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Cyclization Strategies to Polyenes Using Pd(II)-Catalyzed Couplings of Pinacol Vinylboronates

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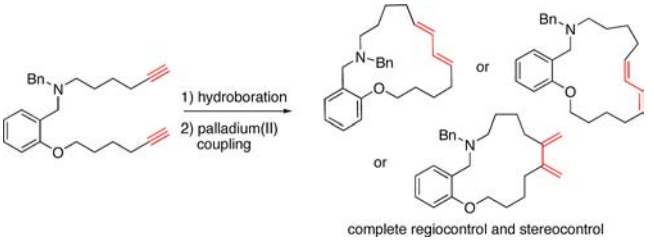
ABSTRACT



As a complement to Pd(0)-catalyzed cyclizations, seven Pd(II)-catalyzed cyclization strategies are reported. α,ω-Diynes are selectively hydroborated to bis(boronate esters), which cyclize under Pd(II)-catalysis producing a diverse array of small, medium, and macrocyclic polyenes with controlled *E,E*, *Z,Z*, or *E,Z* stereochemistry. Various functional groups are tolerated including aryl bromides, and applications are illustrated.

Palladium-catalyzed cross-coupling reactions are exceptionally powerful for the construction of a remarkable diversity of molecules.[1] Widely employed for intermolecular cross-coupling, this chemistry is extremely effective for intramolecular cyclizations.[2] In particular, macrocyclizations using Stille and Suzuki protocols are potent strategies for the synthesis of complex macrolides.[3] However, a significant strategic disadvantage for cyclizations is the numerous synthetic steps required to set up the differentiated end groups with electro- and nucleophilic components. Several other detrimental factors associated with these processes are (i) potentially toxic halogenated substrates, (ii) air-free conditions required for Pd(0) reactions, and (iii) elevated reaction temperatures. In addition, some recently developed methods require expensive specialty phosphine ligands for the key oxidative addition step.[4]

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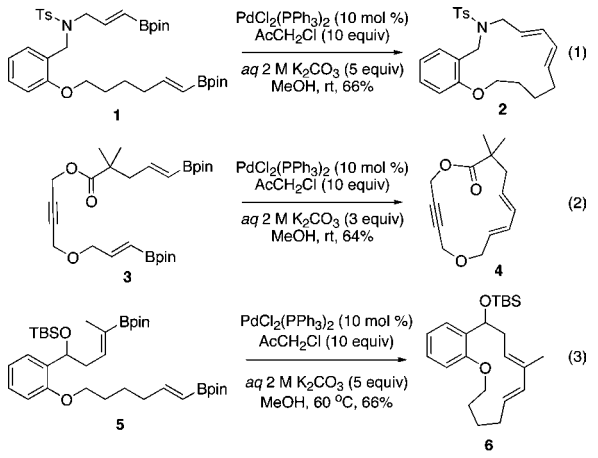
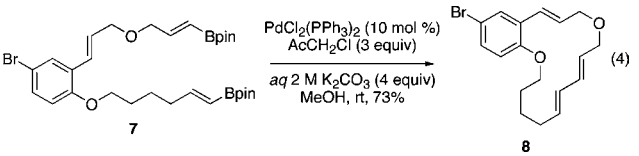
An approach obviating these problems is oxidative cross-coupling,[5] thus bypassing the high-cost oxidative addition step typical of Pd(0) coupling. In contrast with a Pd(0)-catalyzed coupling cycle, a Pd(II)-catalyzed oxidative cross-coupling cycle only requires nucleophilic partners, thus simplifying substrate synthesis. A key cycle component, although extrinsic to the bond forming steps, is reoxidation of the Pd(0) complex after reductive elimination. Other key features include elimination of the problematic aspects of Pd(0) processes such as halogenated substrates, air-free conditions, elevated temperatures, and expensive ligands. These features make a Pd(II)-catalyzed strategy a process chemistry and green chemistry alternative to Pd(0) cross-coupling. Recently, oxidative cross-couplings of alkyl-, alkenyl-, alkynyl-, and aryl-organometallic and even hydrocarbon substrates have been reported.[6] The major challenge is that selective oxidative alkenyl–alkenyl cross-couplings are not known.[5] A solution to this problem is to tether alkenyl substrates together, allowing application of this strategy to important classes of molecules such as polyene macrolides.[3,7] We report herein development of a family of seven different Pd(II)-catalyzed protocols for achieving selective *E,E*, *Z,Z*, *E,Z*, and α,α alkenyl–alkenyl cross-couplings through cyclizations of vinylboronate substrates. These cyclization strategies offer significant advantages over traditional Pd(0) methods and are the beginnings of a series of Pd(II)-catalyzed cyclizations of substrates containing two nucleophilic groups.

