Enyne Cyclization

Addition of Diazoalkanes to Enynes Promoted by a Ruthenium Catalyst: Simple Synthesis of Alkenyl Bicyclo[3.1.0]hexane Derivatives**

*Florian Monnier, Dante Castillo, Sylvie Dérien,
Loïc Toupet, and Pierre H. Dixneuf**

Molecular catalysts are currently playing a key role in innovative synthetic methods.[1] They promote the synthesis of complex, useful molecules, through highly simplified pathways that involve the combination of simple substrates and the formation of several consecutive bonds with high selectivity.[2,3] The activation of these molecules under mild

---

[*] Prof. P. H. Dixneuf, F. Monnier, D. Castillo, Dr. S. Dérien
Institut de Chimie de Rennes, UMR 6509
CNRS-Université de Rennes
Organométalliques et Catalyse
Campus de Beaulieu, 35042, Rennes (France)
Fax: (+33) 2-2323-6939
E-mail: pierre.dixneuf@univ-rennes1.fr

Dr. L. Toupet
Groupe Matière Condensée et Matériaux, UMR 6626
CNRS-Université de Rennes
Campus de Beaulieu, 35042, Rennes (France)

[**] This work was supported by the CNRS and the Ministère de la recherche. The authors are grateful to the latter for a PhD grant to FM and, for additional support, to the European Union through the Cost Program D17, and the Region Bretagne, through a PRIR program (169AOC), and to Institut Universitaire de France for membership (PHD).

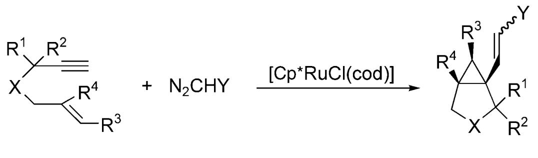
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

© 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim DOI: 10.1002/ange.200352477

conditions are also opening the way to transform stoichiometric reactions into catalytic ones such as the Pauson–Khand[4] or Nicholas[5] reactions. Enynes have recently been at the center of general, useful catalytic transformations. In the presence of alkene metathesis catalysts, they lead to a variety of functional alkenyl cycloalkenes with the 1,3-diene moiety.[6] The research groups of Trost, Murai, and Fürstner have shown that enynes constitute the basis of straightforward routes to bicyclo[3.1.0]hexane[7,8] or bicyclo[4.1.0]heptane[9] derivatives in the presence of Pd^{II} centers,[8] [$RuCl_2L_n$][7] or [$PtCl_2$][9–11] catalysts. One aspect that these transformations have in common is the initial electrophilic activation of the triple bond, which favors its coupling with the double bond and leads to either bicyclic alkylidene–metal[7,8] or stabilized by cationic carbenoid resonance [9] intermediates.

Recently, the ruthenium catalyzed double addition of diazoalkanes to alkynes, has offered a direct route to 1,3-dienes.[12] The attempt to apply this reaction to enynes has actually led to the discovery of a new catalytic reaction that contrasts with the above electrophilically initiated transformations of enynes.[7–9]

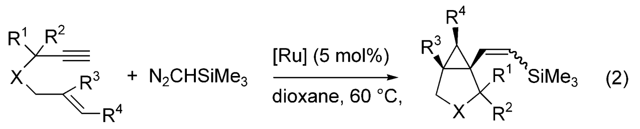
Herein we report the novel one-step reaction of enynes with diazoalkanes, catalyzed by [(Cp*RuCl(cod)] ([Rh]; $Cp^* = C_5Me_5$, cod = cyclooctadiene). The reaction involves the selective formation of three C–C bonds including a cyclopropanation step and directly leads to 1-alkenyl bicyclo[3.1.0]hexane derivatives [Eq. (1)]. This highly stereoselective reaction has potential in synthesis as alkenylcyclopropanes easily give access to 5-membered cycles.[13]



(1)

The reaction of enyne **1a** with an excess of trimethylsilyldiazomethane in dioxane in the presence of 5 mol% of [Cp*RuCl(cod)] under inert atmosphere does not lead to the expected diazoalkane carbene double addition to the C≡C bond,[12] but selectively affords the bicyclic 1-alkenyl bicyclo[3.1.0]hexane product **2a** in 70% yield after 24 h at 60 °C and with complete conversion of **1a** [Eq. (2)]. Under the same conditions the enyne **1b** led to **2b,** which was isolated in 85% yield (*Z*/*E* = 3:1).[14] For the C=C bond disubstituted ether **1c**, the reaction was slower and **2c** was isolated in only 40% yield as a mixture of diastereoisomers (9:1). All compounds **2** formed as a mixture of *Z* > *E* isomers but the cyclopropanation is highly stereoselective.

