ORGANIC LETTERS

2003
Vol. 5, No. 16
2841−2844

“Formal” Ruthenium-Catalyzed [4+2+2] Cycloaddition of 1,6-Diynes to 1,3-Dienes: Formation of Cyclooctatrienes vs Vinylcyclohexadienes

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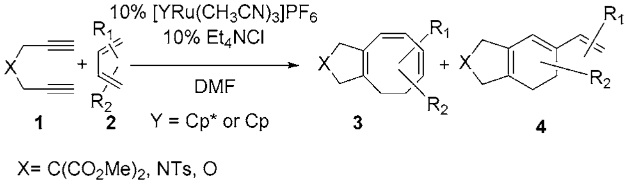
Received May 19, 2003

ABSTRACT



A new “formal” Ru-catalyzed [4+2+2] cycloaddition of 1,6-diynes to 1,3-dienes giving conjugated 1,3,5-cyclooctatrienes and vinylcyclohexadienes is described. This formal cycloaddition is really a tandem process, the Ru(II)-catalyzed formation of (*Z*)-tetraenes or vinyl-(*Z*)-trienes followed by a pure thermal conrotatory 8π- or disrotatory 6π-electrocyclization. The proposed mechanism allows the differences in product ratio to be explained in terms of steric and stereochemical considerations.

Transition-metal-catalyzed cycloaddition reactions constitute powerful methods for the construction of complex polycyclic systems.[1] Medium-sized carbo- and heterocycles, particularly eight-membered rings, have drawn the attention of chemists due to the abundance of these structural cores among natural products with interesting biological activities.[2] Various types of metal-catalyzed cycloaddition leading to the formation of eight-membered rings[3] have been described, including [2+2+2+2],[4] [4+2+2],[5] [5+2+1],[6] [4+4],[7] and [6+2][8] cycloadditions and a rhodium-catalyzed intramolecular hydroacylation leading to cyclooctenones.[9] Very recently, two new methods have been reported, the intermolecular rhodium-catalyzed [4+2+2] cycloaddition of heteroatom-tethered

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[1] For reviews of transition metal-catalyzed cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635.

[2] Barton, D.; Nakanishi, K. *Comprehensive Natural Products Chemistry*; Pergamon: Oxford, UK, 1999.

[3] For recent reviews on metal-mediated cyclooctanoid construction, see: (a) Mehta, G.; Singh, V. *Chem. Rev.* **1999**, *99*, 881. (b) Yet, L. *Chem. Rev.* **2000**, *100*, 2963.

[4] (a) Boussie, T. R.; Streitwieser, A. *J. Org. Chem.* **1993**, *58*, 2377. (b) Walther, D.; Braun, D.; Schulz, W.; Rosenthal, U. *Z. Anorg. Allg. Chem.* **1989**, *577*, 270. (c) Lawrie, C. J.; Gable, K. P.; Carpenter, B. K. *Organometallics* **1989**, *8*, 2274. (d) Colborn, R. E.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, *108*, 5470.

[5] (a) Lautens, M.; Tam, W.; Lautens, J. C.; Edwards, L. G.; Crudden, C. M.; Smith, A. C. *J. Am. Chem. Soc.* **1995**, *117*, 6863 and references therein. (b) Chen, Y.; Snyder, J. K. *J. Org. Chem.* **1998**, *63*, 2060.

[6] Wender, P. A.; Gamber, G. G.; Hubbard, R. D.; Zhang, L. *J. Am. Chem. Soc.* **2002**, *124*, 2876.