While many organometallic reagents could be oxidatively coupled in a cyclization,[5] we chose vinylboronate esters[8] as they are readily synthesized; are compatible with a range of functional groups; are stable to air, water and chromatography; and are not toxic. For example, bis(vinylboronate ester) **1** was easily prepared[9] using Wang's[10] Zr-catalyzed hydroboration of an α,ω-diyne. After optimization, we found that Pd(II)-catalyzed macrocyclization of **1** to **2** was accomplished utilizing the $PdCl_2(PPh_3)_2$ catalyst, chloroacetone reoxidant, and aqueous potassium carbonate in methanol (eq 1). Complex phosphine ligands are unnecessary as transmetalation is a low energy process. Tests employing $Cu(OAc)_2$ as the reoxidant led to coupling of vinylboronates with alcohols,[11] so chloroacetone[12] was used as the Pd(0) reoxidant. Aqueous K_2CO_3 activates boronate esters toward transmetalation.[13] Several solvents were screened, and methanol was found to be optimal; as expected for a macrocyclization, dilution to 0.002 M was necessary to avoid oligomerization. Finally, unlike Pd(0)-catalyzed cross-couplings, which can require elevated temperatures, these reactions readily occurred at rt. Using these standardized conditions, bisboronate **3** cyclized to macrolide **4** (eq 2). Furthermore, a diyne containing an internal alkyne provided access to a macrocyclic diene with a trisubstituted alkene. Synthesis of **5** required more forcing conditions for diyne hydroboration,[9] but Pd(II) cyclization proceeded under mild conditions providing **6** in good yield and excellent stereospecificity (eq 3).



An important substrate to test the Pd(II)-based mechanism and reaction chemoselectivity is compound **7**. Oxidative addition of a Pd(0) species with the aryl bromide followed by Suzuki cross-coupling with a vinylboronate unit would lead to oligomeric products. However, an excellent yield of the desired cyclized product **8** was obtained using our reaction conditions (eq 4). Thus, chloroacetone oxidation of the Pd(0) species generated by reductive elimination of the diene product is considerably faster than aryl bromide oxidative addition.



Switching from *E,E* to *Z,Z* macrocyclic dienes, a modified[9] Srebnik[14] synthesis of a vinylboronate ester provided *Z,Z*-bis(vinylboronate ester) **10** from diyne **9** as a substrate to cyclize to a *Z,Z*-diene product (eq 5). The potentially convenient Miyaura[15] protocol fails to provide *Z*-vinylboronate esters on complex diyne substrates such as this. Substrate **10** cleanly cyclized to the eight-membered ring product **11** under the same reaction conditions. Unlike

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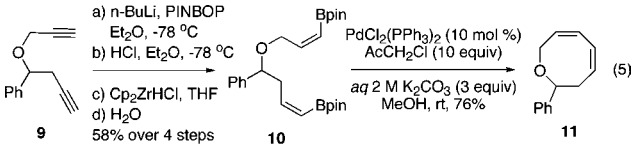
rings containing *E,E* diene units, rings containing *Z,Z* diene units can be as small as five-membered, so a wide variety of structures can be accessed using this cyclization strategy.



PINBOP = 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

The two strategies to *E,E* and *Z,Z* cyclic dienes provide enormous potential for synthetic diversity by introducing the ring-forming coupling partners late in a synthesis. Thus, a specific target can be accessed from a simple common precursor or families of isomeric compounds can be prepared from a common precursor. The cyclization itself is compatible with numerous functional groups. We illustrated these concepts with a diyne that was elaborated into three different macrocycles with high selectivity (Scheme 1). Hydroboration[10] of aminodiyne **12** gave *E,E*-bis(vinylboronate ester) **13**. Standard Pd(II)-catalyzed cyclization afforded *E,E*-macrocyclic diene **14** in a 74% yield. In an alternate strategy, hydroboration of **12** with modified Srebnik conditions[9,14] gave *Z,Z*-bis(vinylboronate ester) **15** and subsequent Pd(II) cyclization afforded *Z,Z*-macrocyclic diene **16** in a 70% yield. Then taking it to the next level, we hydroborated **12** using Hoyveda's[16] Ni-catalyzed protocol to access bis(α-vinylboronate ester) **17**. This cleanly produced the internal boronate ester with exceptional selectivity. Pd(II)-catalyzed cyclization of **17** again using standard reaction conditions afforded macrocyclic exodiene **18** in a 43% yield. We did not optimize this yield, but note that cyclization at elevated temperatures led to increased amounts of substrate protodeboronation.

