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$6\pi e^-$ versus $8\pi e^-$ Electrocyclization of 1-Aryl- and Heteroaryl-Substituted (1*Z*,3*Z*)-1,3,5-Hexatrienes: A Matter of Aromaticity[†]

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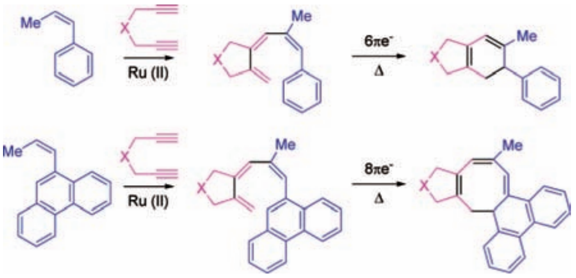
ABSTRACT



Peri **selectivity of the electrocyclization of 1-aryl- and heteroaryl-substituted (1*Z*,3*Z*)-1,3,5-hexatrienes, obtained by Ru-catalyzed linear coupling of 1,6-diynes to *Z*-propenyl(hetero)arenes, can be efficiently modulated depending on the aromaticity of the (hetero)arene: 1,3,5-hexatrienyl(hetero)arenes give $8\pi e^-$ electrocyclization with the exception of 1,3,5-hexatrienylbenzenes, which give $6\pi e^-$ electrocyclization.**

Electrocyclizations are an important type of pericyclic reaction from both a theoretical[1] and an experimental standpoint[2] as they allow the formation of complex polycyclic molecules from simple polyenic compounds. According to the Woodward and Hoffmann rules,[3] 1,3-cyclohexadienes can be obtained by thermal disrotatory $6\pi e^-$ electrocyclization of (3*Z*)-1,3,5-hexatrienes, whereas 1,3,5-cyclooctatrienes can be prepared by thermal conrotatory $8\pi e^-$ electrocyclization of (3*Z*,5*Z*)-1,3,5,7-octatetraenes. We report here an interesting dichotomy showing that (3*Z*,5*Z*)-1,3,5,7-octatetraenes, in which one of the terminal double bonds of the system forms part of an (hetero)aromatic ring, selectively undergo thermal $6\pi e^-$ or $8\pi e^-$ electrocyclizations depending on the nature of the arene.[4]

Besides the $8\pi e^-$ electrocyclization, at least three other electrocyclic processes are also conceivable for (3*Z*,5*Z*)-1,3,5,7-octatetraenes: one $6\pi e^-$ and two $4\pi e^-$ electrocyclizations. According to Cossío's calculations,[5] the transition states for these processes would be associated with activation energies larger than those found for the $8\pi e^-$ electrocyclization, and therefore, (3*Z*,5*Z*)-1,3,5,7-octatetraene would be

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[†] Dedicated to professor Josep Font on the occasion of his 70th birthday.

(1) (a) Fukui, K. *Acc. Chem. Res.* **1971**, *4*, 57. (b) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie International: Deerfield Beach, FL, 1970.

(2) (a) Pindur, U.; Schneider, G. H. *Chem. Soc. Rev.* **1994**, 409. (b) Trost, B. M.; Fleming, I.; Paquette, L. A. *Comprehensive Organic Synthesis*; Pergamon: Oxford, U.K., 1991; Vol. 5, pp 675−784. (c) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980.

(3) Woodward, R. B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, *87*, 395.

(4) (3*Z*)-1,3,5-Hexatrienes and (3*Z*,5*Z*)-1,3,5,7-octatetraenes can be efficiently prepared by Ru-catalyzed linear coupling of 1,6-diynes to alkenes and 1,3-dienes, respectively. (a) García-Rubín, S.; Varela, J. A.; Castedo, L.; Saá, C. *Chem. Eur. J.* **2008**, *14*, 9772. (b) Varela, J. A.; Rubín, S. G.; González-Rodríguez, C.; Castedo, L.; Saá, C. *J. Am. Chem. Soc.* **2006**, *128*, 9262. (c) Varela, J. A.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *5*, 2841.