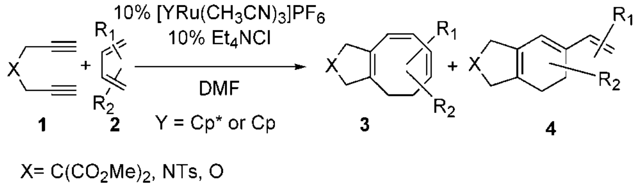
[7] Intermolecular: Itoh, K.; Masuda, K.; Fukahori, T.; Nakano, K.; Aoki, K.; Nagashima, H. *Organometallics* **1994**, *13*, 1020. Intramolecular: (a) For a review on [4+4] cycloadditions, see: Sieburth, S. McN.; Cunard, N. T. *Tetrahedron* **1996**, *52*, 6251. (b) Wender, P. A.; Nuss, J. M.; Smith, D. B.; Súarez-Sobrino, A.; Vagberg, J.; Decosta, D.; Bordner, J. *J. Org. Chem.* **1997**, *62*, 4908 and references therein.

[8] (a) Wender, P. A.; Correa, A. G.; Sato, Y.; Sun, R. J. *J. Am. Chem. Soc.* **2000**, *122*, 7815 and references therein. (b) Rigby, J. H. *Tetrahedron* **1999**, *55*, 4521. (c) Chafee, K.; Huo, P.; Sheridan, J. B.; Barbieri, A.; Aistars, A.; Lalancette, R. A.; Ostrander, R. L.; Rheingold, A. L. *J. Am. Chem. Soc.* **1995**, *117*, 1900.

10.1021/ol0348710 CCC: $25.00

enynes to 1,3-butadiene (affording 1,4-cyclooctadienes[10]) and that of dienynes to alkynes (affording nonconjugated 1,3,6-cyclooctatrienes).[11] Here we describe a new "formal" Ru-catalyzed [4+2+2] cycloaddition,[12] that of carbon- and heteroatom-tethered 1,6-diynes to 1,3-dienes, which affords conjugated 1,3,5-cyclooctatrienes and 1-vinyl-1,3-cyclohexadienes (Scheme 1).[13] Significantly, 1,3,5-cyclooctatrienes have been hypothesized as intermediates in the biosynthesis of SNF4435 C and D, which have strong immunosuppressive activity in vitro.[14]

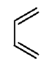
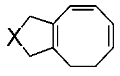
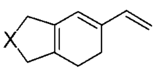
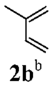
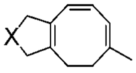
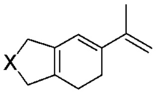
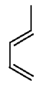
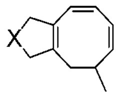
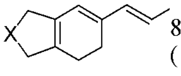
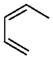
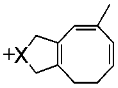
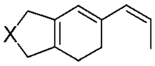
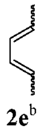
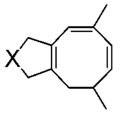
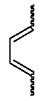
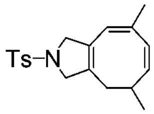
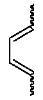
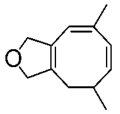
Scheme 1. "Formal" Ruthenium-Catalyzed [4+2+2] Cycloaddition of 1,6-Diynes to 1,3-Dienes



Treatment of diyne **1a** (X = $C(CO_2Me)_2$) with 10% $[Cp^*Ru(CH_3CN)_3]PF_6$ and 10% Et_4NCl under an atmosphere of 1,3-butadiene (**2a**) in DMF at room temperature furnished a 1:2.4 mixture of 1,3,5-cyclooctatriene **3a** and 1,3-cyclohexadiene **4a**[15] in 60% combined yield (Table 1, entry 1).[16] When performed in the absence of Et_4NCl or in the presence of $[n\text{-}Bu_4N]ClO_4$ the reaction gives tiny amounts of cycloadducts and starting **1a**. Use of the sterically less demanding catalyst $[CpRu(CH_3CN)_3]PF_6$ gave the same products, but in a 1:1.1 ratio.[17]

Encouraged by these initial results, we decided to study the scope of this reaction. With **1a** and the monosubstituted diene isoprene (**2b**), 10% $[Cp^*Ru(CH_3CN)_3]PF_6$ gave, at 80 °C, a 1:3.4 mixture of 1,3,5-cyclooctatriene **3b** and 1,3-cyclohexadiene **4b** in 72% combined yield (entry 2), while $[CpRu(CH_3CN)_3]PF_6$ gave a slightly better combined yield (80%) and, once again, a better product ratio, 1.1:1.