The enynes that contain nitrogen are more reactive. The reaction of **3a** with $N_2CHSiMe_3$ after 1 h at 60 °C led to **4a** in 95% yield (*Z*/*E* = 4:1) [Eq. (2)] (Ts = *p*-toluenesulfonyl). It is noteworthy that in this case substitutions at the C=C bond in enynes **3b** and **3c** do not affect either reaction time or yield, and the formation of the bicyclo[3.1.0]hexane derivatives **4b** (80%) and **4c** (85%) is observed. In the case of enyne **3b**, the diastereoisomers **4b** (d.r. = 3:1) are formed and had only a *Z* configuration of the C=C bond.



(2)

X = O 20-48 h	
1a R^1 = Me, R^2 = Ph, R^3 = R^4 = H	**2a** (70%) *Z*/*E* 10:1
1b R^1, R^2 =-$(CH_2)_5$-, R^3 = R^4 = H	**2b** (85%) *Z*/*E* 3:1
1c R^1, R^2 =-$(CH_2)_5$-, R^3 = H, R^4 = Ph	**2c** (40%) *Z*/*E* <1:20 (d.r. = 9:1)
X = NTs 1-2 h	
3a R^1 = R^2 = R^3 = R^4 = H	**4a** (95%) *Z*/*E* 4:1
3b R^1 = R^2 = R^3 = H, R^4 = CH_3, (E/Z = 85:15)	**4b** (80%) *Z*/*E* >20:1 (d.r. = 3:1)
3c R^1 = R^2 = R^4 = H, R^3 = CH_3	**4c** (85%) *Z*/*E* 9:1

The major diastereoisomer of **4b** was purified by chromatography over silica gel. Crystals of this diastereoisomer that were suitable for X-ray crystal-structure analysis were obtained in a mixture of pentane and diethyl ether (Figure 1.)[15] The structure reveals the relative spacial substituent positions on the cyclopropane moiety: both *Z* trimethylsilylvinyl and methyl groups are *cis* and this observation is confirmed by NMR experiments (hmqc, hmbc, NOESY) for the derivatives **2** and **4**.

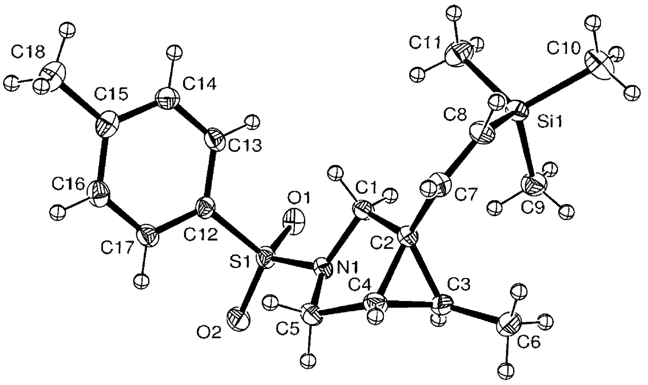
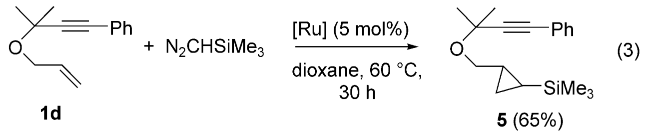


Figure 1. ORTEP drawing of the molecular structure of the major diastereoisomer of **4b**. Thermal ellipsoids are set at the 50% probability level.

The above catalytic reaction seems general, as it is not inhibited by different substitutions on the C=C bond of the starting enynes. The only observed limitation is related to the disubstituted triple bond of the starting enyne **1d**. In that case, the reaction affords the compound **5**, which results from classical cyclopropanation of the double bond. This result suggests that an enyne with sterically hindered C≡C bond inhibits the coordination of the catalyst to the advantage of the C=C bond [Eq. (3)].

