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New Cascade Processes on Group 6 Fischer-Type Carbene Complexes: Cyclopropanation and Metathesis Reactions

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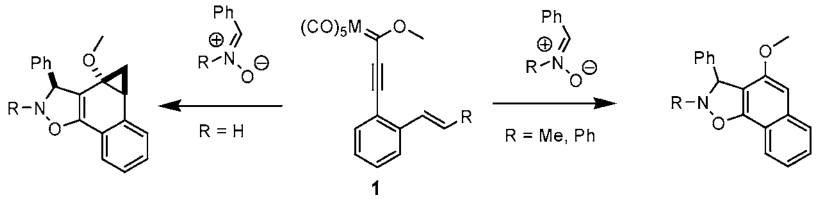
ABSTRACT



Alkynyl Fischer carbene complexes 1, which feature a pendant olefin group, undergo novel cascade processes triggered by [2+2], [3+2], and [4+2] cycloadditions. Competition between cyclopropanation and olefin metathesis is controlled by the substitution at the double bond. The method described can be used to obtain different kind of polycarbo- and -heterocycles. A mechanistic explanation by means of DFT computational modeling is provided.

Chromium and tungsten Fischer carbene complexes are versatile and useful reagents in organic synthesis.[1] An attractive feature of their reactivity is the ability to generate molecules with a high degree of complexity from readily available starting materials through cascade and multicomponent reactions.[2] A particularly interesting type of Fischer carbene complexes are 1-metalla-1,3,5-hexatrienes **I**. For many years, we have been studying the chemistry of these systems, and have shown that, depending on the nature of the C═C double bonds, they can evolve following different reaction pathways, usually through cascades of elementary reactions.[3]

In this context, en−yne derived Ficher carbene complexes **II** are very convenient precursors to the 1-metalla-1,3,5-hexatrienes **I** by means of different types of cycloaddition processes (Figure 1). Depending on the particular cycloaddition reaction applied, [4+2] Diels−Alder reactions,[3f] [3+2] dipolar cycloadditions,[3a,b] and [2+2] cycloadditions,[3e,f,g] several different tandem processes can be triggered.

Taking into account the interesting and diverse reactivity of the carbenes mentioned before, we decided to investigate

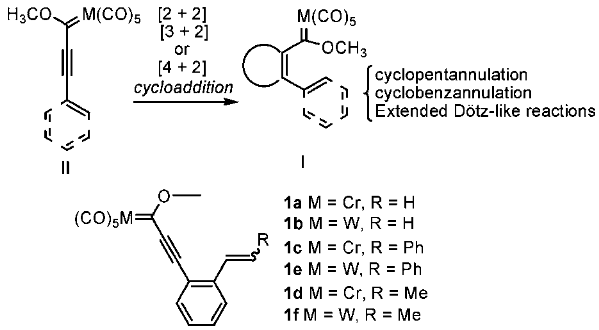


Figure 1. Fischer carbenes **I** and **II**, typical substrates for cascade cyclizations, and the en−yne metal carbenes **1** employed in this study.

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[1] For a revision, see: *Metal Carbenes in Organic Synthesis*; Doöt, K. H., Ed.; Springer-Verlag: Heidelberg, Germany, 2004.

[2] For a review see: Barluenga, J.; Fernández-Rodríguez, M.; Aguilar, E. *J. Organomet. Chem.* **2005**, 539.

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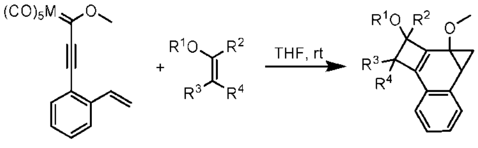
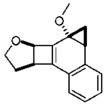
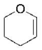
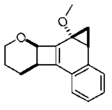
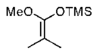
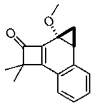
a new type of Fischer carbene complexes featuring an extra double bond in the carbon chain, in the expectation that it might lead to the discovery of new types of cascade processes. We envisioned that carbenes **1** (Figure 1) could serve as precursors of 1-metalla-1,3,5,7-tetraenes, upon typical cycloaddition reactions. Therefore, we set out to investigate their behavior in [2+2], [3+2], and [4+2] cycloaddition reactions.

