CHEMISTRY
A EUROPEAN JOURNAL

DOI: 10.1002/chem.200801088

Recent Advances in “Formal” Ruthenium-Catalyzed [2+2+2] Cycloaddition Reactions of Diynes to Alkenes

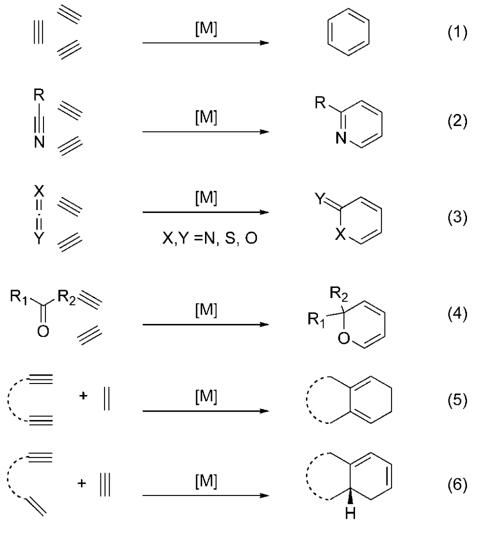
Silvia García-Rubín, Jesús A. Varela, Luis Castedo, and Carlos Saá*[a]

Abstract: “Formal” and standard Ru^{II}-catalyzed [2+2+2] cycloaddition of 1,6-diynes to alkenes gave bicyclic 1,3-cyclohexadienes in relatively good yields. When terminal 1,6-diynes **1** were used, two isomeric bicyclic 1,3-cyclohexadienes **4** or **6** were obtained, depending on the acyclic or cyclic nature of the alkene partner. When unsymmetrical substituted 1,6-diynes **7** were used, the reaction with acyclic alkenes took place regio- and stereoselectively to afford bicyclic 1,3-cyclohexadienes **8**. A cascade process that behaves as a “formal” Ru^{II}-catalyzed [2+2+2] cycloaddition explained these results. Initially, a Ru-catalyzed linear coupling of 1,6-diynes **1** and **7** with acyclic alkenes occurs to give open 1,3,5-trienes of type **3**, which after a thermal disrotatory 6e$^-$ π-electrocyclization led to the final 1,3-cyclohexadienes **4** and **8**. When disubstituted 1,6-diyne **10** was used with electron-deficient alkenes, new *exo*-methylene cyclohexadienes **12** arose from a competitive reaction pathway.

Keywords: alkenes • catalysis • cycloaddition reactions • cyclohexadienes • diynes • ruthenium

Introduction

The development of new reactions that allow an increase in molecular complexity from readily available starting materials, but in an environmentally friendly way and with atom economy, is one of the major goals in modern synthetic organic chemistry.[1] Among the reactions available for this purpose, transition-metal-catalyzed cycloadditions represent a powerful tool for the construction of polycyclic molecules under very mild conditions.[2] Metal catalysts can complex to an olefin, diene, or acetylene and significantly modify the reactivity of this moiety to provide new opportunities for highly selective cycloaddition reactions. For carbocyclic systems containing six-membered rings, the inter- and intramolecular metal-catalyzed [2+2+2] cycloaddition reactions of alkynes are very well established for the preparation of numerous benzene and polycyclic benzene derivatives (reaction type 1, Scheme 1).[3] Heteroarenes and unsaturated heterocycles have also been obtained by using alkynes and carbon–heteroatom multiple bonds, such as nitriles (reaction type 2), heterocumulenes (reaction type 3), or carbonyls (reaction type 4).[4]



Scheme 1. Metal-catalyzed [2+2+2] cycloaddition reactions.

However, the corresponding metal-catalyzed [2+2+2] cycloadditions between alkynes and alkenes to give 1,3-cyclohexadienes are much less developed owing to either the necessity of equimolar amounts of metal promoters[5] or to the lack of generality (reaction types 5 and 6, Scheme 1).[6]

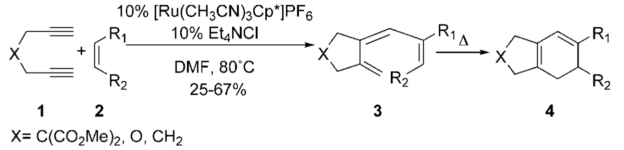
As a further contribution to the above methodology, we recently described a new “formal” [2+2+2] cycloaddition of

---

[a] S. García-Rubín, Dr. J. A. Varela, Prof. L. Castedo, Prof. C. Saá
Departamento de Química Orgánica
Facultad de Química, Universidad de Santiago de Compostela
15782 Santiago de Compostela (Spain)
Fax: (+34) 981-595-012
E-mail: carlos.saa@usc.es

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.200801088.

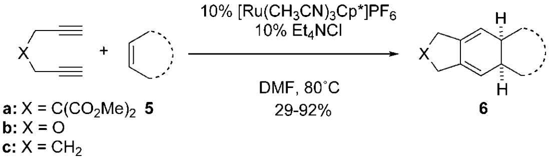
terminal 1,6-diynes **1** with acyclic alkenes **2** in the presence of 10% of an equimolar amount of [Ru(CH$_3$CN)$_3$Cp*]PF$_6$ (Cp* = pentamethylcyclopentadienyl) and Et$_4$NCl to give 1,3-cyclohexadienes **4** (Scheme 2).[7]



Scheme 2. "Formal" Ru-catalyzed [2+2+2] cycloaddition of terminal 1,6-diynes **1** with acyclic alkenes **2**.

