The [2 + 1] and [4 + 3] Cyclization Reactions of Fulvenes with Fischer Carbene Complexes: New Access to Annulated Cyclopentanones

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The pentafulvene system represents a very attractive structural unit, not only as a model for theoretical studies but also as a valuable building block to access polycyclic cyclopentanoids through a diverse array of cyclizations.[1] From a different point of view, one can realize whether this framework might be a suitable synthetic equivalent of the short-lived cyclopentadienone unit.[2,3] Therefore, we became interested on the cyclopropanation reaction of fulvenes using Fischer carbene complexes.[4,5] Surprisingly, only isolated examples concerning the cyclopropanation of fulvenes appear in the literature[6] despite the synthetic significance of the reaction itself. In this contribution, we report the selective cyclopropanation reaction of pentafulvenes with alkyl and aryl(methoxy)carbene complexes of group 6. The alkynylcarbene complexes also effect the cyclopropanation or, under well-established reaction conditions, the [4 + 3] cyclization.

First, chromium alkoxycarbenes **1** and substituted fulvenes **2** (molecular ratio 1:1.2; $c = 0.07-0.08$ mol/L) were heated in MeCN at 80 °C for 12 h. The reaction mixture was taken in hexanes/EtOAc, 5:1, demetalated (light-air, 4–8 h) and filtered off through Celite. This solution gave cleanly the homofulvenes **3**, which were further chromatographed (SiO$_2$; hexanes/EtOAc, 5:1) and isolated in 63–95% yield (Scheme 1; Table 1, entries a–c, e–i). The cyclopropanation reaction takes place at the endocyclic C=C bond, giving rise preferentially to the *E*-isomer in the case of unsymmetrical fulvenes (R^3 = H). Of particular interest was the finding that a total control of diastereoselectivity was reached in all cases in favor of the *endo* cycloadducts **3** (NMR analysis of the reaction crude).[7,8]

The single cyclopropanation reaction could be successfully extended for the first time to Fischer alkynyl carbene complexes (Scheme 2).[9] Thus, 6,6-dialkyl and 6-aryl fulvenes **2** reacted with tungsten pentacarbonyl[phenylethynyl(methoxy)]carbene complex **4a** (R^1 = Ph) at 60 °C in hexane and THF, respectively, to produce the alkynyl homofulvenes **5** in 65–73% yield after air-light demetalation and column chromatography purification (SiO$_2$; hexanes/EtOAc, 5:1) (Table 1, entries a–d). In contrast to simple carbene complexes, the alkynyl carbene complex **4a** led preferentially (entries a,b) or exclusively (entries c,d) to the *exo* diastereoisomer of **5**. In turn, the homofulvenes **5c,d** were formed as the *E*-isomer exclusively.

A mechanistic proposal that might account well for the observed selectivity of these cyclopropanation reactions is based on the Harvey's model for the cyclopropanation of 1,3-dienes[7a,10] (Scheme 3). The process initiates by CO dissociation and formation of the η^1-metallacyclobutane **I**, which would be in rapid equilibrium with the corresponding η^3-species **II**. The reductive elimination would give rise to intermediate **III** wherein the metal coordinates to the

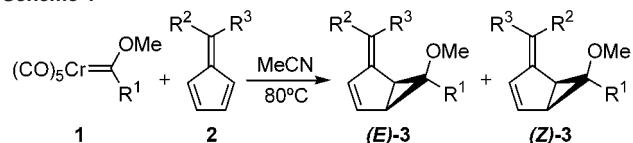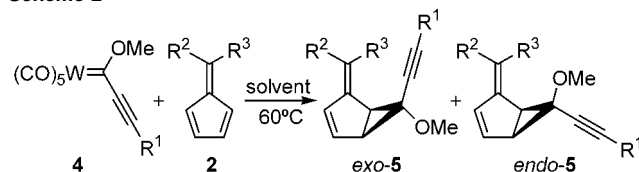* To whom correspondence should be addressed. E-mail: barluenga@sauron.quimica.uniovi.es.