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10.1021/ol802925q CCC: $40.75

Scheme 1. Ru-Catalyzed Synthesis and $6\pi e^-$ Electrocyclization of 1,3,5-Hexatrienylbenzenes **3**

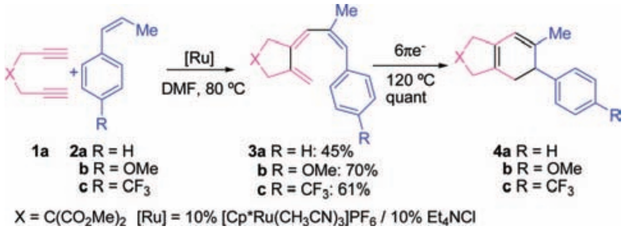
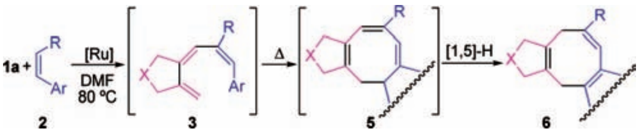
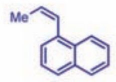
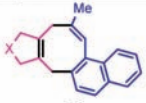
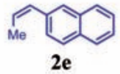
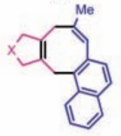
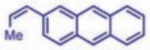
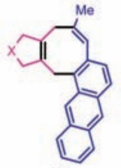
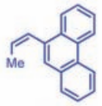
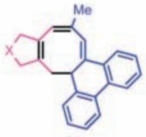
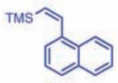


Table 1. Ru-Catalyzed Cascade Reaction of 1,6-Diyne **1a** with [(*Z*)-1-Propenyl]arenes **2**



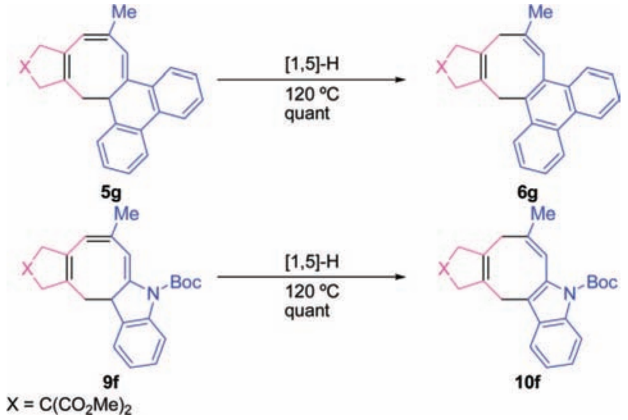
entry	*Z*-propenylarene **2**	cyclooctatriene	yield[a]
1	 **2d**	 **6d**	56
2	 **2e**	 **6e**	79
3	 **2f**	 **6f**	75
4	 **2g**	 **5g**	66
5	 **2h**	 **6h**	58

[a] Isolated yields from reactions performed at 80 °C by slow addition, over 4 h, of 0.5 mmol of **1a** in DMF to a mixture of 3 equiv of **2**, 10% Et$_4$NCl, and 10% [Cp*Ru(CH$_3$CN)$_3$]PF$_6$ in DMF. X = C(CO$_2$Me)$_2$.

expected to cyclize to 1,3,5-cyclooctatriene with complete *peri* selectivity.

However, we found that when (1*Z*,3*Z*)-1,3,5-hexatrienylbenzene **3a**[6] (which can be seen as an (3Z,5Z)-1,3,5,7-octatetraene being one of the terminal double bonds part of the benzene ring) was heated under reflux in toluene,

Scheme 2. Thermal [1,5]-Hydrogen Shift of 1,3,5-Cyclooctatrienes **5g** and **9f** to 1,3,6-Cyclooctatrienes **6g** and **10f**



cyclohexadiene **4a** was obtained selectively and quantitatively as the product of the thermal $6\pi e^-$ electrocyclization (Scheme 1). Not unexpectedly, the same reactivity was observed when an electron-rich (**3b**) or an electron-poor (**3c**) hexatrienylbenzene was heated, thus showing that the electronic richness of the aromatic moiety does not affect the *peri* selectivity of the electrocyclization reaction.