We also found that cyclic alkenes **5** reacted with diynes **1** to afford tricyclic cyclohexadienes **6** (Scheme 3).[7] Unlike their acyclic alkene analogues **2**, the double bonds in cyclohexadienes **6** are in the position expected for a [2+2+2] cycloadduct (as observed by Itoh).[6f,g]

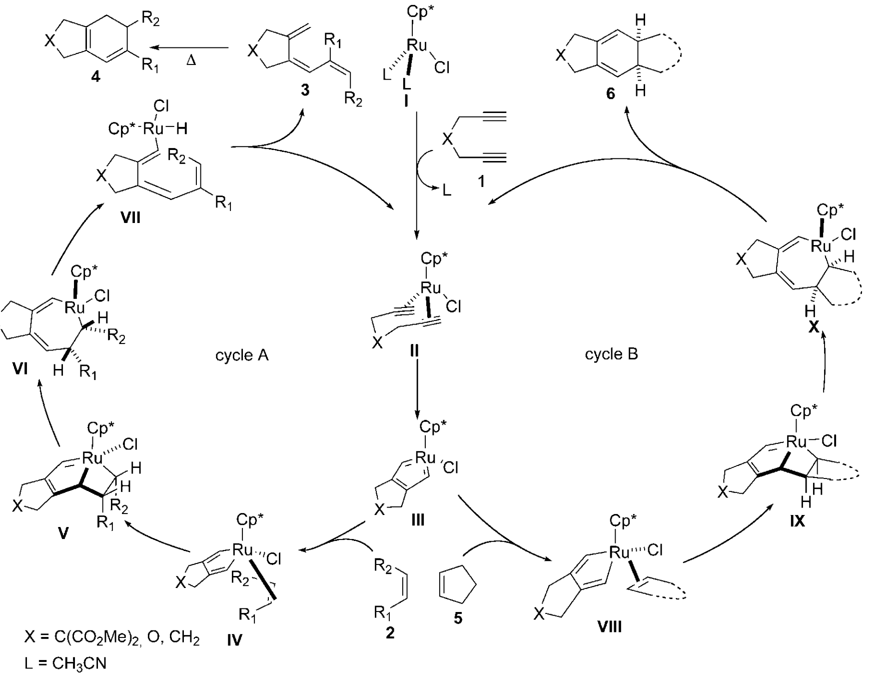
Our mechanistic hypothesis for the Ru-catalyzed reaction of diynes and alkenes involves two possible pathways, depending on the alkene used (Scheme 4).[8] When mixed with Et$_4$NCl, the cationic catalyst [Ru(CH$_3$CN)$_3$Cp*]PF$_6$ probably generates the neutral complex [RuL$_2$ClCp*] (**I**, L = CH$_3$CN), as suggested by changes in the ^{1}H NMR spectrum.[9] Coordination to diyne **1** followed by oxidative coupling would form the bis-carbene species **III**, which after coordination to the alkene would give rise to ruthenacyclic species of type **IV** for acyclic alkenes (*endo* approach) or **VIII** for cyclic alkenes (*exo* approach). Formation of Ru-bicyclic complexes **V** and **IX** followed by electrocyclic opening would afford ruthenacycloheptadienes **VI** and **X**, from which two alternatives can be envisioned depending on the nature of the alkene: 1) the well-established reductive elimination to cyclohexadienes **6** in the case of cyclic alkenes[6g] and 2) a new β-elimination leading to the ruthenium hydride **VII**, followed by a reductive elimination to give the open hexatrienes **3** in the case of acyclic alkenes. The hexatrienes **3** undergo a pure thermal disrotatory 6e$^-$ π-electrocyclization to give the observed cyclohexadienes **4**.



Scheme 3. Standard Ru^{II}-catalyzed [2+2+2] cycloaddition of 1,6-diynes **1** with cyclic alkenes **5**.

Herein, we present our recent advances in the regioselectivity of the "formal" Ru-catalyzed [2+2+2] cycloaddition when using unsymmetrical diynes and also interesting new reaction avenues when using disubstituted diynes as partners.[10]

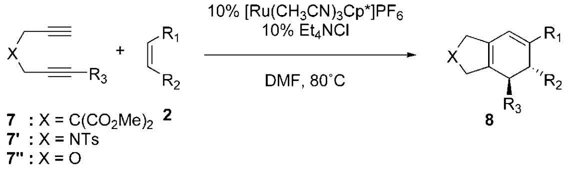
Results and Discussion



Scheme 4. Proposed mechanisms for the "formal" and standard Ru-catalyzed [2+2+2] cycloadditions of terminal 1,6-diynes with acyclic and cyclic alkenes.

Regioselectivity: For a better understanding of the ruthenium-catalyzed cycloaddition of diynes to alkenes, we now decided to explore the regioselectivity of the reaction by using unsymmetrical 1,6-diynes. For this purpose, reactions between selected alkenes and unsymmetrical 1,6-diynes **7** were performed. Slow addition of a solution of **7a** in DMF to a heated DMF solution of methyl acrylate (**2a**) and the usual catalytic mixture afforded exclusively the cyclohexadiene **8aa** in excellent yield (moderate-to-good yields were obtained with heterosubstituted diynes **7′a** and **7″a**, Table 1, entry 1).[11] When the substituted alkene **2b**, with a metal-coordinating heteroatom, and the nonactivated alkene **2c** were used, disubstituted cyclohexadienes **8ab** and **8ac** were obtained in quite good yields (entries 2 and 3). As expected, all the observed products derive from the corresponding Ru complexes **V** (proposed intermediate), in which the insertion of the alkene occurs at the less-substituted Ru–C bond of

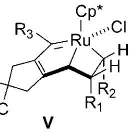
Table 1. "Formal" Ru^{II}-catalyzed [2+2+2] cycloaddition of unsymmetrical diynes **7** with acyclic alkenes **2**.



