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

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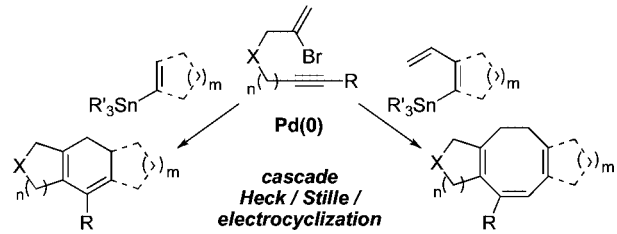
ABSTRACT

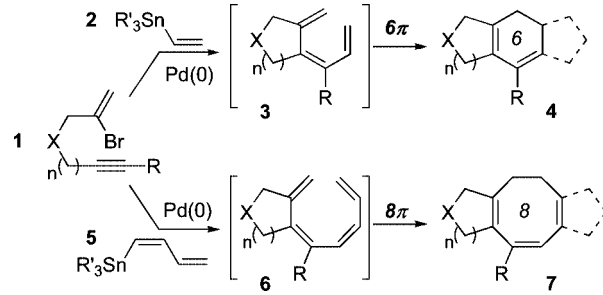


A versatile palladium-catalyzed cyclization/cross-coupling/electrocyclization strategy for the synthesis of fused bi- and tricyclic ring systems is described. Excellent yields of the polycyclic products are obtained with a range of tethering ring sizes and functionality, including an unprecedented 5,6,4,5-fused 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 **3**, which could undergo 6π-electrocyclization to polycycle **4**. An alternative coupling with a dienylstannane (**5**) would terminate with an 8π-electrocyclization of tetraene **6** to afford polycycle **7**. Overall, these processes achieve the formation

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



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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.

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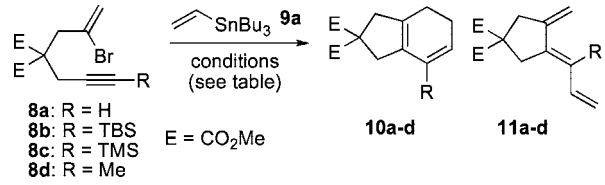
of three carbon−carbon bonds and two rings in a single step and, significantly, represent a general and diversifiable approach to fused rings with polyene cores primed for further chemistry.

Although palladium-mediated carbopalladations[2] 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 Meijere[5] 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 $Pd(PPh_3)_4$ 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
				24	74	1:0
4		$Pd(PPh_3)_4$	PhMe	1	—[d]	5:1
				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		$Pd(PPh_3)_4$ (1 mol %)	PhMe	7	94	1:0
7		$Pd(PPh_3)_4$ (0.1 mol %)	PhMe	20	77	1:0
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.

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* isomerization[9] 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 $PdCl_2(PPh_3)_2$ 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

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(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.; Stary, 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 fenestrane 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.

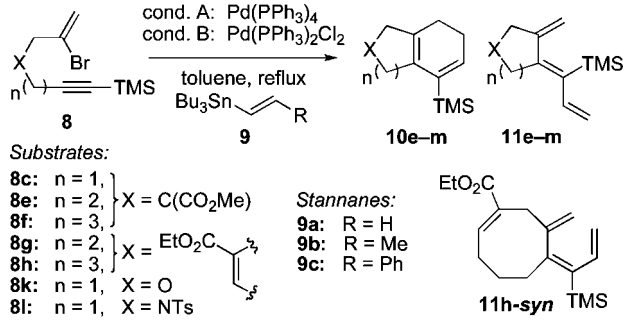
(7) See the Supporting Information for details of substrate preparation and proof of stereochemistry.

