

A Cascade Palladium-Mediated Cross-Coupling/Electrocyclization Approach to the Construction of Fused Bi- and Tricyclic Rings

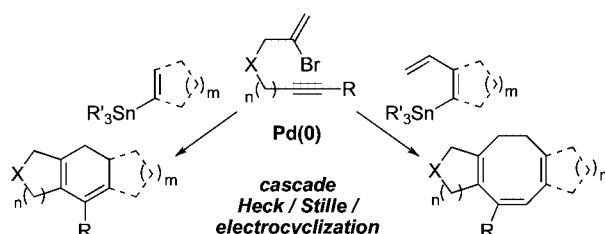
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ABSTRACT

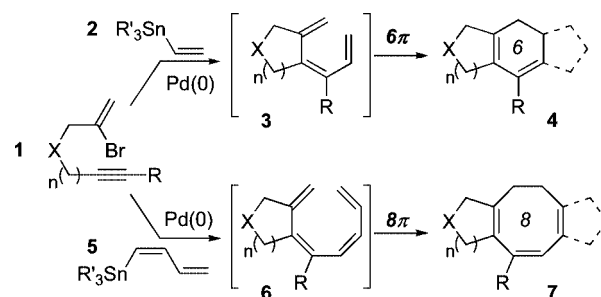


A versatile palladium-catalyzed cyclization/cross-coupling/electrocyclization strategy for the synthesis of fused bi- and tricyclic ring systems is described. Excellent yields of the polycyclic products are obtained with a range of tethering ring sizes and functionality, including an unprecedented 5,6,4,5-fused tetracycle. The reaction mechanism features two unusual palladium-mediated isomerizations prior to electrocyclization.

The use of cascade reactions to construct complex molecular skeletons with high efficiency is an appealing strategy in organic synthesis.¹ Transition metal-catalyzed reactions in particular offer exciting opportunities due to their high functional group tolerance and ability to construct multiple carbon–carbon bonds in a single step. We report a versatile palladium-catalyzed cascade cyclization which accesses a wide range of fused ring systems from acyclic precursors and which features two unusual palladium-mediated isomerizations.

We envisaged that treatment of a suitable bromoenyne (**1**, Scheme 1) with a palladium(0) catalyst would initiate a cascade polycyclization: initial *syn*-carbopalladation followed by cross-coupling with alkenylstannane **2** would give triene

Scheme 1. Conceptual Cascade Approach to Bi- and Tricyclic Rings



3, which could undergo 6 π -electrocyclization to polycycle **4**. An alternative coupling with a dienylystannane (**5**) would terminate with an 8 π -electrocyclization of tetraene **6** to afford polycycle **7**. Overall, these processes achieve the formation

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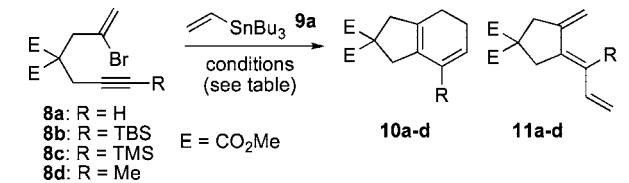
(1) (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. (b) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

of three carbon–carbon bonds and two rings in a single step and, significantly, represent a general and diversifiable approach to fused rings with polyene cores primed for further chemistry.

Although palladium-mediated carbopalladations² of haloenynes and their subsequent cross-couplings^{3,4} have been well studied, the incorporation of an in situ electrocyclization has less precedent, with the exception of the elegant work of de Meijere⁵ and Suffert.⁶ The potential to generalize such a reaction to access a wide array of valuable polycyclic skeletons remains an important aim.

We began our investigations into the feasibility of this cascade process using the malonate-derived bromoenyne **8a**⁷ (Table 1), treatment of which with vinyltributyltin and 10 mol % of Pd(PPh₃)₄ in refluxing benzene led to a single product (73%, entry 1). ¹H NMR spectroscopy NOE studies revealed that this product was not the anticipated electrocyclized 5,6-bicyclic diene **10a**, but rather the *anti*-triene **11a**,⁷ which had presumably arisen from an unexpected

Table 1. Initial Cascade Reaction Optimization^a



entry	sm	catalyst	solvent	time (h)	yield ^b (%)	10/11 ^c
1	8a	Pd(PPh ₃) ₄	PhH	10	73	0:1
2	8b	Pd(PPh ₃) ₄	PhH	4	70	1:0
3	8c	Pd(PPh ₃) ₄	PhH	10	— ^d	2:1
		Pd(PPh ₃) ₄	PhMe	24	74	1:0
4		Pd(PPh ₃) ₄	PhMe	1	— ^d	5:1
		Pd(PPh ₃) ₄	PhMe	24	86	1:0
5		PdCl ₂ (PPh ₃) ₂	PhMe	4	— ^d	8:1
		PdCl ₂ (PPh ₃) ₂	PhMe	24	86	1:0
6		Pd(PPh ₃) ₄	PhMe	7	94	1:0
		(1 mol %)				
7		Pd(PPh ₃) ₄	PhMe	20	77	1:0
		(0.1 mol %)				
8	8d	Pd(PPh ₃) ₄	PhMe	20	83	1:0

^a Conditions: reflux, 1.3 equiv of **9a**, 10 mol % of catalyst, unless indicated. ^b Isolated yields. ^c Ratios determined by ¹H NMR spectroscopy. ^d Ratio determined by ¹H NMR during the reaction; products not isolated.