Entry	R_3	Diyne	R_1	R_2	Alkene	**8**	Yield [%][a]
1	Me	**7a**	CO_2Me	H	**2a**	**8aa**	90 (82)
		7'a				**8'aa**	60
		7''a				**8''aa**	50
2[b]	Me	**7a**	CH_2OEt	H	**2b**	**8ab**	70 (73)
3	Me	**7a**	C_5H_{11}	H	**2c**	**8ac**	69 (66)
4	Me	**7a**	CO_2Me	CO_2Me	**2d**	**8ad**	70 (60)
5	CO_2Me	**7b**	CO_2Me	H	**2a**	**8ba**	68
6	CO_2Me	**7b**	CH_2OEt	H	**2b**	**8bb**	70[b]
7	CO_2Me	**7b**	C_5H_{11}	H	**2c**	**8bc**	63
8	CO_2Me	**7b**	CO_2Me	CO_2Me	**2d**	–	–[c]
9	Ph	**7c**	CO_2Me	H	**2a**	**8ca**	40
10	Ph	**7c**	CH_2OEt	H	**2b**	**8cb**	78[b]
11	Ph	**7c**	C_5H_{11}	H	**2c**	**8cc**	47
12	Ph	**7c**	CO_2Me	CO_2Me	**2d**	–	–[c]

[a] Isolated yields from reactions performed at 80 °C by slow addition, over 4 h, of 0.5 mmol of **7** in DMF to a mixture of 3 equiv of **2**, 10 % Et_4NCl, and 10 % $[Ru(CH_3CN)_3Cp^*]PF_6$ in DMF (conditions A). In brackets, yields when neutral [RuCl(COD)Cp*] complex was used under the same reaction conditions. [b] Reaction performed by using 10 equiv of **2** without slow addition of **7** (conditions B). [c] Unreacted alkene **2** and diyne **7** were recovered.

ruthenacyclopentadienes **IV** and the less-bulky substituent (R_2 = H) is located α to the ruthenium (steric control).



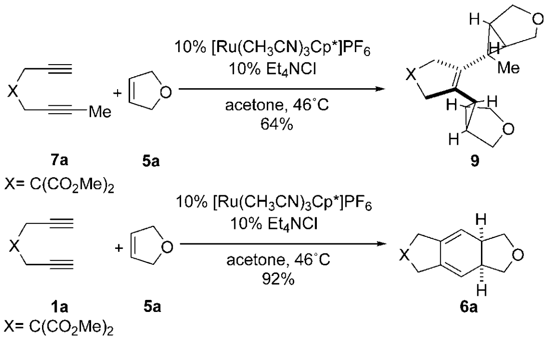
V

To gain further insight into the catalytic species operative in the reaction, we carried out the above experiments by using a preformed neutral ruthenium complex, [RuCl(cod)Cp*] (cod = 1,5-cyclooctadiene) instead of the equimolar mixture of the cationic complex $[Ru(CH_3CN)_3Cp^*]PF_6$ with Et_4NCl (Table 1, entries 1–4, yields in brackets). In all cases, comparable yields were obtained, which showed that most probably the neutral species "RuClCp*", generated in situ when the cationic complex is used, is the operative catalytic species. Thus, for convenient reasons we used the mixture of $[Ru(CH_3CN)_3Cp^*]PF_6$ with Et_4NCl throughout the whole study.

We then evaluated the influence of other substituents in the diyne partner by reaction of selected alkenes with unsymmetrical 1,6-diyne **7b** containing a conjugated methoxycarbonyl group and **7c** containing a phenyl group (Table 1, entries 5–8 and 9–12, respectively). Both electron-poor and conjugated diynes showed similar or slightly lower reactivity than the electron-rich diyne **7a** when reacted with monosubstituted alkenes. As above, the reaction took place regioselectively producing the expected products (steric control) for a "formal" Ru^{II}-catalyzed [2+2+2] cycloaddition with acyclic alkenes.

Interestingly, the reaction also took place stereoselectively illustrated by the fact that the reaction of **7a** with dimethyl maleate (**2d**) only gave the *trans*-substituted cyclohexadiene **8ad** (Table 1, entry 4). Diynes **7b** and **7c** failed to react with dimethyl maleate **2d**, probably due to severe steric hindrance (entries 8 and 12).

Unexpectedly, when 2,5-dihydrofuran (**5a**) was used, the bis-cyclopropanated product **9** was obtained in a reasonably good yield (Scheme 5). The structure of **9** was elucidated by X-ray analysis (Figure 1, see the Supporting Information for details).[12] Interestingly, this result clearly contrasts with that obtained between **5a** and **1a** (X = $C(CO_2Me)_2$) in which an excellent 92 % yield of cyclohexadiene **6a** was obtained.[7] The formation of the bis-cyclopropane **9** is probably due to the presence of the methyl group in **7a**, which inhibits the standard [2+2+2] cycloaddition mechanism from the corresponding ruthenabicyclocarbene **IX** favoring the reductive elimination to a cyclopropane ring; then, a second cyclopropanation of the resulting Ru–carbene species gives the observed bis-cyclopropane product **9**.[13]



Scheme 5. Ru^{II}-catalyzed reactions of diynes **7a** and **1a** with dihydrofuran **5a**.