Table 1. Ruthenium-Catalyzed Reactions of Diynes **1a**−**c** with 1,3-Dienes **2a**−**e**

entry	diyne	diene	products	yield (ratio)[c,d,e]
1	**1a**	 **2a**[a]	 **3a**  **4a**	60% (1:2.4) *60%* *(1:1.1)*
2	**1a**	 **2b**[b]	 **3b**  **4b**	72% (1:3.4) *80%* *(1.1:1)*
3	**1a**	 **2c**[b]	 **3c**  **4c**	83% (1:4.8)
4	**1a**	 **2d**[b]	**3c**+ **3d**  **4d**	70% (1:1.2:4)[f]
5	**1a**	 **2e**[b]	 **3e**	65% (58%)[g] *41%*
6	**1b**	 **2e**	 **3'e**	70%
7	**1c**	 **2e**	 **3''e**	62%

[a] Reactions carried out at room temperature as described in the text. [b] Reactions performed at 80 °C by slow addition, over 4 h, of 0.5 mmol of **1** to a mixture in DMF of 3 equiv of **2**, 10% Et_4NCl and 10% $[Cp^*Ru(CH_3CN)_3]PF_6$ or 10% $[CpRu(CH_3CN)_3]PF_6$ in DMF. [c] Isolated yields. [d] Ratios of products (in parentheses) were determined by capillary GLC and ^1H NMR on samples of the crude reaction mixture. [e] Yields and product ratios obtained with $[CpRu(CH_3CN)_3]PF_6$ and 10% Et_4NCl are in italics. [f] **3c**:**3d**.**4d**. [g] Yield obtained when *cis,cis*-**2e** was used (*cis,cis*-**2e** was slightly contaminated with other isomers). X = $C(CO_2Me)_2$.

In the previous results it is striking that the double bonds in the cyclohexadiene and cyclooctatriene products are not in the positions expected to result from a cycloaddition reaction.[15] To explain these findings we hypothesize that the Ru-catalyzed reaction between 1,6-diynes and 1,3-dienes occurs through the mechanisms that for the case of $[Cp^*Ru(CH_3CN)_3]PF_6$ as catalyst are shown in Scheme 2.

When mixed with Et_4NCl, the cationic catalyst $[Cp^*Ru(CH_3CN)_3]PF_6$ probably generates the neutral complex $Cp^*Ru^{II}L_2Cl$ (**I**, L = CH_3CN) in situ, as is suggested by the changes observed in the ^1H NMR spectrum. In the presence of a 1,6-diyne and a 1,3-diene, this species might either

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(9) Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610.

(10) Evans, P. A.; Robinson, J. E.; Baum, E. W.; Fazal, A. N. *J. Am. Chem. Soc.* **2002**, *124*, 8782.

(11) Gilbertson, S. R.; DeBoef, B. *J. Am. Chem. Soc.* **2002**, *124*, 8784.

(12) (i) For an excellent review on Ru-catalyzed C−C formation, see: Trost, B. M.; Dean Toste, F.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (ii) For Ru-catalyzed [2+2+2] cycloadditions, see: (a) Yamamoto, Y.; Takagishi, H.; Itoh, K. *J. Am. Chem. Soc.* **2002**, *124*, 28 and 6844. (b) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189. (c) Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117. (d) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* **2000**, 1102. (e) Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* **2000**, 549. (f) Yamamoto, Y.; Kitahara, H.; Ogawa, R.; Itoh, K. *J. Org. Chem.* **1998**, *63*, 9610.

(13) For a Ru(II)-catalyzed [2+2+2] cycloaddition, see: Trost, B. M.; Imi, K.; Indolese, A. F. *J. Am. Chem. Soc.* **1993**, *115*, 8831.