Interestingly, the electrocyclic *peri* selectivity changed when other aromatic nuclei were present in the starting polyene. For example, when 1-(hexatrienyl)naphthalene **3d**[6] was heated under reflux in toluene, 1,3,6-cyclooctatriene **6d** was selectively obtained in quantitative yield (56% overall yield, entry 1, Table 1).[7] The cyclooctatriene most probably arises from a thermal conrotatory $8\pi e^-$ electrocyclization, followed by a [1,5]-hydrogen shift to allow the aromaticity of the naphthalene ring to be recovered.[8] When isomeric 2-(propenyl)naphthalene **2e** and 2-(propenyl)anthracene **2f**[9] were used in the Ru-catalyzed linear coupling with **1a**, the

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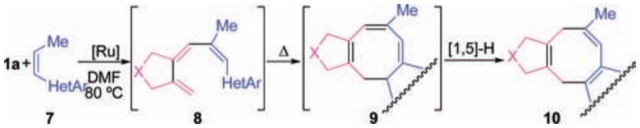
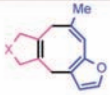
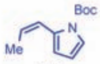
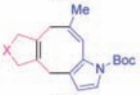
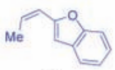
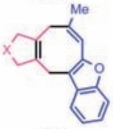
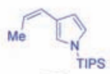
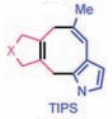
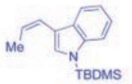
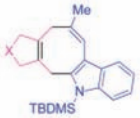
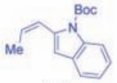
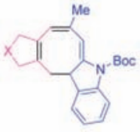
(6) 1,3,5-Hexatrienylarenes **3** were obtained by Ru-catalyzed linear coupling of diynes **1** and (*Z*)-1,3-dienes **2**, while (*E*)-1,3-dienes **2** failed to give the linear coupling reaction. See ref 4 for more details and Supporting Information for X-ray data for compound **3a**.

(7) For reviews on metal-mediated cyclooctanoid construction, see: (a) Yet, L. *Chem. Rev.* **2000**, *100*, 2963. (b) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. For [2 + 2 + 2 + 2] cycloadditions, see: (c) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 13402. (d) Bouissie, T. R.; Streitwieser, A. *J. Org. Chem.* **1993**, *58*, 2377. (e) Walther, D.; Braun, D.; Schulz, W.; Rosenthal, U. *Z. Anorg. Allg. Chem.* **1998**, *577*, 270. (f) Diercks, R.; Stamp, L.; tom Dieck, H. *Chem. Ber.* **1984**, *117*, 1913. For [4 + 2 + 2] cycloadditions, see: (g) DeBoef, B.; Counts, W. R.; Gilbertson, S. R. *J. Org. Chem.* **2007**, *72*, 799. (h) Wender, P. A.; Christy, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 5354. (i) Murakami, M.; Ashida, S.; Matsuda, T. *J. Am. Chem. Soc.* **2006**, *128*, 2166. (j) Baik, M. H.; Baum, E. W.; Burland, M. C.; Evans, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 1602. For [5 + 2+1] cycloadditions, see: (k) Wang, Y.; Wang, J.; Su, J.; Huang, F.; Jiao, L.; Liang, Y.; Yang, D.; Zhang, S.; Wender, P. A.; Yu, Z. X., *J. Am. Chem. Soc.* **2007**, *129*, 10060. For [4 + 4] cycloadditions, see: (l) Murakami, M.; Itami, K.; Ito, Y. *Synlett* **1999**, 951. (m) Sieburth, S. M.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251. (n) Baldenius, K.-U.; tom Dieck, H.; Köning, W. A.; Icheln, D.; Runge, T. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 305. (o) Wender, P. A.; Ihle, N. C. *J. Am. Chem. Soc.* **1986**, *108*, 4678. For [6 + 2] cycloadditions, see: (p) Tenaglia, A.; Gaillard, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2454. (q) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. *J. Am. Chem. Soc.* **2000**, *122*, 7815. (r) Achard, M.; Mosrin, M.; Tenaglia, A.; Buono, G. *J. Org. Chem.* **2006**, *71*, 2907.