Scheme 1

Table 1. Cyclopropanation of Fulvenes **2** with Complexes **1** and **4**

entry	R^1	R^2	R^3	3 %^{c}	3 E/Z^d	5 %^{c}	5 exo/endo^d
a	Ph	Me	Me	65	—	65^a	3:1
b	Ph	−(CH$_2$)$_4$−		72	—	68^a	8:1
c	Ph	Ph	H	70	5:1	65^b	>30:1
d	Ph	pClPh	H	—	—	73^b	>30:1
e	Ph	i-Pr	H	85	4:1	—	—
f	Ph	t-Bu	H	95	>30:1	—	—
g	Ph	AcO	H	63	2:1	—	—
h	pMeOPh	Me	Me	68	—	—	—
i	n-Bu	t-Bu	H	65	10:1	—	—

^{a} Solvent: hexane. ^{b} Solvent: THF. ^{c} Isolated yields. ^{d} *E/Z* and *exo/endo* ratio determined by ^{1}H NMR (300 MHz) of the crude mixture.
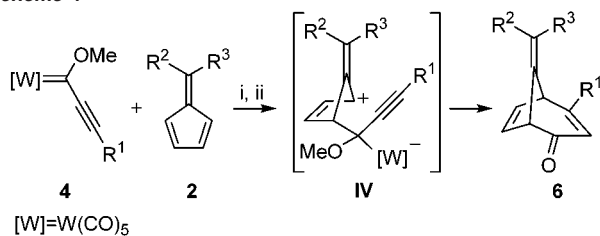
Scheme 2

Scheme 3
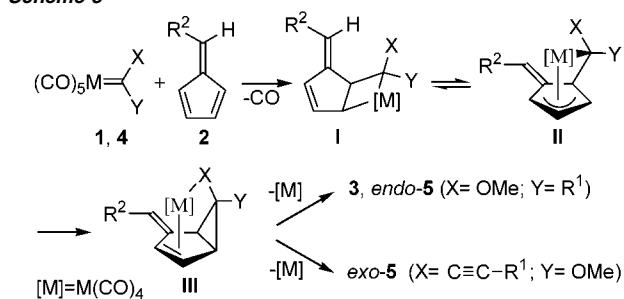
C=C and X groups, thus dictating the *endo* orientation of the X group in the final cyclopropane ring. Therefore, the formation of *endo*-**3** and *endo*-**5** implies a metal−OMe coordination whereas the coordination of metal to the alkynyl function would be responsible for the presence of *exo*-**5**.

Accordingly, the cyclopropanation reaction was inhibited in the presence of CO, and the [4 + 3] cyclization of alkynylcarbene complexes **4** could be brought about (Scheme 4). The heptannulation was best effected by heating at 60 °C a hexane or DMF

Scheme 4 [a]

[W]=W(CO)$_5$

[a] (i) Solvent, 60°C, CO (20 bar), 6h; (ii) SiO$_2$.

Entry	R^1	R^2	R^3	Solvent	% [a]	E,Z [b]
a	Ph	Me	Me	DMF	88	-
b	Ph	pMeOPh	H	hexane	75	2:1
c	Ph	t-Bu	H	hexane	65	3:1
d	Ph	AcO	H	hexane	70	2:1
e	1-cyclo hexenyl	Me	Me	DMF	50	-

The header spans: **6** covering % [a] and E,Z [b].

[a] Isolated yields. [b] E,Z ratio determined by ^{1}H NMR (300 MHz) of the crude mixture.