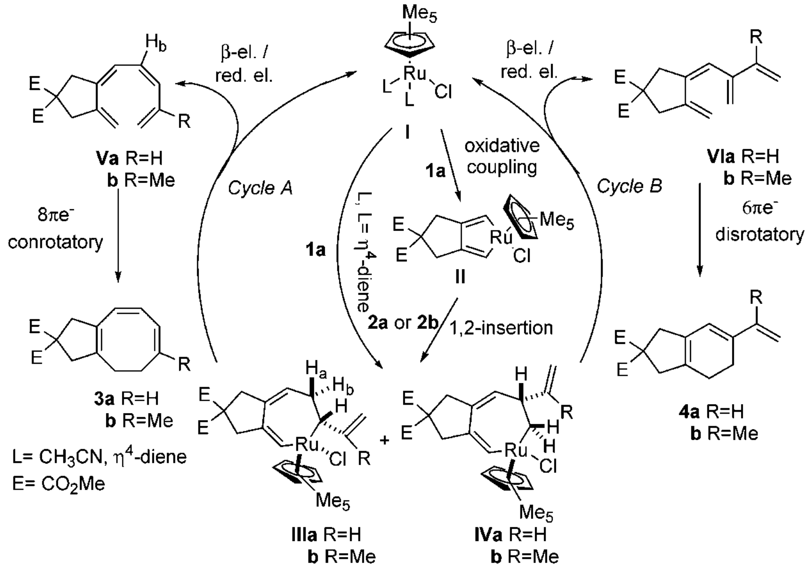
(14) Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221.

(15) The expected 1,3-cyclohexadienes have been observed in Ru-catalyzed [2+2+2] cycloaddition of 1,6-diynes to cyclic allyl ethers (ref 12f). However, when acyclic allyl ethers are used, regioisomeric 1,3-cyclohexadienes (analogues of **4**) are obtained in good yield, a result attributed to the expected [2+2+2] cycloaddition being accompanied by a 1,5-H shift.

(16) For an early mechanistic study of an Ru-mediated cycloaddition of acetylene to 1,3-dienes, see: Masuda, K.; Ohkita, H.; Kurumatani, S.; Itoh, K. *Organometallics* **1993**, *12*, 2221.

(17) Minor amounts of dimers and trimers of **1a** are also obtained when using either of the two catalysts.

Scheme 2. Mechanistic Proposal for the "Formal" Ru-Catalyzed [4+2+2] Cycloaddition of 1,6-Diynes to 1,3-Dienes



couple oxidatively with the diyne to form ruthenacyclic species **II** or undergo replacement of its remaining acetonitrile ligands by an η^4-diene to give **I** (L,L = η^4-diene). In the former case, it is hypothesized that **II** then undergoes insertion of one of the diene alkenes (in the case of the butadiene **2a**) or the nonsubstituted diene alkene (in the case of the isoprene **2b**) into a carbon−ruthenium bond, which affords either **III**, in which a vinyl group inherited from the diene is located α to the ruthenium, or **IV**, in which the vinyl lies β to Ru (Scheme 2). The same species (**III** and **IV**) would result from oxidative coupling of the diyne to diene-substituted **I**. In the case of **III** (*cycle A*), successive β-elimination and reductive elimination would afford (*Z*)-tetraene **V**, allowing its smooth thermal conrotatory 8π-electrocyclization to the octacycle **3**.[18] In the case of **IV** *(cycle B)*, successive β-elimination and reductive elimination would afford vinyl-(*Z*)-hexatriene **VI**, which would undergo thermal disrotatory 6π-electrocyclization to the vinylcyclohexadiene **4**. In fact, a clear proof for support of this mechanistic hypothesis showed up when in room temperature experiments starting from **1a** and **2b**, a mixture of **4b** and the corresponding hexatriene intermediate **VIb** was observed by ^{1}H NMR spectroscopy, and after separation from the catalyst this mixture was totally converted to **4b** by heating at 80 °C. Finally, the **3**:**4** ratio will be favored by using [CpRu-$(CH_3CN)_3]PF_6$ rather than [Cp*Ru$(CH_3CN)_3]PF_6$ because of Cp being smaller than Cp*, which for **2a**,**b** will have favored insertion with the vinyl α to Ru.