Table 2. Ru-Catalyzed Cascade Reaction of 1,6-Diyne **1a** with [(*Z*)-1-Propenyl]heteroarenes **7**

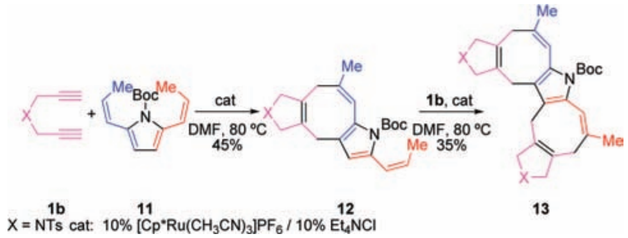


entry	HetAr 7	cyclooctatriene	yield[a]
1	 **7a**	 **10a**	52
2	 **7b**	 **10b**	66
3	 **7c**	 **10c**	72[b]
4	 **7d**	 **10d**	54
5	 **7e**	 **10e**	41
6	 **7f**	 **9f**	38

[a] Isolated yields following the same reaction conditions as in Table 1. [b] **10c** was obtained by further heating at 120 °C of the initially isolated mixture of **9c** and **10c**. X = C(CO$_2$Me)$_2$.

electrocyclization of the putative intermediates **3e** and **3f** took place in a regio- and *peri*-selective manner to afford

Scheme 3. Double Ru-Catalyzed Cascade Reaction of 1,6-Diyne **1b** with Bis(Z-propenyl)pyrrole **11**



cyclooctatrienes **6e** and **6f** in 79% and 75% yields, respectively (entries 2 and 3, Table 1). Curiously, a Ru-catalyzed linear coupling reaction of 9-(propenyl)phenanthrene **2g** and **1a** enabled the isolation of 1,3,5-cyclooctatriene **5g** in 66% yield (entry 4, Table 1). Further heating at 120 °C afforded **6g** quantitatively through a [1,5]-H shift (Scheme 2). Non-propenyl arenes such as silylated vinylnaphthalene **2h** also participate in the cascade reaction to give the expected cyclooctatriene **6h** in 58% yield (entry 5, Table 1).

We then turned our attention to [(*Z*)-1-propenyl]heteroarenes **7**. In all of the examples tested, i.e., 2-(propenyl)furan **7a**, 2- and 3-(propenyl)pyrroles **7b** and **7d**, 2-(propenyl)benzofuran **7c**, and 3-(propenyl)indole **7e**, the corresponding 1,3,6-cyclooctatrienes **10a**−**e**[10] were obtained *peri* selectively from 8πe$^-$ electrocyclizations followed by [1,5]-H shifts (entries 1−5, Table 2). The exception was the case of 2-(propenyl)indole (**7f**), from which 1,3,5-cyclooctatriene **9f** was obtained (entry 6, Table 2). Further heating at 120 °C afforded **10f** quantitatively through a [1,5]-H shift (Scheme 2).

To gain further insights into the influence of the arene in the electrocyclization of 1,3,5-hexatrienylarenes, DFT calculations were performed for the 6πe$^-$ and 8πe$^-$ electrocyclizations of compounds **3a′** and **8f′** (Figure 1). The results clearly show that 8πe$^-$ electrocyclizations are kinetically favored, whereas 6πe$^-$ electrocyclizations are thermodynamically favored. In the case of benzene derivative **3a′**, the loss of aromaticity of the benzene ring involved in the 8πe$^-$ electrocyclization makes this process highly endothermic