(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.

of the substrate tether length showed that the methodology was able to accommodate a variety of ring sizes (Table 2,

Table 2. Cascade Cross-Coupling/6π-Electrocyclization: Synthesis of *n*,6-Bicycles



entry	sm	stannane	product	condns,[a] time (h)	yield[b] (%)	ratio[c] **10:11**
1	**8e**	**9a**	**10e**	A, 1	–	2:1
				24	88	3:1
				72[d]	88	1:0
				B, 1	89	10:1
2	**8f**	**9a**	**10f**	A, 1	–	3:1
				24	90	3.5:1
				72[d]	90	1:0
				B, 1	96	5:1
3	**8g**	**9a**	**10g**	A, 1	71	5:1
4	**8h**	**9a**	**10h**	A, 4	66	1.4:1[e]
5	**8c**	**9b**	**10i**	A, 0.5	97	1:0
6	**8c**	**9c**	**10j**	A, 0.5	90	1:0
7	**8k**	**9b**	**10k**	A, 1	95	1:0
8	**8l**	**9b**	**10l**	A, 0.5	77	1:0

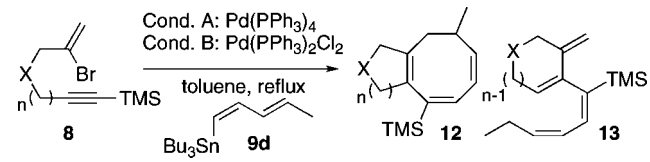
[a] Reactions conducted with 10 mol % of catalyst, 1.3 equiv of stannane. [b] Isolated yields. [c] Ratios determined by ^{1}H NMR spectroscopy. [d] Time required for complete conversion of **11** to **10**. [e] Ratio of **10h**/**11h**-*syn*.

entries 1−5), and formation of the 6,6-bicycle **10e** (88%) and the more demanding 7,6-bicycles **10f** (90%) and **10g** (71%) posed no difficulties.

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 stannanes[7] **9b** and **9c** proved excellent substrates, affording the cyclized products (**10i** and **10j**, entries 5, 6) in excellent yields and short reaction times. Both the nitrogen- and oxygen-tethered bromoenynes **8k** and **8l** also underwent smooth cyclization with **9b**, leading to the formation of heterocycles **10k** (95%) and **10l** (77%) (entries 7, 8). In several cases, the yields, product ratios, and reaction times could be improved by using $PdCl_2(PPh_3)_2$ as catalyst.

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

Table 3. Cascade Cross-Coupling/8π-Electrocyclization: Synthesis of *n*,8-Bicycles[a]



entry	sm	product	condns, time (h)	yield[b] (%)	**12**:**13**[c]
1	**8c**	**12c**	A, 1	80	–
2	**8k**	**12k**	A, 3	83	–
3	**8l**	**12l**	A, 1.5	60	–
4	**8e**	**12e**	B, 2	72	1:1
5	**8f**	**12f**	B, 1	83	6.5:1
6	**8g**	**12g**	B, 4	72	8:1

[a] Reactions conducted with 10 mol % of catalyst and 1.3 equiv of stannane. [b] Isolated yields. [c] Ratios determined by ^{1}H NMR spectroscopy.

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 8π-cascade (entries 1−3). As is precedented in fused ring systems,[11] no subsequent 6π-electrocyclization was observed, likely due to the increase in ring strain that would result at the n,6,4-ring junction carbon.

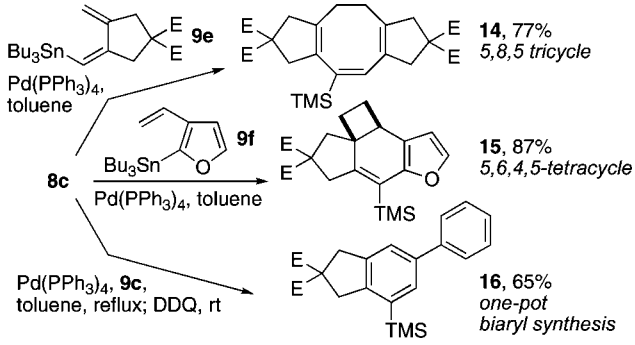
(10) Bialy, L.; Waldmann, H. *Chem. Eur. J.* **2004**, *10*, 2759.

(11) For an example of fused-ring cyclooctatrienes that do not undergo 6π-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 $PdCl_2(PPh_3)_2$ 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] 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 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-electrocylic rearomatization[13] 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**.

Scheme 2. Extension to Polycycles and a Biaryl Ring System



In conclusion, we have developed a cascade reaction which sequences carbopalladation/cross-coupling with a 6π- or 8π-electrocylization 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.

OL8007952

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

(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 8π/6π-cyclization was reported by Suffert; see ref 6f.