To evaluate the influence of the position and orientation of the substituent in the diene we repeated the experiment with piperylenes **2c** and **2d**. Slow addition of a solution of diyne **1a** in DMF to a mixture of *trans*-piperylene **2c**, 10% [Cp*Ru$(CH_3CN)_3]PF_6$, and 10% Et_4NCl in DMF at 80 °C afforded a 1:4.8 mixture of 1,3,5-cyclooctatriene **3c** and 1,3-cyclohexadiene **4c** in which the exocyclic olefin is trans, in 83% combined yield (Table 1, entry 3). When the same experiment was carried out with *cis*-piperylene **2d**, a 70% yield of a 1:1.2:4 mixture of three products was obtained: the two 1,3,5-cyclooctatrienes **3c** and **3d** and the 1,3-cyclohexadiene **4d** in which the exocyclic olefin is cis (entry 4). These results clearly show the different reactivities of *cis*- and *trans*-alkenes. According to the proposed mechanism, in the case of *trans*-piperylene **2c**, ruthenacycle **II** only undergoes insertion by the nonsubstituted diene alkene into a carbon−ruthenium bond, affording either ruthenacycles **IIIc** or **IVc** (Figure 1), which evolve to cyclooctatriene **3c**

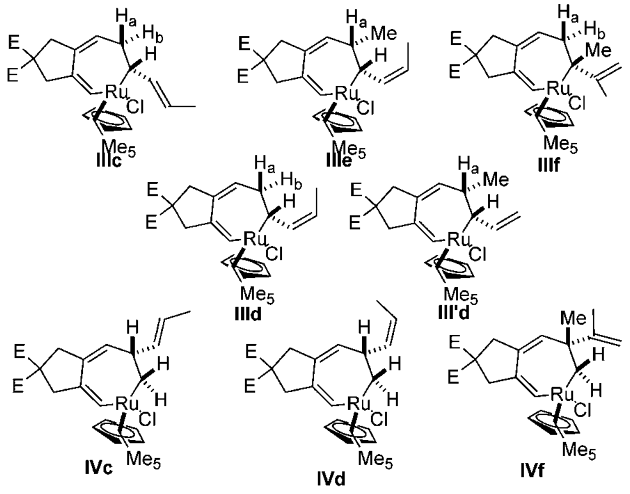


Figure 1. Intermediate ruthenacycles for the formation of 1,3,5-cyclooctatrienes and vinyl-1,3-cyclohexadienes.

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[18] The half-life of a related tetraene **V** was limited to a few minutes at room temperature and its cyclization occurs with a low activation energy (E_a = 14.2 kcal mol^{-1}). Pohnert, G.; Boland, W. *Tetrahedron* **1994**, *50*, 10235.

and cyclohexadiene **4c**, respectively. In the case of *cis*-piperylene **2d**, ruthenacycle **II** could undergo insertion by both diene alkenes; insertion of the nonsubstituted alkene would afford both **IIId** and **IVd** ruthenacycles (Figure 1), while insertion of the substituted diene alkene would afford only ruthenacycle **III′d** (Figure 1) because steric interaction with Cp* is more severe with the bulky methyl group than with the vinyl. Evolution of **IIId** and **III′d** gave rise to octatrienes **3c** and **3d**, respectively, whereas **IVd** evolves to cyclohexadiene **4d**. From the results it has been shown that 1-substituted diene alkenes insert into **II** only if the geometry of the alkene is cis, putting the vinyl substituent α to the Ru (**III′d**).