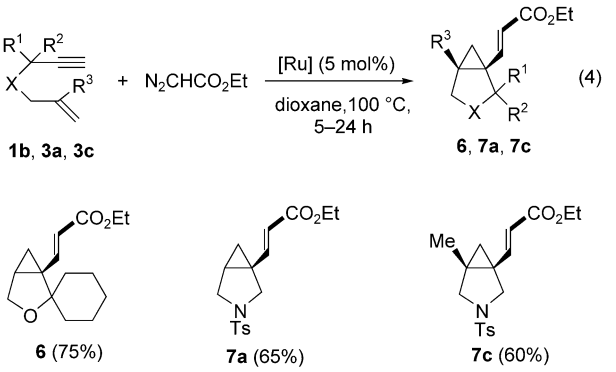
Ethyl diazoacetate and phenyldiazomethane are less reactive than trimethylsilyldiazomethane and require more energetic conditions. Thus, the reaction of **1b, 3a** and **3c** to afford derivatives **6, 7a**, and **7c,** respectively, in yields of 60–

© 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



1d **5** (65%) (3)

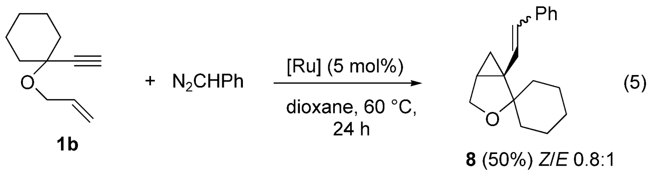
75% requires three equivalents of N_2CHCO_2Et in dioxane at 100°C for 5–24 h [Eq. (4)]. Under these conditions the reaction affords exclusively the *E* isomer.



1b, **3a**, **3c** **6**, **7a**, **7c** (4)

6 (75%) **7a** (65%) **7c** (60%)

The reaction of **1b** with an excess of N_2CHPh at 60°C in dioxane and after 24 h led to **8** isolated in 50% yield. This relatively low yield is related to the parallel formation of stilbene by decomposition of the phenyldiazomethane [Eq. (5)].

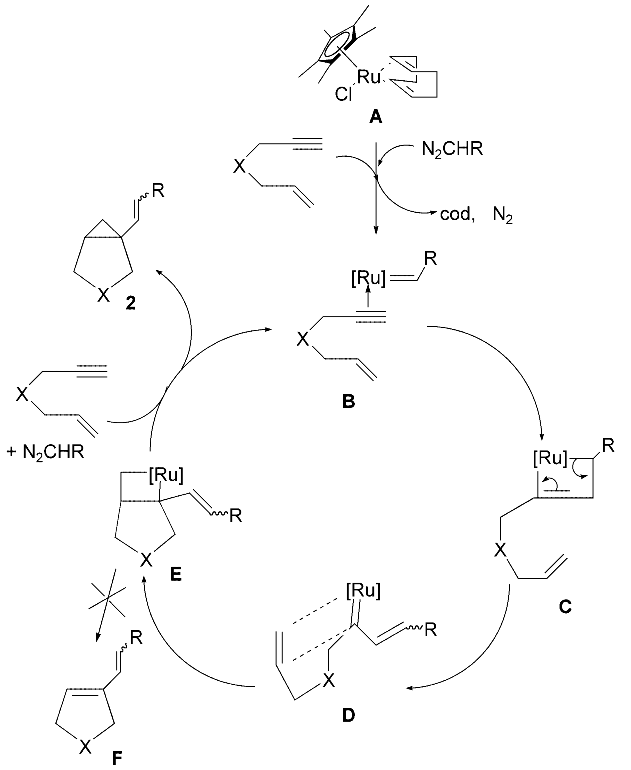


1b **8** (50%) *Z*/*E* 0.8:1 (5)

These results show that the catalyst [Cp*RuCl(cod)] selectively transforms 1,6-enynes into 1-alkenyl bicyclo[3.1.0]hexanes and the stereochemistry of the alkene group depends on the nature of the diazoalkane and thus reaction conditions. For the enynes **1a, 1b, 3a** with $N_2CHSiMe_3$ the isomer *Z* is the major product formed at 60°C and N_2CHCO_2Et preferentially leads to the *E* isomer at 100°C.