Scheme 5 [a]
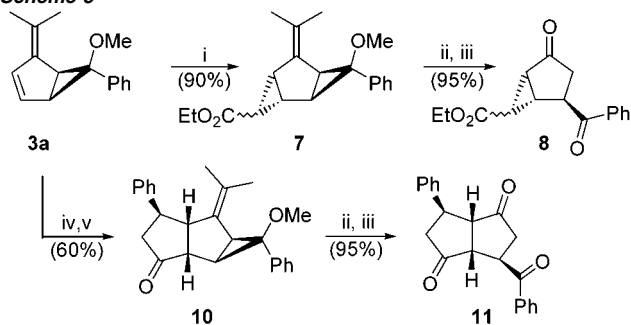
[a] (i) N$_2$CHCO$_2$Et, Rh$_2$(OAc)$_4$ (0.1 mol%), CH$_2$Cl$_2$, 25 °C, 2 h; (ii) 1. O$_3$, MeOH-CH$_2$Cl$_2$, −78 °C. 2. Me$_2$S; (iii) concentrated HCl (drops), Me$_2$CO, 25 °C; (iv) (CO)$_5$Cr=C(OMe)(CH=CHPh) **9**, THF, 100 °C, 12 h; (v) 1. Aqueous 2 N HCl, CH$_2$Cl$_2$, 25 °C. 2. Chromatographic separation.

solution of tungsten carbenes **4** and fulvenes **2** under CO pressure (20 bar).[11] In this way, the W(CO)$_6$ could be quantitatively recovered, and bicyclo[3.2.1]octadien-2-ones **6** were obtained in satisfactory yields (50−88%) after purification by column chromatography (SiO$_2$; hexanes/EtOAc, 5:1).[12] The formation of **6** very likely involves two key steps, (i) 1,2-addition of fulvene to the metal−carbene function to generate the intermediate **IV** and (ii) regioselective cyclization promoted by 1,2-[W(CO)$_5$] shift, according to a well-established pathway.[13]

Finally, in Scheme 5 are depicted two examples which are intended to anticipate that the fulvene−metal carbene combination might be useful to access more elaborated cyclopentane frameworks. The homofulvene **3a** undergoes a second cyclopropanation with ethyl diazoacetate/Rh$_2$(OAc)$_4$ to produce in very high yield **7** as a 4:1 mixture of epimers. Compound **7** was readily transformed into the elaborated cyclopentanone **8** (95% yield) by ozonolysis and acid hydrolysis. Moreover, **3a** reacted with the alkenylcarbene **9** (THF, sealed tube, 100 °C, 12 h) to furnish, after acid hydrolysis and column chromatography separation, the cyclopentannulation adduct **10** in 60% yield, as the major stereoisomer.[14,15] Further ozonolysis and hydrolysis of **10** led to the functionalized diquinane **11** (95% yield). The overall processes illustrate the use of 6,6-dimethylfulvene as a substitute for the elusive cyclopentadienone.
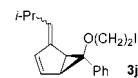
In conclusion, the first cyclopropanation and cycloheptannulation reactions of alkyl-, aryl-, and acetoxyfulvenes with transition-metal−carbene complexes are reported. Unlike previous cyclopropanation reactions of dienes with simple Fischer carbene complexes, the process shown here displays complete diastereoselectivity.[7] This strategy makes mono- and bis-annulated cyclopentanones readily accessible. Further work directed to study the scope of this reaction, particularly the usefulness of the fulvene system as a masked cyclopentadienone, is in progress.[16]

Supporting Information Available: Experimental procedures and characterization data for the new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Neuenschwander, M. In *The Chemistry of Double-Bonded Functional Groups*, Suppl. A; Patai, S., Ed.; J. Wiley & Sons, Ltd: Chichester, 1989; Vol. 2, pp 1131−1286.

(2) (a) Ogliaruso, M. A.; Romanelli, M. G.; Becker, E. I. *Chem. Rev.* **1965**, *65*, 261. (b) DePuy, C. H.; Isaks, M.; Eilers, K. L.; Morris, G. F. *J. Org. Chem.* **1964**, *29*, 3503.