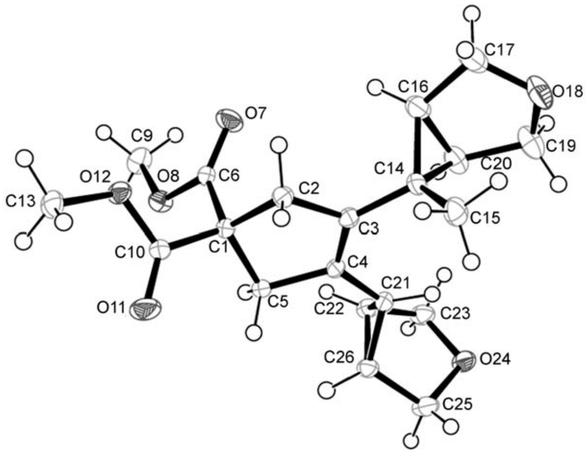
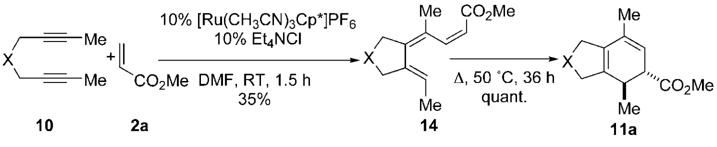


Figure 1. ORTEP diagram of the structure of bis-cyclopropane **9**.

Cycloadditions of disubstituted 1,6-diyne 10 with acyclic alkenes: We next turned our attention to the Ru-catalyzed reaction of 2,7-nonadiyne **10**, which possesses two internal alkyne termini,[14] with selected acyclic alkenes (Table 2). To our surprise, when a solution of diyne **10** in DMF was slowly added over 4 h to a heated solution of alkene **2a** and the usual catalytic mixture, an almost 1:1 ratio of the unexpected cyclohexadiene regioisomer **11a** and the new methylene derivative **12a**[15] was obtained in a 55 % combined yield (Table 2, entry 1). This is the first time that the observed product, cyclohexadiene **11a**, does not present the substituent (CO_2Me) in the diene moiety. Furthermore, methylene derivative **12d**, with the two esters in relative *trans* positions, was exclusively obtained in a moderate 42 % yield when the alkene partner was maleate **2d** (entry 2).[16] Conversely, when allylic ether **2b** was used, the major product was the expected cyclohexadiene **11b** (65 %) with the open hexatriene **13** (12 %) formed as an unexpected minor product (entry 3). Nonactivated 1-heptene (**2c**) gave the expected "formal" [2+2+2] cycloadduct **11c** in low yield (31 %) (entry 4), thus demonstrating the lower reactivity of the starting disubstituted diyne **10** in these reactions (see Table 1 for comparison).



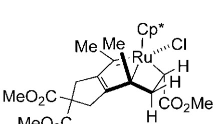
10 **2a** **14** **11a**

X = $C(CO_2Me)_2$

Scheme 6. "Formal" Ru-catalyzed [2+2+2] cycloaddition of disubstituted diyne **10** and methyl acrylate (**2a**).

For a better understanding of the above reactions, we performed experiments at room temperature by using alkenes **2a** and **2b** under conditions B. Addition of diyne **10** at room temperature to a DMF solution of 10 equiv of methyl acrylate (**2a**) containing the catalytic mixture afforded exclusively the open triene **14**[17] in a 35 % yield (Scheme 6). It was necessary to heat a solution of the open triene in $CDCl_3$ at 50 °C for 36 h to obtain cyclohexadiene **11a** in quantitative yield through a 6e$^-$ π-electrocyclization. Further heating of **11a** at 80 °C for several hours did not lead to any change, which indicated that neither **14** nor **11a** are intermediates in the formation of **12a** (Scheme 6).

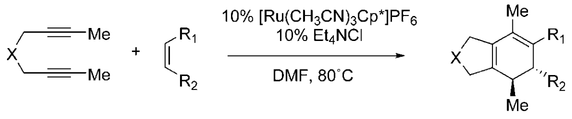
The formation of the open triene **14** can be explained on the basis of the formation of the less-crowded ruthenabicycle **Va′** (proposed intermediate), which results from the coordination and addition of alkene **2a** to the ruthenium biscarbene, thus locating the alkene substituent α to the ruthenium, in which coordination of the carbonyl group to the ruthenium cannot be ruled out.



Va′

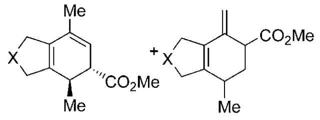
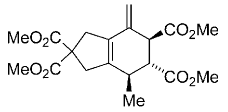
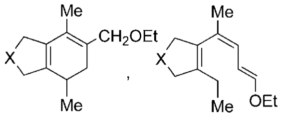
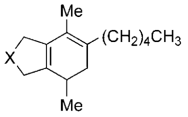
Reaction of alkene **2b** with diyne **10** at room temperature in the presence of the Ru catalyst gave the two isomeric trienes **15** and **13** in 49 and 15 % yields, respectively. Heating triene **15** at 50 °C for 22 h smoothly afforded cyclohexadiene **11b** in quantitative yield (Scheme 7).

Table 2. "Formal" Ru^{II}-catalyzed [2+2+2] cycloaddition of disubstituted diyne **10** with acyclic alkenes **2**.



10 **2** **11**

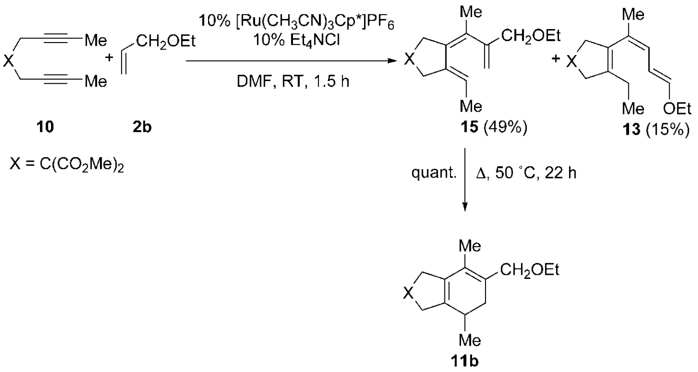
X = $C(CO_2Me)_2$

Entry	Alkene	Products	Yield [%][a]
1	$R_1 = CO_2Me$ $R_2 = H$ **2a**	 **11a** **12a**	55[b]
2	$R_1 = CO_2Me$ $R_2 = CO_2Me$ **2d**	 **12d**	42
3[c]	$R_1 = CH_2OEt$ $R_2 = H$ **2b**	 **11b** **13**	65, 12
4	$R_1 = C_5H_{11}$ $R_2 = H$ **2c**	 **11c**	31