(2) For an excellent review, see: (a) Negishi, E.-I.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365. (b) *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; John Wiley and Sons, Inc.: New York, 2002; Vol. 1, Section IV. (c) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959. (d) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65.

(3) Selected examples of carbopalladation/Stille coupling: (a) Burns, B.; Grigg, R.; Ratananukul, P.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1988**, *29*, 5565. (b) Negishi, E.-I.; Noda, Y.; Lamaty, F.; Vawter, E. J. *Tetrahedron Lett.* **1990**, *31*, 4393. (c) Luo, F.-T.; Wang, R.-T. *Tetrahedron Lett.* **1991**, *52*, 7703. (d) Nuss, J. M.; Murphy, M. M.; Rennels, R. A.; Heravi, M. H.; Mohr, B. J. *Tetrahedron Lett.* **1993**, *34*, 3079. (e) Fretwell, P.; Grigg, R.; Sansano, J. M.; Sridharan, V.; Sukirthalingam, S.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7525. See also refs 8 and 9.

(4) Selected carbopalladations terminating with other cross-coupling manifolds; see ref 2a and: (a) Zhang, Y.; Negishi, E.-I. *J. Am. Chem. Soc.* **1989**, *111*, 3454. (b) Negishi, E.-I.; Ay, M.; Sugihara, T. *Tetrahedron* **1993**, *49*, 5471. (c) Ishikura, M. *J. Chem. Soc., Chem. Commun.* **1995**, 409. (d) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803. (e) Oh, C. H.; Lim, Y. M. *Tetrahedron Lett.* **2003**, *44*, 267. (f) Couty, S.; Liégault, B.; Meyer, C.; Cossy, J. *Org. Lett.* **2004**, *6*, 2511. (g) Torii, S.; Okumoto, H.; Nishimura, A. *Tetrahedron Lett.* **1991**, *32*, 4167. (h) Teply, F.; Stará, I. G.; Sary, I.; Kollarovic, A.; Saman, D.; Fiedler, P. *Tetrahedron* **2002**, *58*, 9007. (i) Burns, B.; Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron Lett.* **1989**, *30*, 1135. (j) Wang, R.-T.; Chou, F.-L.; Luo, F.-T. *J. Org. Chem.* **1990**, *55*, 4846.

(5) de Meijere has focused mainly on fully intramolecular variants: (a) Meyer, F. E.; Henniges, H.; de Meijere, A. *Tetrahedron Lett.* **1992**, *33*, 8039. (b) Meyer, F. E.; Brandenberg, J.; Parsons, P. J.; de Meijere, A. *J. Chem. Soc., Chem. Commun.* **1992**, 390. (c) Henniges, H.; Meyer, F. E.; Schick, U.; Funke, F.; Parsons, P. J.; de Meijere, A. *Tetrahedron* **1996**, *52*, 11545. For a review, see: (d) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88. For a stepwise construction of the electrocyclization substrate, see: (e) von Zezschwitz, P.; Petry, F.; de Meijere, A. *Chem. Eur. J.* **2001**, *7*, 4035.

(6) Suffert has mainly studied specific 4- and 5-*exo-dig* cyclizations; for leading references, see: (a) Suffert, J.; Salem, B.; Klotz, P. *J. Am. Chem. Soc.* **2001**, *123*, 12107. (d) Salem, B.; Klotz, P.; Suffert, J. *Org. Lett.* **2003**, *5*, 845. (c) Salem, B.; Klotz, P.; Suffert, J. *Synthesis*, **2004**, 298. (d) Salem, B.; Suffert, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2826. (e) Bour, C.; Blond, G.; Salem, B.; Suffert, J. *Tetrahedron* **2006**, *62*, 10567, and references therein. (f) Bour, C.; Suffert, J. *Eur. J. Org. Chem.* **2006**, 1390. For an outstanding recent application to fenestranes synthesis, see: (g) Hulot, C.; Blond, G.; Suffert, J. *J. Am. Chem. Soc.* **2008**, *130*, 5046. For other related 6π-processes, see: (h) Grigg, R.; Savic, V.; Sridharan, V.; Terrier, C. *Tetrahedron* **2002**, *58*, 8613. (i) Wang, F.; Tong, X.; Cheng, J.; Zhang, Z. *Chem. Eur. J.* **2004**, *10*, 5338. (j) Tambar, U. K.; Kano, T.; Zepernick, J. F.; Stoltz, B. M. *J. Org. Chem.* **2006**, *71*, 8357. For a review of cross-coupling/electrocyclization in synthesis, see: (k) Beaudry, C. M.; Malerich, J. P.; Trauner, D. *Chem. Rev.* **2005**, *105*, 4757.