It is noteworthy that the stoichoimetric reaction of enynes with metal–carbene complexes, $[(OC)_5M{=}C(OR)R^1]$ derivatives of chromium[16] and molybdenum,[17] have been shown to lead to the synthesis of alkenyl bicyclo[3.1.0]hexane derivatives.[18] Thus the above reaction appears to be the first catalytic version of the Hoye–Harvey reaction.[16,17]

The mechanism of the reaction can be explained according to Scheme 1. The initial step is expected to involve the formation of a Ru=CHR moiety from the diazoalkane and its coupling with the alkyne to form **C**, as postulated for the first step of the catalytic double diazoalkane addition to alkyne by the same catalyst,[12] or as shown for the first step of stoichiometric addition of metal carbenes to enyne.[19] This is also supported by the reaction inhibition of disubstituted hindered enyne C≡C bond (**1d** to **5**, [Eq. (3)]). The formation of intermediates **D** and **E** corresponds to alkene and enyne metathesis key steps. The novelty of this catalytic reaction is related to the last step: a promoted reductive elimination from **E** to give **2**, rather than the classical formation of the enyne metathesis product the alkenylcycloalkene **F**. On interaction of ruthenium–carbene moiety with an alkene, this reductive elimination step is favoured[20] probably because of the steric hindrance of the C_5Me_5–Ru group, as we showed that [Cp*RuCl(cod)] also catalyzed the same reaction but afforded derivatives of **2** in lower yield.



Scheme 1. Catalytic cycle.

In the reaction reported here, the diazoalkane carbene, which is known to involve a variety of functional groups, is not involved in the cyclopropane ring but in the pendent chain. Thus, this new reaction leading to alkenyl cyclopropane derivatives has a broad spectrum of applications in synthesis.

Experimental Section

General procedure for the catalytic synthesis of **2,4–8**: [Cp*RuCl(cod)] (0.0625 mmol, 5 mol%) was added to a solution of enyne (1.25 mmol, 1 equiv) and diazoalkane (2–4 equiv) in 1 mL of degassed dioxane at 60–100°C under an inert atmosphere. The reaction mixture was stirred for between 1 h to 48 h according to the natures of the enyne and diazoalkane. The solvent was then removed under vacuum, and the products were isolated by column chromatography on silica gel to give bicyclic products (1-alkenyl bicyclo[3.1.0]hexane). The yields are based on the enyne. All compounds were fully characterized by spectroscopic methods (see Supporting Information). Selected data for **7c**: ^{1}H NMR (200.131 MHz, $CDCl_3$): $\delta = 0.89$ (d, 1H, $J = 5.3$ Hz, CH_2); 1.16 (s, 3H, Me); 1.26 (t, 3H, $J = 7.1$ Hz, CH_3) ; 1.29 (d, 1H, $J = 5.3$ Hz, CH_2); 2.44 (s, 3H, Me); 2.80 (d, 1H, $J = 9.1$ Hz, CH_2N); 3.10 (d, 1H, $J = 9.0$ Hz, CH_2N); 3.60 (d, 2H, $J = 9.1$ Hz, CH_2N); 4.16 (q, 2H, $J = 7.1$ Hz, OCH_2); 5.68 (d, 1H, $J = 15.8$ Hz, =CH); 6.66 (d, 1H, $J = 15.8$ Hz, =CH); 7.34 (d, 2H, $J = 8.0$ Hz, Ph); 7.68 ppm (d, 2H, $J = 8.0$ Hz, Ph). ^{13}C NMR (50.329 MHz, $CDCl_3$): $\delta = 166.5$, 147.3, 144.2, 133.3, 130.2, 128.1, 120.1, 60.8, 55.1, 51.7, 33.4, 33.3, 23.2, 22.0, 15.8, 14.7. HRMS: m/z calcd for ($C_{18}H_{23}NO_4S$) [M^+] 349.1347, found 349.1348; FTIR (KBr): $\tilde{\nu} = 2928$, 1707, 1637, 1598 cm^{-1}. Elemental analysis calcd (%) for $C_{18}H_{23}NO_4S$: C 61.87, H 6.63; found: C 61.87, H 6.71.