The required Fischer carbene complexes **1** were synthesized from the corresponding terminal alkynes through the conventional methods (see the Supporting Information for details). At first, we employed the carbene complexes **1a** and **1b**, in an attempt to verify whether a possible, and predictable, tandem cycloaddition/cyclopropanation process might occur. Indeed, when typical procedures for [2+2] cycloadditions with alkynyl carbene complexes were used,[4] homonaphthalenes **3a**−**d** were formed in a diastereoselective way and were isolated with excellent yields (Table 1).

Table 1. Synthesis of Homonaphthalenes **3**



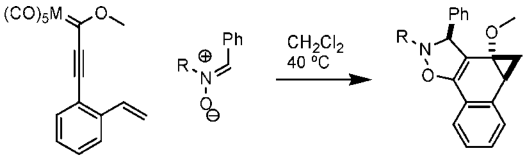
1a-b **2** **3**

entry	M	2	3	yield %[a]
1	Cr			90
2	W[b]	**2a**	**3a**	73
3	Cr			57[c]
4	W[b]	**2b**	**3b**	61
5	Cr			81[d]
6	W[b]	**2c**	**3c**	73[d]

[a] Isolated yield based on the starting carbene complex. [b] Reactions with the W carbenes were carried out at 40 °C. [c] 80% conversion. [d] After hydrolysis of the reaction crude.

Following a similar protocol, [3+2] cycloadditions with nitrones **4** were used as initiator reactions.[5] In this case, benzoisoxazola derivatives **5** were obtained with very good yield.

Table 2. Synthesis of Isooxazoles **5**



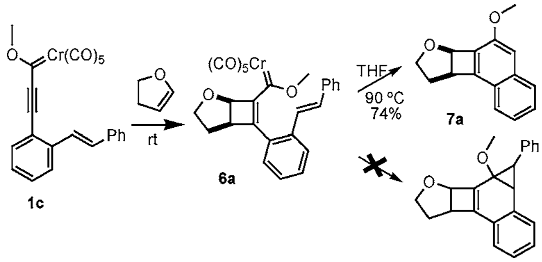
1a-b **4** **5**

compd	M	R	yield,[a] %
5a	Cr	*t*-Bu	82
5b	Cr	Bn	73
5a	W	*t*-Bu	57[c]
5b	W[b]	Bn	61

[a] Isolated yield based on the starting carbene complex.

At this point we decided to evaluate the scope of the reaction by introducing a substituent on the terminal olefin. When the complex **1c** was stirred with 3 equiv of 2,3-dihydrofuran **2a** at room temperature the anticipated [2+2] cycloadduct **4a** was obtained (Scheme 1). Subsequent heating of the cyclobutene carbene (**6a**) in a sealed tube for 2 h triggered the formation of naphthalene **7a** instead of the expected cyclopropanation product. Formation of naphthalene **7a** could be explained by a metathesis reaction, a type of process that has been scarcely observed in Fischer carbene chemistry.[6]

Scheme 1. Cycloaddition/Metathesis Sequence on Complex **1b**



This reaction was generalized by using several enol ethers, chromium and tungsten carbene complexes, and different substitution in the olefin (R = Ph, Me) (Table 3, entries 1−12). In all cases the naphthalene derivatives **5** were isolated in good yields. Identical results were obtained when *Z* or *E* olefin configurations were investigated.