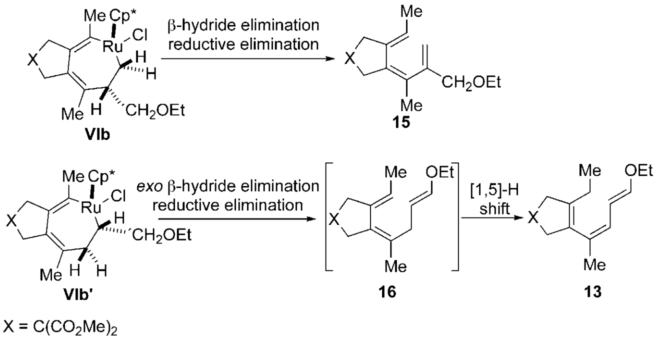
[a] Isolated yields following conditions A as in Table 1. [b] Isolated yield of a 1.25:1 mixture of **11a** and **12a**. [c] Conditions B, as in Table 1 were used.

Formation of isomeric trienes **15** and **13** can be explained by considering the two regioisomeric ruthenacycles **VIb** and **VIb′** (Scheme 8). β-Hydride elimination from **VIb** followed by reductive elimination would afford triene **15**, whereas β-hydride elimination of the exocyclic hydrogen[18] from **VIb′** followed by reductive elimination and a subsequent [1,5]-hydrogen shift of the resulting triene **16** would afford **13** (Scheme 8).

Finally, dimethyl maleate (**2d**) did not participate in the reaction with diyne **10** at room temperature, with only a small amount of the dimer of the diyne isolated from the reaction.[19] Surprisingly, the slow addition (4 h) of a solution of diyne **10** in DMF to a heated solution of dimethyl fumarate (**2d′**)[20] containing the catalytic mixture gave the same yield of the same methylenecyclohexene derivative **12d** as when **2d**



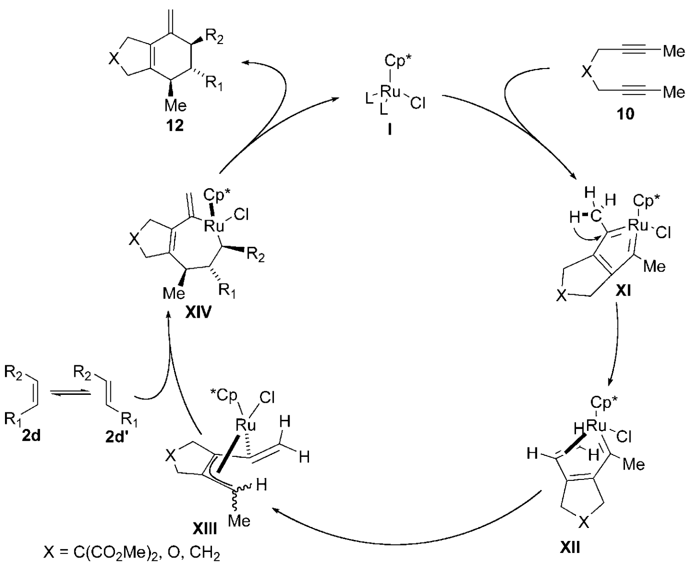
Scheme 7. "Formal" Ru-catalyzed [2+2+2] cycloaddition of disubstituted diyne **10** and ethyl allyl ether (**2b**).



Scheme 8. Formation of trienes **15** and **13** from ruthenacycloheptadiene intermediates **VIb** and **VIb′**.

was used (Table 2, entry 2). The formation of compounds **12a** and **12d** and the reactivity shown by *trans* alkenes suggests the possibility of a new competitive pathway to the "formal" Ru^{II}-catalyzed [2+2+2] cycloaddition of diynes to alkenes, which is operative only when internal alkynes such as **10** are used (Scheme 9).

The proposed mechanism would start with the formation of Ru–bis-carbene **XI** by coordination of diyne **10** to **I** followed by oxidative coupling. If the reaction is performed at 80 °C or above, activation of a C–H bond of an α-substituent by an electrophilic carbene would occur to afford the ruthenium carbene **XII**,[21] which rearranges to the allyl–ruthenium species **XIII**. These types of complexes (**XII** and **XIII**) have been observed and characterized by X-ray diffraction in the group of Kirchner when monosubstituted alkynes were reacted with an equimolecular amount of the cationic Ru complex [Ru(CH$_3$CN)$_2$(Cp)SbPh3]PF$_6$.[22] If a conjugated alkene is present, it is able to insert into the Ru η^3-allyl bond to give rise to the ruthenacycloheptene **XIV** that, after reductive elimination, would afford the methylenecyclohexene derivative **12** and, therefore, make the whole process catalytic. The observed relative *trans* geometry in **12**, regardless of whether maleate **2d** or fumarate **2d′** is used, can be explained only if the *trans*-alkene **2d′** is involved in the reaction.[23]



X = C(CO$_2$Me)$_2$, O, CH$_2$
L = CH$_3$CN

Scheme 9. New Ru^{II}-catalyzed cycloisomerization of diyne **10** and conjugated alkenes **2**.