Received: July 25, 2003 [Z52477]

Keywords: cyclization · diazo compounds · enynes · heterocycles · ruthenium

---

[1] a) S. J. Connon, S. Blechert, *Angew. Chem.* **2003**, *115*, 1944; *Angew. Chem. Int. Ed.* **2003**, *42*, 1900; b) B. M. Trost, F. D. Toste, A. B. Pinkerton, *Chem. Rev.* **2001**, *101*, 2067; c) B. Cornils, W. A. Herrmann, *Applied homogeneous catalysis with organometallic compounds*, Wiley-VCH, Weinheim **2002**; d) A. Fürstner, *Topics in Organometallic Chemistry, Vol. 1*, Springer, Heidelberg, **1998**; e) T. Naota, H. Takaya, S. Murahashi, *Chem. Rev.* **1998**, *98*, 2599.

[2] a) B. M. Trost, *Acc. Chem. Res.* **2002**, *35*, 695; b) C. Bruneau, P. H. Dixneuf, *Acc. Chem. Res.* **1999**, *32*, 311; c) C. Bruneau, P. H. Dixneuf, *Chem. Commun.* **1997**, 507.

[3] N. Chatani, A. Kamitani, S. Murai, *J. Org. Chem.* **2002**, *67*, 7014.

[4] a) T. Morimoto, N. Chatani, Y. Fukumoto, S. Murai, *J. Org. Chem.* **1997**, *62*, 3762; b) T. Kondo, N. Suzuki, T. Okada, T. Mitsudo, *J. Am. Chem. Soc.* **1997**, *119*, 6187.

[5] a) K. M. Nicholas, *Acc. Chem. Res.*, **1987**, *20*, 207; b) Y. Nishibayashi, M. Yoshikawa, Y. Inada, M. Hidai, S. Uemura, *J. Am. Chem. Soc.* **2002**, *124*, 11846.

[6] a) S. Imhof, S. Blechert, *Synlett*, **2003**, 609; b) A. Kinoshita, M. Mori, *Synlett*, **1994**, 1020; c) M. Mori, *Topics in Organometallic Chemistry, Vol. 1*, Springer, Heidelberg, **1998**, 133.

[7] a) N. Chatani, T. Morimoto, T. Muto, S. Murai, *J . Am. Chem. Soc.* **1994**, *116*, 6049; b) N. Chatani, K. Kataoka, S. Murai, N. Furukawa, Y. Seki, *J. Am. Chem. Soc.* **1998**, *120*, 9104.

[8] a) B. M. Trost, M. K. Trost, *J. Am. Chem. Soc.* **1991**, *113*, 1850; b) B. M. Trost, A. S. K. Hashmi, *Angew. Chem.* **1993**, *105*, 1130; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1085; c) B. M. Trost, A. S. K. Hashmi, R. G. Ball, *Adv. Synth. Catal.*, **2001**, *343*, 490; d) B. M. Trost, A. S. K. Hashmi, *J. Am. Chem. Soc.* **1994**, *116*, 2183.

[9] A. Fürstner, F. Stelzer, H. Szillat, *J. Am. Chem. Soc.* **2001**, *123*, 11863.

[10] M. Mendez, M. Paz Munoz, C. Nevado, D. J. Cardenas, A. M. Echavarren, *J. Am. Chem. Soc.* **2001**, *123*, 10511.

[11] E. Mainetti, V. Mouriès, L. Fensterbank, M. Malacria, J. Marco-Contelles, *Angew. Chem.* **2002**, *114*, 2236; *Angew. Chem. Int. Ed.* **2002**, *41*, 2132.

[12] J. Le Paih, S. Dérien, I. Özdemir, P. H. Dixneuf, *J. Am. Chem. Soc.* **2000**, *122*, 7400.

[13] a) A. de Meijere, S. I. Kozhushkov, *Chem. Rev.* **2000**, *100*, 93; b) H.-U. Reissig, R. Zimmer, *Chem. Rev.* **2003**, *103*, 1151; c) J. E. Baldwin, *Chem. Rev.* **2003**, *103*, 1197.