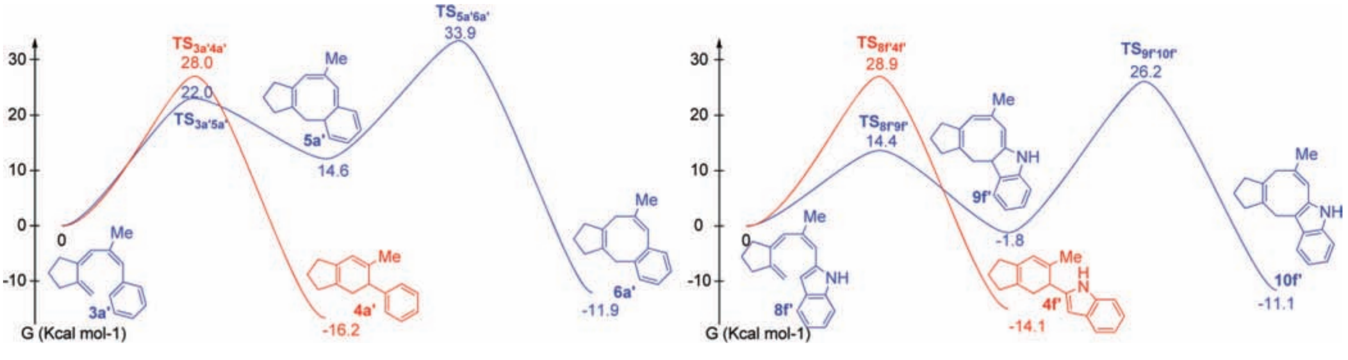


Figure 1. Energy profile (*G* in Kcal mol^{-1} at 298 K and 1 atm) for the 6e$^-$ and 8πe$^-$ electrocyclizations followed by a [1,5]-H shift in the latter of compounds **3a′** and **8f′**.

(14.6 Kcal mol^{-1}), with the competitive 6πe$^-$ electrocyclization more favored. Conversely, if the 8πe$^-$ electrocyclization involves an heteroaryl ring, e.g., indole **8f′**, the process becomes exothermic (-1.8 Kcal mol^{-1}) with an activation barrier of 14.4 Kcal mol^{-1}, therefore making this process more favorable. The final [1,5]-H shift of **9f′**, which allows to recover the aromaticity of the indole nucleus **10f′**, has to overcome the activation barrier $\Delta G^{\ddagger} = 28.0$ Kcal mol^{-1} with $\Delta G^{\circ} = -9.3$ Kcal mol^{-1}.

Interestingly, the double Ru-catalyzed cascade reaction of diyne **1b** with bis-propenylpyrrole **11** gave rise to the pentacyclic pyrrole derivative **13**, in which pyrrole units are fused to cyclooctene rings (Scheme 3).

In conclusion, 1-aryl- and heteroaryl-substituted (1*Z*,3*Z*)-1,3,5-hexatrienes, obtained by Ru-catalyzed linear coupling of 1,6-diynes to *Z*-propenyl(hetero)arenes, undergo thermal 8πe$^-$ electrocyclizations followed by [1,5]-H shifts to afford the corresponding 1,3,6-cyclooctatrienes. The exceptions are 1,3,5-hexatrienylbenzenes, which gave 1,3-cyclohexadienes derived from 6πe$^-$ electrocyclizations.

Acknowledgment. This work was supported by the MICINN (CTQ2005-08613 and CTQ2008-06557), Consolider Ingenio 2010 (CSD2007-00006), and the Xunta de Galicia (2007/XA084 and INCITE08PXIB209024PR). S.G-R. thanks the MEC for a FPU fellowship. We are also grateful to the CESGA for computational time.

Supporting Information Available: A typical procedure for the Ru-catalyzed cascade reaction, spectral data for all new compounds, X-ray structures, and optimized geometric parameters for all the calculated structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) For a computational study involving a [1,5]-H shift and 8pe$^-$ electrocyclization, see: (a) Zhu, Y.; Guo, Y.; Zhang, L.; Xie, D. *J. Comput. Chem.* **2007**, *28*, 2164. For a computational study of 8πe$^-$ electrocyclic reactions, see ref 5. For other examples of cascade metal-mediated reactions/electrocyclization, see: (c) Kan, S. B. J.; Anderson, E. A. *Org. Lett.* **2008**, *10*, 2323. (d) Salem, B.; Suffert, J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2826. (e) von Zezschwitz, P.; Petry, F.; de Meijere, A. *Chem. Eur. J.* **2001**, *7*, 4035. (f) de Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88.

(9) The isomeric 9-(propenyl)anthracene did not participate in the reaction, probably due to steric hindrance caused by the anthracene ring.

(10) See Supporting Information for X-ray data for compounds **10c** and **9f**.