(7) See the Supporting Information for details of substrate preparation and proof of stereochemistry.

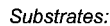
complete isomerization of the alkenylpalladium intermediate prior to intermolecular cross-coupling (a formal *anti*-carbopalladation). Although such processes are precedented,⁸ their generality and origin has not been explored, and this degree of isomerization is highly unusual.

Hypothesizing that the steric bulk of palladium relative to hydrogen might drive this *syn*–*anti* isomerization, we subjected TBS-substituted bromoenyne **8b** to the same reaction conditions. To our delight, this led *exclusively* to the formation of the 5,6-bicycle **10b** (70%, entry 2). Interestingly, the sterically less demanding TMS substituent of **8c** gave a 2:1 mixture of products (10 h, entry 3), albeit in favor of the desired 5,6-bicycle **10c**. Even more gratifying but rather surprising was the observation that under prolonged heating (24 h), the undesired *anti*-triene **11c** was converted to the targeted bicycle **10c** (74% overall), presumably through a *second* isomerization⁹ of **11c** back to the *syn*-triene, followed by electrocyclization. Further optimization (entries 4–7) showed that the use of toluene as solvent led to shorter reaction times, that PdCl₂(PPh₃)₂ was also a suitable catalyst, and that the catalyst loading could be reduced with no loss of reaction efficiency. Alkyl-substituted alkyne **11d** also underwent efficient cyclization under the optimized conditions (83%, entry 8).

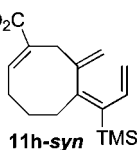
With suitable reaction conditions established, efforts were now concentrated on exploring the reaction scope. Variation

(8) See refs 3e, 6, and: (a) Chung, W. S.; Patch, R. J.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. For an informative mechanistic discussion, see: (b) Amatore, C.; Bensalem, S.; Ghalem, S.; Jutand, A. *J. Organomet. Chem.* **2004**, *689*, 4642.

(9) (a) Sen, A.; Lai, T. W. *Inorg. Chem.* **1984**, *23*, 3257. (b) Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627.

cond. A: Pd(PPh₃)₄

Stannanes:
9a: R = H
9b: R = Me
9c: R = Ph

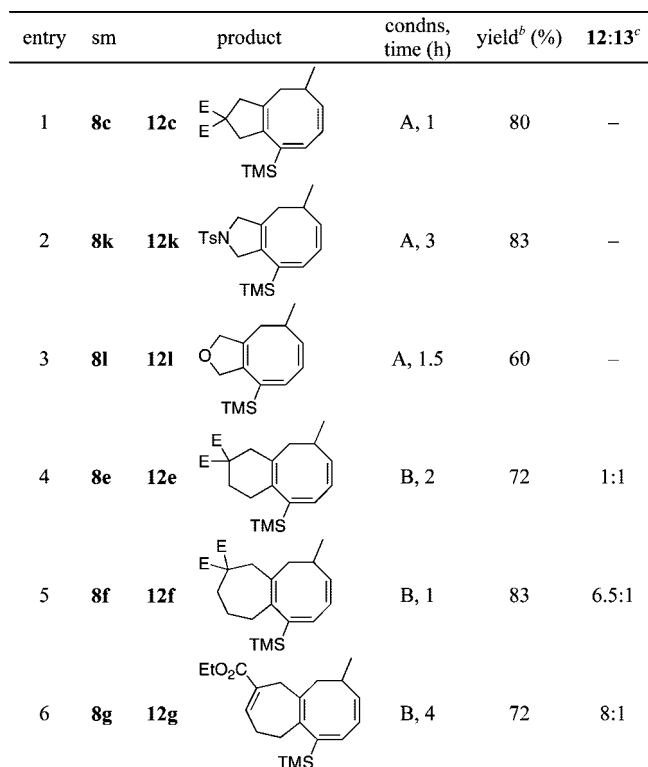


^a Reactions conducted with 10 mol % of catalyst, 1.3 equiv of stannane. ^b Isolated yields. ^c Ratios determined by ¹H NMR spectroscopy. ^d Time required for complete conversion of **11** to **10**. ^e Ratio of **10h/11h-syn**.