[14] The double-bond stereochemistry of all products obtained with trimethylsilyldiazomethane was based on larger coupling constants between the two vinyl protons for the *trans* (18–19 Hz) with respect to the *cis* (14–15 Hz) isomer and was confirmed by X-ray structure of **4b**.

[15] Crystal structure analysis: $SSiNC_{18}H_{27}O_2$, $M_r = 349.56$, monoclinic, $P2_1/a$, $a = 13.5714(2)$, $b = 7.3787(1)$, $c = 19.5966(4)$ Å, $\beta = 104.157(1)°$, $V = 1902.8(1)$ Å^{-3}, $Z = 4$, $D_x = 1.220$ Mg.m^{-3}, l(MoKα) = 0.71073 Å, $\mu = 2.42$ cm^{-1}, F(000) = 752, $T = 120$ K. The sample ($0.25 \times 0.12 \times 0.12$ mm) is studied on a NONIUS Kappa CCD with graphite monochromatized $Mo_{K\alpha}$ radiation. The cell parameters are obtained with Denzo and Scalepack (Otwinowski & Minor , 1997) with ten frames (psi rotation: 1° per frame). The data collection (Nonius, 1999) ($2\theta_{max} = 54°$, 230 frames through 1.8° omega rotation and 20 s per frame, range HKL: H 0.17, K 0.9, L −25.24) gives 27966 reflections. The data reduction with Denzo and Scalepack (Otwinowski and Minor, 1997) leads to 4323 independent reflections from which 3489 with $I > 2.0\sigma(I)$. The structure was solved with SIR-97 (Altomare et al., 1998) which reveals the non hydrogen atoms of the molecule. After anisotropic refinement, many hydrogen atoms may be found with a Fourier Difference. The whole structure was refined with SHELXL97: G. M. Sheldrick, SHELXS-97, Program for the Solution of Crystal Structures, University of Göttingen, Göttingen (Germany), **1997** by the full-matrix least-square techniques (use of F square magnitude; *x, y, z*, β_{ij} for Si, S, O, C, and N atoms, *x, y, z* in riding mode for H atoms ; 208 variables and 3489 observations with $I > 2.0\sigma(I)$; calcd $w = 1/[\sigma^2(Fo^2) + (0.098P)^2 + 1.48P]$ in which $P = (Fo^2 + 2Fc^2)/3$ with the resulting $R = 0.050$, $R_w = 0.142$ and $S_w = 1.020$, $\Delta\rho < 0.54$ eÅ^{-3}. CCDC 215613 (**4b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

[16] a) P. F. Korkowski, T. R. Hoye, D. B. Rydberg, *J. Am. Chem. Soc.* **1988**, *110*, 2676; b) T. R. Hoye, G. M. Rehberg, *J. Am. Chem. Soc.* **1990**, *112*, 2841; c) T. R. Hoye, T. J. Katz, G. X.-Q. Yang, *Tetrahedron Lett.* **1991**, *32*, 5895.

[17] D. F. Harvey, M. F. Brown, *Tetrahedron Lett.* **1991**, *32*, 5253.

[18] More recently such a stoichiometric reaction was observed with $[RuCl_2(=CHPh)(PCy_3)$(heterocyclic carbene)] and enyne as a side reaction of the catalytic enyne metathesis. In that case the reductive elimination step in the absence of a source of carbene does not allow the regeneration of the ruthenium carbene catalyst. See: T. Kitamura, Y. Sato, M. Mori, *Chem. Commun.* **2001**, 1258.

[19] a) T. J. Katz, T. M. Sivavec, *J. Am. Chem. Soc.* **1985**, *107*, 737; b) T. M. Sivavec, T. J. Katz, M. Y. Chiang, G. X.-Q. Yang, *Organometallics* **1989**, *8*, 1620.

[20] Y. Yamamoto, H. Kitahara, R. Ogawa, H. Kawaguchi, K. Tatsumi, K. Itoh, *J. Am. Chem. Soc.* **2000**, *122*, 4310.

© 2003 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim