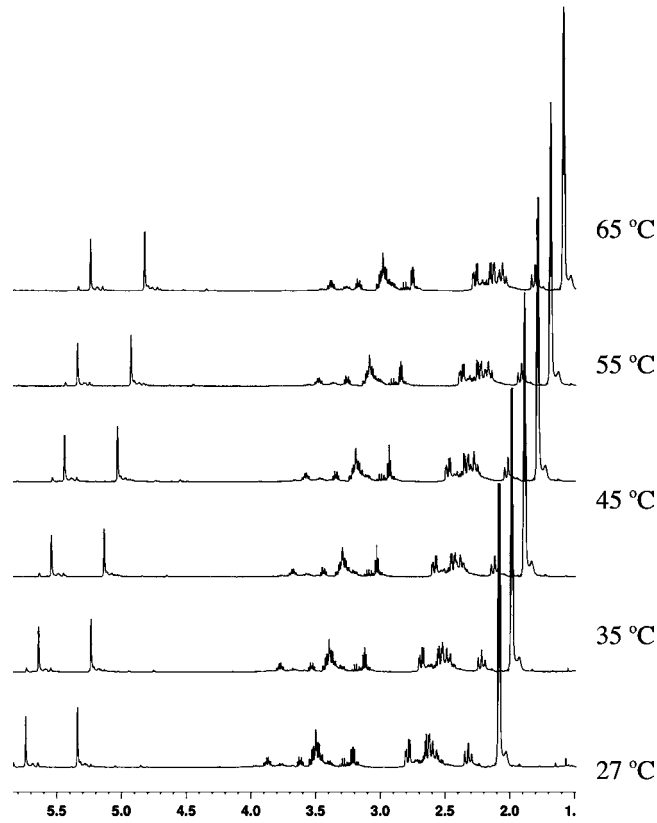


Figure 9. VT ^{1}H NMR spectra (toluene-d_8) of **41**.

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 was varied between −50 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 on the basis of 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, 1H, J_{Sn-H} = 75 Hz, SnC*H*), 5.559 (s, 1H, BC*H*), 3.292 (ABq, ν_A = 3.386, ν_B = 3.199, J_{AB} = 12 Hz, 2H, benzylic CH_2, CH_2C═C(H)B), 3.250−3.358 (m, d, 2H, benzylic CH_2, CH_2C═C(H)Sn). VT ^{1}H NMR analysis (toluene-d_8) showed that the peaks due to the C(sp^2) hydrogens and the benzylic hydrogens exhibited no changes as the temperature was raised. As the solution was cooled, some line broadening was observed, which can often be ascribed to changes in viscosity of the solvent.[3] VT ^{1}H NMR spectra of pinacolboronate **19** also showed no evidence of isomerization.

Adducts from enantiopure D-tartrate-derived diyne **12** (Table 1, entry 7) represent a different class of chiral substrate (C_2-symmetric) for which, as before, the cyclization is atropselective, with only a *single* diastereomer formed in the reaction. The ^{1}H NMR analysis showed only two vinylic hydrogens in product **40** and its boronate derivative **41**. The corresponding ^{13}C NMR spectra also showed 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 ^{1}H and ^{13}C NMR spectra. While the absolute configurations of the [B−Sn] adduct **40** (Table 1, entry 7) and its derivative **41** have not been established, VT ^{1}H NMR

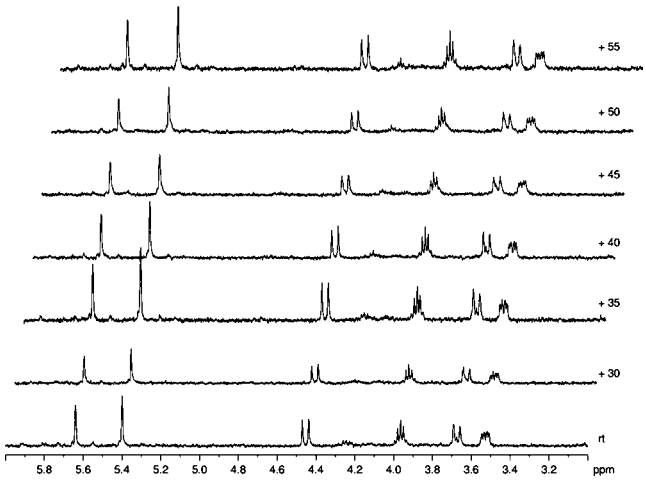


Figure 10. VT ^{1}H NMR spectra (toluene-d_8) of **44a**.

analysis (Figure 9) clearly suggested that the coalescence temperature for the helical isomerization in this system is >65 °C.

The major diastereomeric adduct derived from the highly functionalized β-lactam **43a** and the corresponding pinacolboronate **44a** are also configurationally stable, as judged by VT NMR studies. The major product **44a**, whose structure was determined by X-ray crystallography, was dissolved in toluene-d_8, and its ^{1}H NMR spectrum was monitored between 23 and 55 °C. There were 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 [−N(Me)CH_2CH_2(Me)N−]B−$SnMe_3$ (**16**) is a superior reagent capable of effecting bisfunctionalization−cyclization in several 1,*n*-diynes for which 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 backbone increase the activation barrier for the helical isomerization in (*Z*,*Z*)-dienes that are generated in a cyclization event. In the biphenyl and dioxolane systems, the reactions proceed with surprisingly good regio- and stereoselectivity. The diazaborolidine derivatives are hydrolytically unstable but can be isolated by recrystallization or precipitation. For further synthetic applications, it is advantageous to convert these compounds in situ into the corresponding dioxaborolidines with either retention of the Me_3Sn group or replacement of this group via 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 syntheses of these compounds will be reported in due course.

Acknowledgment. Financial assistance for this research from the 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, ^{1}H and ^{13}C NMR spectra of key compounds, and a CIF for **43a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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