Interestingly, enoate **8h** gave a 1.4:1 mixture of the 8,6-diene **10h** and the “correct” *syn*-triene, suggesting a reduced tendency of this alkenylpalladium intermediate to isomerize relative to those of other tethering ring sizes. β -Substituted stannanes⁷ **9b** and **9c** proved excellent substrates, affording the cyclized products (**10i** and **10j**, entries 5, 6) in excellent

Satisfied with the synthesis of *n*,6-bicycles, we now investigated the formation of fused *n*,8-rings, using dienylnastannane **9d**¹⁰ (Table 3). Pleasingly, the 5,8-bicyclic products

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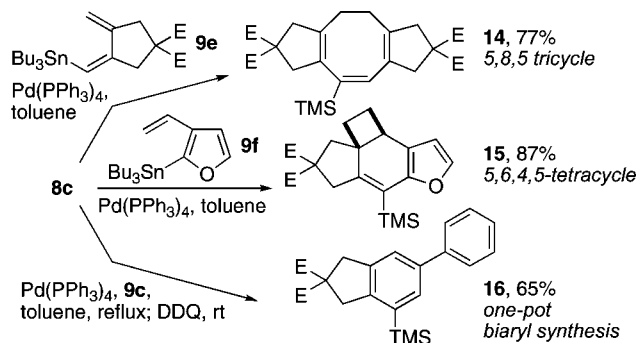
12c (80%), **12k** (83%), and **12l** (60%) were formed from the reactions of bromoenyne **8c**, tosylamide **8k**, and ether **8l** respectively, demonstrating the success of the 8 π -cascade (entries 1–3). As is precedented in fused ring systems,¹¹ no subsequent 6 π -electrocyclization was observed, likely due to the increase in ring strain that would result at the n,6,4-ring junction carbon.

(11) For an example of fused-ring cyclooctatrienes that do not undergo 6 π -electrocyclization, see: (a) Paquette, L. A.; Photis, J. M.; Micheli, R. P. *J. Am. Chem. Soc.* **1977**, 99, 7899. (b) Hayashi, R.; Fernández, S.; Okamura, W. H. *Org. Lett.* **2002**, 4, 851. (c) Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, 5, 2841. See also ref 10.

Interestingly, reaction of substrate **11e** (entry 4) led to an inseparable 1:1 mixture of two products: the expected 6,8-fused bicycle **12e**, and tetraene **13e** (72%). The latter had arisen from a 1,7-hydride shift of the *anti*-tetraene (from formal *anti*-carbopalladation), which prevents reisomerization/electrocyclization. Of particular note is the highly efficient preparation of 7,8-fused medium-ring systems **12f** (72%) and **12g** (83%) (entries 5, 6), for which the use of $\text{PdCl}_2(\text{PPh}_3)_2$ reduced the levels of 1,7-hydride shift products.

Attention was next turned to the challenging preparation of *n*,8,*m*-tricycles (Scheme 2). Cyclic dienyl stannane **9e**¹²

Scheme 2. Extension to Polycycles and a Biaryl Ring System



was first employed as the coupling partner, and, to our delight, underwent cross-coupling/ 8π -cyclization with **8c** to give 5,8,5-tricycle **14** (77%). Variation of the position of

(12) Lautens, M.; Smith, N. D.; Ostrovsky, D. *J. Org. Chem.* **1997**, 62, 8970.

the third ring was tested using vinylfuranylstannane **9f**. Reaction with **8c** led to a single product (87%), which was identified as the remarkable 5,6,4,5-fused tetracycle **15**. The formation of this skeleton is likely driven by 6π -electrocyclic rearomatization¹³ of the intermediate tetraene furan obtained upon 8π -electrocyclization. Finally, we briefly examined a product application which increases the reaction scope; a direct oxidative workup of the reaction of **8c** with **9c** (DDQ) led to a 65% yield of the highly functionalized biaryl **16**.

In conclusion, we have developed a cascade reaction which sequences carbopalladation/cross-coupling with a 6π - or 8π -electrocyclization to provide a variety of polycyclic fused ring systems, including one-pot construction of 8-membered bicycles and an unprecedented 5,6,4,5-tetracycle. Ongoing work toward the elucidation of the isomerization mechanisms, further exploitation of the cyclization products, and applications in synthesis, will be reported in due course.

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Supporting Information Available: Spectroscopic data for cyclization substrates and products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(13) For a single previous instance of a presumed 8π /aromatization-driven 6π -cyclization, see: Pelly, S. C.; Parkinson, C. J.; van Otterlo, W. A. L.; de Koning, C. B. *J. Org. Chem.* **2005**, 70, 10474. While this work was in progress, an elegant synthesis of fenestranes via $8\pi/6\pi$ -cyclization was reported by Suffert; see ref 6f.