Conclusion

The course of the Ru^{II}-catalyzed [2+2+2] cycloaddition between 1,6-diynes and alkenes to give 1,3-cyclohexadienes changes with the nature of the starting alkene: 1) if cyclic alkenes are present, standard tricyclic 1,3-cyclohexadienes are obtained from the reductive elimination of intermediate **X**; 2) if acyclic alkenes are used, linear coupling of diynes and alkenes to give 1,3,5-hexatrienes occurs through β-elimination of intermediate **VI** followed by reductive elimination. Then, a pure thermal 6e$^-$ π-electrocyclization gives the bicyclic 1,3-cyclohexadienes. The whole cascade process can be considered as a "formal" [2+2+2] cycloaddition of alkynes and alkenes. Experimental observations and DFT calculations support this mechanism. When a nonterminal 1,6-diyne **10** and conjugated alkenes were used, new methylenecyclohexene derivatives **12** were obtained from the initially formed substituted Ru–bis-carbene of type **XI**.

Experimental Section

General procedures for the Ru-catalyzed reactions between alkenes and 1,6-diynes

Conditions A: synthesis of trimethyl 7-methyl-1,3,6,7-tetrahydro-2H-indene-2,2,5-tricarboxylate (**8aa**). Alkene **2a** (129 mg, 0.14 mL, 1.5 mmol, 3 equiv) was added to a stirred solution of [Ru(CH$_3$CN)$_3$Cp*]PF$_6$ (25 mg, 10 % mol) and Et$_4$NCl (8 mg, 10 % mol) in DMF (1.5 mL) at room temperature. After stirring for 10 min, a solution of diyne **7a** (111 mg, 0.5 mmol, 1 equiv) in DMF (2 mL) was added over 4 h by syringe pump and the solution was heated at 80 °C. Stirring was continued for 1 h after completion of the slow addition. The reaction was quenched with saturated aqueous NH$_4$Cl (10 mL) and extracted with diethyl ether (3 × 10 mL). The organic layers were combined, dried over anhydrous Na$_2$SO$_4$, and evaporated under vacuum. The resulting residue was chromatographied on silica gel by using ethyl acetate/hexane 2:8 as the eluent to afford 1,3-cyclohexadiene **8aa** in 90% yield.

*Conditions B: synthesis of dimethyl 6-(ethoxymethyl)-4-methyl-1,3,4,5-tetrahydro-2*H*-indene-2,2-dicarboxylate* (**8ab**). A solution of [Ru(CH_3CN)$_3$Cp*]PF_6 (25 mg, 10% mol) and Et_4NCl (8 mg, 10% mol) in DMF (1.5 mL) was prepared in a 10 mL round-bottomed flask under argon. After stirring for 10 min at room temperature, alkene **2b** (430 mg, 0.57 mL, 5 mmol, 10eq) was added. After stirring for another 10 min, diyne **7a** (111 mg, 0.5 mmol, 1 equiv) was added and the resulting solution was heated at 80°C for 2 h. The reaction was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with diethyl ether (3×10 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, and evaporated under vacuum. The resulting residue was chromatographied on silica gel by using ethyl acetate/hexane 2:8 as the eluent to afford 1,3-cyclohexadiene **8ab** in 70% yield.

Acknowledgements

This work was supported by the M.E.C. (Spain) and FEDER (CTQ2005–08613), Consolider Ingenio 2010 (CSD2007–00006), and by the Xunta de Galicia (2007/XA084 and PGIDIT06PXIC209041PN). S.G-R. and J.A.V. thank the M.E.C. for a FPU fellowship and a Ramón y Cajal research contract, respectively.

---

[1] a) L. F. Tietze, F. Haunert, *Stimulating Concepts in Chemistry*, Wiley-VCH, Weinheim, **2000**, pp. 39–64; b) B. M. Trost, *Angew. Chem.* **1995**, *107*, 285–307; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259–281; c) B. M. Trost, *Science* **1991**, *254*, 1471–1477.

[2] For reviews on metal-mediated reactions, see: a) B. C. G. Söderberg, *Coord. Chem. Rev.* **2008**, *252*, 57–133; b) L. Yet, *Chem. Rev.* **2000**, *100*, 2963–3007; c) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49–92; d) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635–662.

[3] a) K. Tanaka, K. Takeishi, K. Noguchi, *J. Am. Chem. Soc.* **2006**, *128*, 4586–4587; b) G. Nishida, N. Suzuki, K. Noguchi, K. Tanaka, *Org. Lett.* **2006**, *8*, 3489–3492; c) Y. Yamamoto, J. Ishii, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 9625–9631; d) G. Hilt, T. Vogler, W. Hess, F. Galbiati, *Chem. Commun.* **2005**, 1474–1475. For reviews, see: e) P. R. Chopade, J. Louie, *Adv. Synth. Catal.* **2006**, *348*, 2307–2327; f) V. Gandon, C. Aubert, M. Malacria, *Chem. Commun.* **2006**, 2209–2217; g) S. Kotha, E. Brahmachary, K. Lahiri, *Eur. J. Org. Chem.* **2005**, 4741–4767; h) Y, Yamamoto, *Curr. Org. Chem.* **2005**, *9*, 503–519; i) S. Saito, Y. Yamamoto, *Chem. Rev.* **2000**, *100*, 2901–2915; see also reference [2].