(3) For an excellent review on the use of 4-acetoxy-2-cyclopenten-1-one as a substitute for cyclopentadienone, see: Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480.

(4) For cyclopropanation with transition-metal−carbene complexes, see: Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411.

(5) We have reported recently the [6 + 3] cyclization of chromium alkenyl carbene complexes and fulvenes. See: Barluenga, J.; Martínez, S.; Suárez-Sobrino, A. L.; Tomás M. *J. Am. Chem. Soc.* **2001**, *123*, 11113.

(6) (a) For cyclopropanation with dichloro- and dimethoxycarbenes, see: Moss, R. A.; Young, C. M.; Pérez, L. A.; Krogh-Jespersen, K. *J. Am. Chem. Soc.* **1981**, *103*, 2413. (b) For CuCl-catalyzed cyclopropanation with ethyl diazoacetate, see: Decock-le Reverend, B.; Durand, M.; Merenyi, R. *Bull. Soc. Chim. Fr.* **1978**, 369.

(7) High levels of diastereoselectivity have been reported for 1,3-dienes. See: (a) Harvey, D. F.; Lund, K. P. *J. Am. Chem. Soc.* **1991**, *113*, 8916. (b) Buchert, M.; Reissig, H.-U. *Chem. Ber.* **1992**, *125*, 2723.

(8) Cyclopropanes with a removable *O*-substituent, e.g., **3j** (80%, *E/Z* = 5:1), are thus available (for a precedent, see: Barluenga, J.; López, S.; Trabanco, A. A.; Flórez, J. *Chem. Eur. J.* **2001**, *7*, 4723).

(9) (a) In a recent paper Aumann et al. provided strong evidence for the cyclopropanation with this type of complex. See: Wu, H.-P.; Aumann, R.; Fröhlich, Saarenketo, P. *Chem. Eur. J.* **2001**, *7*, 700. (b) The cyclopropanation with alkynyldiazoacetates/rhodium(II) has been reported. See: Davies, H. M. L.; Boebel, T. A. *Tetrahedron Lett.* **2000**, *41*, 8189.

(10) This mechanism was later applied by Reissig for electron-deficient 1,3-dienes. See: (a) Buchert, M.; Hoffmann, M.; Reissig, H.-U. *Chem. Ber.* **1995**, *128*, 605. (b) Hoffmann, M.; Reissig, H.-U. *Synlett* **1995**, 625.

(11) In the case of chromium carbene complexes the [4 + 3] adduct is formed along with variable amounts of the corresponding cyclopropane.

(12) The [4 + 3] cycloaddition of fulvenes with oxyallyl cations leading to a different regioisomer, bicyclo[3.2.1]octadien-3-ones, has been reported and suffers from serious limitations to generate the three-carbon reagent. See: (a) Rawson, D. I.; Carpenter, B. K.; Hoffmann, H. M. R. *J. Am. Chem. Soc.* **1979**, *101*, 1786. (b) Noyori, R.; Hayakawa, Y. *Org. React.* **1983**, *29*, 163.

(13) Barluenga, J. *Pure Appl. Chem.* **1999**, *71*, 1385.

(14) The iterative cyclopropanation of **3a** with carbene complexes of type **1** failed because of the rigid *s-trans* conformation of the diene system of **3** (ref 7a). Therefore, the protocol for unactivated alkenes already described was followed, see: Barluenga, J.; López, S.; Trabanco, A. A.; Fernández-Acebes, A.; Flórez, J. *J. Am. Chem. Soc.* **2000**, *122*, 8145.

(15) The epimer of **10** wherein the Ph group is placed in an *endo* orientation was also formed in about 10% yield and separated.

(16) The structural characterization of **3**, **5**−**8**, **10**, **11** was based on the NMR data (HMQC, HMBC, and NOESY experiments). All compounds gave satisfactory elemental analyses and HRMS data.

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