Copper-catalyzed hydroboration chemistries developed by Yun[17] and Lipshutz[18] provided access to two more cyclization modalities. α,ω-Diynoate **19** was converted regio- and stereoselectively to either bis(β-borylenoate) **20** or bis(α-borylenoate) **22** (Scheme 2). Copper chloride catalyzed hydroboration[17] with bis(pinacolato)diboron provided **20** as a stable, isolable compound that cyclized under our standard Pd(II) conditions to give **21** in a 76% yield. In contrast, hydroboration with Stryker's copper hydride catalyst[18] and pinacol borane provided **22**. While stable to water,[18] **22** was unstable in the basic methanol of our Pd-catalyzed cyclization. Thus, a one- pot hydroboration/cyclization in THF provided product **23**. The modest yield might be attributed to the instability of **22** or the unoptimized cyclization in a different solvent. These two examples illustrate regioselective and stereoselective construction of novel densely functionalized tetrasubstituted-diene macrocyclic targets.

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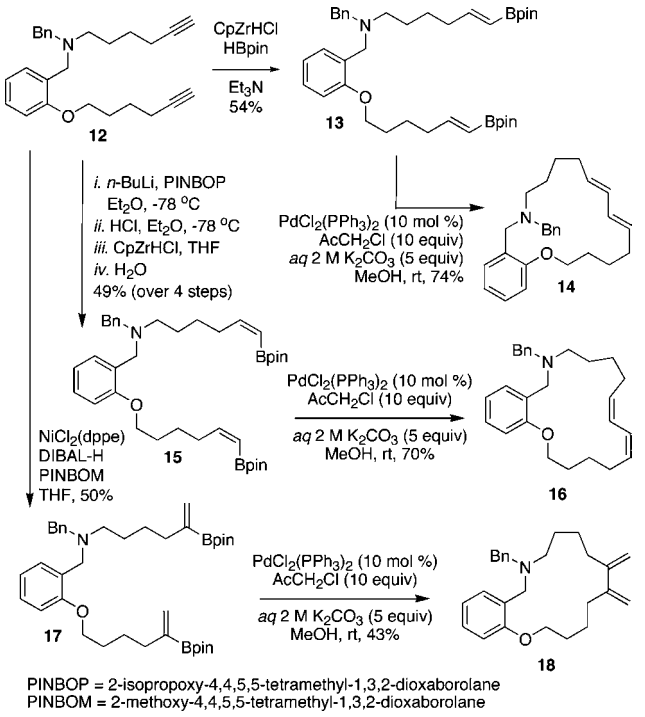
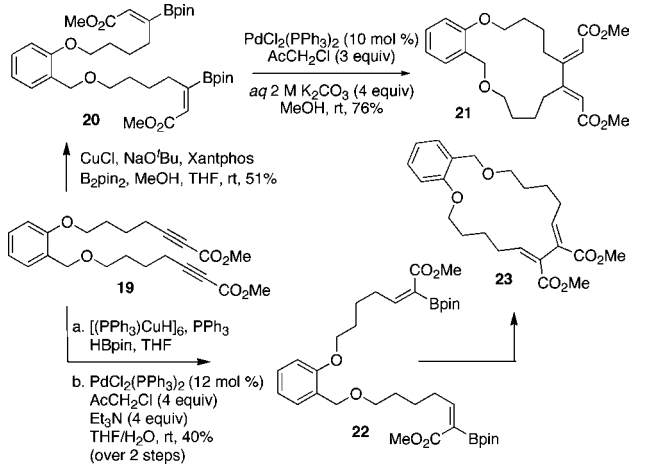
Scheme 1. Synthesis of Macrocyclic Dienes



PINBOP = 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane
PINBOM = 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