[4] For reviews, see: a) B. Heller, M. Hapke, *Chem. Soc. Rev.* **2007**, *36*, 1085–1094; b) I. Nakamura, Y. Yamamoto, *Chem. Rev.* **2004**, *104*, 2127–2198; c) J. A. Varela, C. Saá, *Chem. Rev.* **2003**, *103*, 3787–3801; d) D. B. Grotjahn, *Transition Metal Alkyne Complexes: Transition Metal-Catalyzed Cyclotrimerization in Comprehensive Organometallic Chemistry II, Vol. 12* (Eds. E. W. Abel, F. G. A. Stone, G. Wilkinson, L. S. Hegedus), Pergamon, Oxford, **1995**, pp. 741–770; e) H. Boennemann, W. Brijoux, *Adv. Heterocycl. Chem.* **1990**, *48*, 177–222; f) K. P. C. Vollhardt, *Angew. Chem.* **1984**, *96*, 525–541; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 539–556; g) N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081–1119; for addition of alkynes to nitriles involving Ru: h) Y. Yamamoto, K. Kinpara, R. Ogawa, H. Nishiyama, K. Itoh, *Chem. Eur. J.* **2006**, *12*, 5618–5631; i) Y. Yamamoto, K. Kinpara, F. Saigoku, H. Takagishi, S. Okuda, H. Nishiyama, K. Itoh, *J. Am. Chem. Soc.* **2005**, *127*, 605–613; j) J. A. Varela, L. Castedo, C. Saá, *J. Org. Chem.* **2003**, *68*, 8595–8598; Co: k) R. Hrdina, I. G. Stará, L. Dufková, S. Mitchel, I. Císaøová, M. Kotora, *Tetrahedron* **2006**, *62*, 968–976; l) A. Gutnov, B. Heller, C. Fischer, H.-J. Drexler, A. Spannenberg, B. Sundermann, C. Sundermann, *Angew. Chem.* **2004**, *116*, 3883–3886; *Angew. Chem. Int. Ed.* **2004**, *43*, 3795–3797; m) A. W. Fatland, B. E. Eaton, *Org. Lett.* **2000**, *2*, 3131–3133; n) Y. Wakatsuki, O. Nomura, K. Kitaura, K. Morokuma, H. Yamazaki, *J. Am. Chem. Soc.* **1983**, *105*, 1907–1912; o) D. J. Brien, A. Naiman, K. P. C. Vollhardt, *J. Chem. Soc. Chem. Commun.* **1982**, 133–134; Rh: p) K. Tanaka, N. Suzuki, G. Nishida, *Eur. J. Org. Chem.* **2006**, 3917–3922; Ni: q) T. N. Tekavec, G. Zuo, K. Simon, J. Louie, *J. Org. Chem.* **2006**, *71*, 5834–5836; r) M. M. McCormick, H. A. Duong, G. Zuo, J. Louie, *J. Am. Chem. Soc.* **2005**, *127*, 5030–5031; for addition of alkynes to heterocumulenes involving Co: s) L. V. R. Boñaga, H. C. Zhang, D. A. Gauthier, I. Reddy, B. E. Maryanoff, *Org. Lett.* **2003**, *5*, 4537–4540; Ru: t) see reference [4i]; Rh: u) K. Tanaka, A. Wada, K. Noguchi, *Org. Lett.* **2006**, *8*, 907–909; for addition of alkynes to carbonyl compounds involving Ru: v) Y. Yamamoto, H. Takagishi, K. Itoh, *J. Am. Chem. Soc.* **2002**, *124*, 6844–6845; Ni: w) T. N. Tekevac, J. Louie, *Org. Lett.* **2005**, *7*, 4037–4039.

[5] Co-mediated reactions: a) C. Aubert, P. Betschmann, M. J. Eichberg, V. Gandon, T. J. Heckrodt, J. Lehmann, M. Malacria, B. Masjost, E. Paredes, K. P. C. Vollhardt, G. D. Whitener, *Chem. Eur. J.* **2007**, *13*, 7443–7465; b) V. Gandon, D. Leboeuf, S. Amslinger, K. P. C. Vollhardt, M. Malacria, C. Aubert, *Angew. Chem.* **2005**, *117*, 7276–7280; *Angew. Chem. Int. Ed.* **2005**, *44*, 7114–7118; c) P. Eckenberg, U. Groth, *Synlett* **2003**, 2188–2192; d) F. Slowinski, C. Aubert, M. Malacria, *J. Org. Chem.* **2003**, *68*, 378–386; e) reference [4e]; f) Y. Wakatsuki, K. Aoki, H. Yamazaki, *J. Am. Chem. Soc.* **1979**, *101*, 1123–1130; g) Y. Wakatsuki, H. Yamazaki, *J. Organomet. Chem.* **1977**, *139*, 169–177; h) Y. Wakatsuki, T. Kuramitsu, H. Yamazaki, *Tetrahedron Lett.* **1974**, *15*, 4549–4552; Ti-mediated reactions: i) M. J. Sung, J. H. Pang, S. B. Park, J. K. Cha, *Org. Lett.* **2003**, *5*, 2137–2140; j) G. J. Balaich, I. P. Rothwell, *J. Am. Chem. Soc.* **1993**, *115*, 1581–1583; Cr-mediated reactions: k) T. Nishikawa, H. Kakiya, H. Shinokubo, K. Oshima, *J. Am. Chem. Soc.* **2001**, *123*, 4629–4630.