Gratifyingly, when **1a** was slowly added to a heated (80 °C) mixture of 10% $[Cp^{*}Ru(CH_3CN)_3]PF_6$, 10% Et_4NCl, and isomers of the disubstituted diene 2,4-hexadiene (**2e**), the latter was smoothly converted into 1,3,5-cyclooctatriene **3e** in reasonably good yield (65%) without any cyclohexadiene being detected (Table 1, entry 5).[19] In this case, the use of $[CpRu(CH_3CN)_3]PF_6$ as catalyst gave a lower yield, 41%. The different reactivities of geometric isomers of substituted dienes again emerged when the reaction was carried out with *cis*,*cis*-2,4-hexadiene (*cis*,*cis*-**2e**) and *trans*,*trans*-2,4-hexadiene (*trans*,*trans*-**2e**): whereas *cis*,*cis*-**2e** gave a 48% unoptimized yield of cyclooctatriene **3e**, *trans*,*trans*-**2e** gave no cycloadduct (entry 5). Similarly, cyclization of heteroatom-tethered 1,6-diynes **1b** (X = N-Ts) and **1c** (X = O) with isomers of the disubstituted diene 2,4-hexadiene (**2e**) gave exclusively 1,3,5-cyclooctatrienes **3′e** and **3″e**, respectively, in rather good yields (70% and 62%, entries 6 and 7). Once again these results are easily explained in terms of steric and stereochemical considerations. As in the case of *cis*-piperylene **2d**, the formation of ruthenacycle **IIIe** (Figure 1) is only possible with the methyl group in the β-position to ruthenium, which, following *cycle A*, affords the observed cyclooctatriene **3e**. It is very remarkable that *trans*-alkenes failed to insert into **II** (neither in the case of *trans*-piperylene **2c** nor *trans*,*trans*-2,4-hexadiene **2e**). Thus, neither cyclohexadiene nor cyclooctatriene, products derived from the insertion of one *trans*-alkene into **II**, has ever been observed. On the other hand, if the alkene inserted into **II** has a cis geometry, so will all the double bonds of **V**, allowing its smooth thermal conrotatory 8π-electrocyclization to the octacycle **3**.

Other disubstituted alkenes were also checked. 2,3-Dimethyl-1,4-butadiene failed to afford cocyclized products with **1a**. As expected from the results of isoprene (**2b**), ruthenacycle **IIIf** (Figure 1) would have serious steric hindrance around the ruthenium and the other possible ruthenacycle **IVf** (Figure 1) would not have hydrogens available for β-elimination. *trans*-2-Methyl-1,3-pentadiene also failed because one of the alkenes has trans geometry and the other a substitution pattern as before. Finally, tetrasubstituted 2,5-dimethyl-2,4-hexadiene also failed either because of the steric hindrance caused by the two methyls to be placed α to the ruthenium or by the absence of suitable hydrogens for β-elimination if they are placed in the β position.

In summary, we have described a "formal" Ru-catalyzed [4+2+2] cycloaddition of 1,6-diynes to 1,3-dienes to form 1,3,5-cyclooctatrienes and vinyl-1,3-cyclohexadienes. This formal cycloaddition is really a tandem process, the Ru(II)-catalyzed formation of (*Z*)-tetraenes or vinyl-(*Z*)-trienes followed by a pure thermal conrotatory 8π- or disrotatory 6π-electrocyclization, respectively. The effects of the substitution on the 1,3-diene partner have been studied and showed that 1,4-substituted dienes gave exclusively 1,3,5-cyclooctatrienes. The type of partners that can be utilized and electronic factors involved are currently under investigation in our laboratories.

Acknowledgment. We thank the Xunta de Galicia (Project PGIDT00PXI20908) and the Ministerio de Ciencia y Tecnología (Spain) and the European Regional Development Fund (Project BQU2002-02135) for financial support.

Supporting Information Available: A typical procedure for the Ru-catalyzed reaction 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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[19] Other conditions gave lower yields: rt, 21%; slow addition of **1a** (2 h), rt, 47%; slow addition of **1a** (4 h), rt, 58%. Dimers of **1a** have also been observed in variable amounts.