Scheme 2. Synthesis of Macrocyclic Dienediesters

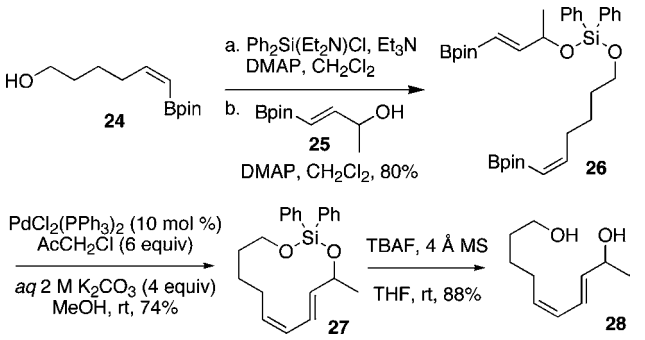


A major question was whether a Pd(II) strategy could access *E,Z*-diene products. All bis(vinylboronate ester) substrates above were prepared in one step via diyne hydroboration. Alternatively, separate preparation of vinylboronates followed by connecting them provides an *E,Z*-bis(vinylboronate ester) substrate. To examine this concept, **24** and **25** were linked using $Ph_2Si(Et_2N)Cl$[19] to yield substrate **26** (Scheme 3).[9] Cyclization of **26** under our Pd(II) conditions yielded *E,Z*-macrocycle **27** in good yield.

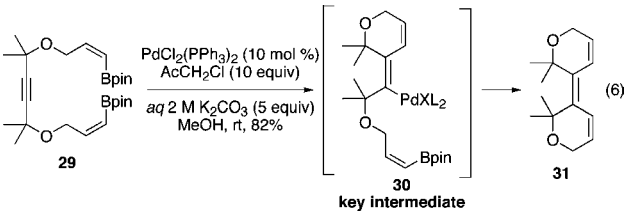
(19) Matsui, R.; Seto, K.; Fujita, K.; Suzuki, T.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2010**, *49*, 10068.

This illustrates access to **27** and acyclic *E,Z*-diene **28** through fluoride-promoted desilylation, presenting a net selective intermolecular oxidative cross-coupling of vinylboronate esters. While the stepwise assembly here is reminiscent of the typical coupling of electro- and nucleophilic moieties in a Pd(0)-catalyzed process, Pd(II) catalysis obviates the need for potentially toxic halogenated substrates and air-free conditions.

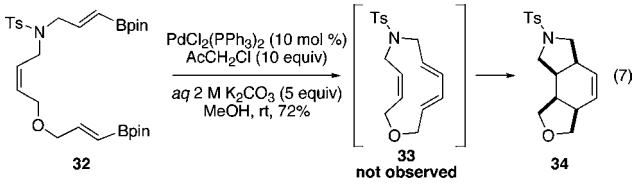
Scheme 3. Synthesis of Cyclic and Acyclic Dienes



A powerful reaction of Pd(II) intermediates is insertion of moieties such as CO, alkynes, alkenes, dienes, and allenes.[20] As long as the rate of insertion is faster than the second intramolecular transmetalation step, a variety of new Pd(II)-catalyzed cyclization strategies become available. To illustrate this concept, we opted for an intramolecular alkyne insertion. Thus, substrate **29** was prepared using the modified Srebnik conditions and cyclized to yield 82% of bipyranylidene *Z,Z,Z*-triene **31** as a single isomer (eq 6). The internal alkene *Z* stereochemistry was assumed based upon well-established precedents for cis insertions via intermediate **30**.[20] This system demonstrates yet another Pd(II) cyclization strategy starting from a simple diyne.[21]



Potential synthetic applications are significant, and many reported Pd(0)-catalyzed macrocyclizations might have employed these strategies.[3] One application is preparation of substrates for transannular Diels–Alder (TADA) reactions[22] which are immensely powerful for the synthesis of complex natural products.[3c,23,24] Indeed, Pd(II) cyclization of *E,E*-bis(vinylboronate ester) **32**, prepared by Wang hydroboration[10] of an enediyne,[9] *at rt* led to **34** in 72% yield as the sole product (eq 7). No intermediate macrocycle **33** was observed during the reaction. We will report details on this and other TADA applications of our Pd(II) cyclization strategy in a subsequent paper.



In conclusion, we demonstrated seven new efficient Pd(II) cyclization strategies for cyclic polyene synthesis. The cyclizations occurred at rt, were not air sensitive, and avoided potentially genotoxic vinyl halide substrates. α,ω-Diynes were rapidly converted stereospecifically and regioselectively to cyclic *E,E*- or *Z,Z*- or exodimethylene dienes. A Pd(II) catalytic cycle was supported by compatibility with an aryl bromide. A bis(ynoate) led to either α,α- or *β,β*-linked cyclic dienediesters. Access to acyclic or macrocyclic *E,Z*-dienes was demonstrated, and adding alkyne insertion into the catalytic cycle led to a strategy for a cyclic *Z,Z,Z*-triene. Finally, rapid synthesis of a TADA substrate was demonstrated. These Pd(II) cyclization strategies should find wide application for synthesis of cyclic molecules.

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Supporting Information Available. Experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.