[6] Nickel: a) S. Ikeda, H. Kondo, T. Arii, K. Odashima, *Chem. Commun.* **2002**, 2422–2423; Ni–Al: b) N. Mori, S. Ikeda, Y. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 2722–2727; Ni–Zn: c) T. Sambaiah, L. P. Li, D. J. Huang, C. H. Lin, D. K. Rayabarapu, C. H. Cheng, *J. Org. Chem.* **1999**, *64*, 3663–3670; d) S. Ikeda, H. Watanabe, Y. Sato, *J. Org. Chem.* **1998**, *63*, 7026–7029; Ru: e) T. Kondo, Y. Kaneko, F. Tsunawaki, T. Okada, M. Shiotsuki, Y. Morisaki, T. Mitsudo, *Organometallics* **2002**, *21*, 4564–4567; f) Y. Yamamoto, H. Kitahara, R. Ogawa, H. Kawaguchi, K. Tatsumi, K. Itoh, *J. Am. Chem. Soc.* **2000**, *122*, 4310–4319; g) Y. Yamamoto, H. Kitahara, R. Ogawa, K. Itoh, *J. Org. Chem.* **1998**, *63*, 9610–9611; Rh: h) P. A. Evans, E. W. Baum, A. N. Fazal, K. W. Lai, J. E. Robinson, J. R. Sawyer, *Arkivoc* **2006**, 338–358; i) K. Tsuchikama, Y. Kuwata, T. Shibata, *J. Am. Chem. Soc.* **2006**, *128*, 13686–13687; j) P. A. Evans, K. W. Lai, J. R. Sawyer, *J. Am. Chem. Soc.* **2005**, *127*, 12466–12467; k) T. Shibata, Y. Arai, Y. Tahara, *Org. Lett.* **2005**, *7*, 4955–4957; l) C. H. Oh, H. R. Sung, S. H. Jung, Y. M. Lim, *Tetrahedron Lett.* **2001**, *42*, 5493–5495; m) R. Grigg, R. Scott, P. Stevenson, *J. Chem. Soc. Perkin Trans. 1* **1988**, 1365–1369; Ir: n) S. Kezuka, T. Okado, E. Niou, R. Takeuchi, *Org. Lett.* **2005**, *7*, 1711–1714; Pd: o) Y. Yamamoto, S. Kuwabara, Y. Ando, H. Nagata, H. Nishiyama, K. Itoh, *J. Org. Chem.* **2004**, *69*, 6697–6705; p) B. M. Trost, G. J. Tanoury, *J. Am. Chem. Soc.* **1987**, *109*, 4753–4755.

[7] J. A. Varela, S. G. Rubín, C. González-Rodríguez, L. Castedo, C. Saá, *J. Am. Chem. Soc.* **2006**, *128*, 9262–9263.

[8] DFT calculations support this mechanism: J. A. Varela, S. G. Rubín, L. Castedo, C. Saá, *J. Org. Chem.* **2008**, *73*, 1320–1332.

[9] B. M. Trost, A. B. Pinkerton, *J. Am. Chem. Soc.* **2002**, *124*, 7376–7389.

[10] a) C. Bruneau, P. H. Dixneuf, *Angew. Chem.* **2006**, *118*, 2232–2260; *Angew. Chem. Int. Ed.* **2006**, *45*, 2176–2203; b) B. M. Trost, M. U. Frederiksen, M. T. Rudd, *Angew. Chem.* **2005**, *117*, 6788–6825; *Angew. Chem. Int. Ed.* **2005**, *44*, 6630–6666; c) *Ruthenium in Organic Synthesis* (Ed.: S.-I. Murahashi), Wiley-VCH, Weinheim, **2004**; d) *"Ruthenium Catalysts and Fine Chemistry", Topics in Organometallic Chemistry, Vol. 11* (Eds.: C. Bruneau, P. H. Dixneuf), Springer, **2004**.

[11] Slow addition of 1,6-diynes **7** avoids self-dimerization or trimerization to form benzene derivatives.

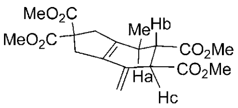
[12] This type of compounds has also been observed in Ru-catalyzed reactions of 1,6-diynes with electron-deficient cycloalkenes, see reference [6f]. CCDC-690287 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[13] Coordination of the ruthenium to the oxygen present in **5a** could facilitate the reaction because other cyclic alkenes failed (cyclopentene, cyclohexene), with only the dimerized product of diyne **7a** observed.

[14] Y. Yamamoto, T. Arakawa, R. Ogawa, K. Itoh, *J. Am. Chem. Soc.* **2003**, *125*, 12143–12160.

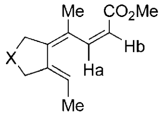
[15] Relative stereochemistry (Me and CO_2Me) not determined.

[16] The relative stereochemistry of the methylenecyclohexene derivative **12d** was determined by measurement of the two coupling constants for the proton H_b (dd, $J = 11.5$, 9.8 Hz) and by NOE experiments (NOE of H_a with H_c and NOE of H_a and H_b with the methyl).



12d

[17] The geometry of the disubstituted double bond in **14** was elucidated from the value of the coupling constant between H_a and H_b ($J = 12.1$ Hz), typical of a *cis* relationship.



14

[18] B. M. Trost, J. P. N. Papillon, T. Nussbaumer, *J. Am. Chem. Soc.* **2005**, *127*, 17921–17937.

[19] The dimer of disubstituted diyne **10** has also been obtained in the synthesis of benzenes by Ru^{II}-catalyzed [2+2+2] cycloaddition of **10** with alkynes; see reference [14].

[20] *Trans* olefins such as dimethyl fumarate do not participate in the "formal" Ru^{II}-catalyzed [2+2+2] cycloaddition reaction with terminal diynes **1**: J. A. Varela, L. Castedo, C. Saá, *Org. Lett.* **2003**, *5*, 2841–2844.

[21] This process can be seen as a β-hydride elimination followed by reductive elimination of the resulting Ru−H bond.

[22] a) R. Schmid, K. Kirchner, *Eur. J. Inorg. Chem.* **2004**, 2609–2626; b) E. Becker, E. Ruba, K. Mereiter, R. Schmid, K. Kirchner, *Organometallics* **2001**, *20*, 3851–3853.

[23] Isomerization of dimethyl maleate **2d** to dimethyl fumarate **2d′** has been observed when the reaction mixture is heated under the reaction conditions in the absence of diyne **10**.

Received: June 4, 2008