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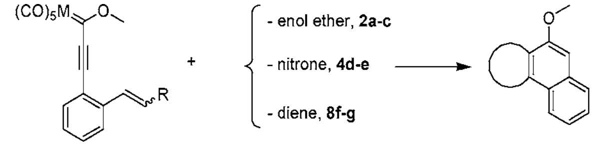
(3) (a) Barluenga, J.; Aznar, F.; Palomero, M. A.; Barluenga, S. *Org. Lett.* **1999**, *1*, 541. (b) Barluenga, J.; Aznar, F.; Palomero, M. A. *Chem. Eur. J.* **2002**, *8*, 4149. (c) Barluenga, J.; Fernández-Rodríguez, M. A.; Aguilar, E.; Fernández-Marí, F.; Salinas, A.; Olano, B. *Chem. Eur. J.* **2001**, *7*, 3533. Corrigendum: *Chem. Eur. J.* **2001**, *7*, 4323. (d) Merino, I.; Laxmi, Y. R. S.; Flórez, J.; Barluenga, J.; Ezquerra, J.; Pedregal, C. *J. Org. Chem.* **2002**, *67*, 648. (e) Barluenga, J.; Aznar, F.; Palomero, M. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4346. (f) Barluenga, J.; Aznar, F.; Barluenga, S.; Fernández, M.; Martín, A.; García-Granda, S.; Piñera-Nicolás, A. *Chem. Eur. J.* **1998**, *4*, 2280. (g) Barluenga, J.; Fañanás-Mastral, M.; Palomero, M. A.; Aznar, F.; Valdés, C. *Chem. Eur. J.* **2007**, DOI: 10.1002/chem.200700413.

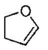
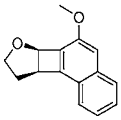
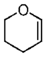
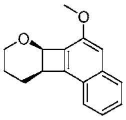
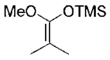
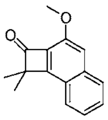
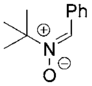
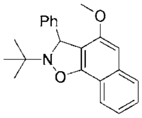
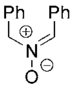
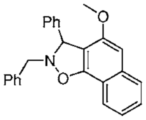
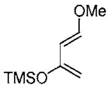
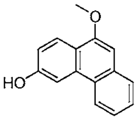
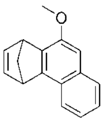
(4) (a) Faron, K. L.; Wulff, W. D. *J. Am. Chem. Soc.* **1988**, *110*, 8727. (b) Wulff, W. D.; Faron, K. L.; Su, J.; Springer, J. P.; Rheingold, A. L. *J. Chem. Soc., Perkin Trans. I* **1999**, 197. (c) Wu, H-p.; Aumann, R.; Fröhlich, R.; Wibbeling, B. *Eur. J. Org. Chem.* **2000**, 1183. (d) Semmelhack, M. F.; Tomada, S.; Nagaoka, H.; Boettger, S. D.; Jurst, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 747. (e) Miesch, M.; Wendling, F.; Frank-Neumann, M. *Tetrahedron Lett.* **1990**, *40*, 839. (f) Gollnick, K.; Fries, S. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 832.

(5) (a) Kreissl, F. R.; Fischer, E. O.; Kreiter, C. G. *J. Organomet. Chem.* **1973**, *57*, C9. (b) Chan, K. S.; Wulff, W. D. *J. Am. Chem. Soc.* **1986**, *108*, 5229. (c) Barluenga, J.; Aznar, F.; Palomero, M. A. *Chem. Eur. J.* **2001**, *7*, 5318. (d) Chan, K. S.; Yeung, M. L.; Li, W. K.; Liu, H. K.; Wang, Y. *J. Org. Chem.* **1998**, *63* 7670. (e) Chan, K. S.; Yeung, M. L.; Chan, W. K.; Wang, R. J.; Mak, T. C. W. *J. Org. Chem.* **1995**, *60*, 1741. (f) Merlic, C. A.; Baur, A.; Aldrich, C. C. *J. Am. Chem. Soc.* **2000**, *122*, 7398.

Table 3. Synthesis of Naphthalene Derivatives through Metathesis of Fischer Carbene Complexes



1c - f **7**

entry	M	R	2, 4 or 8	7	yield (%)[a]
1	Cr	Me	 **2a**	 **7a**	74
2	Cr	Ph			76
3	W	Me			52
4	W	Ph			59
5	Cr	Me	 **2b**	 **7b**	58[b]
6	Cr	Ph			55[c]
7	W	Me			59
8	W	Ph			57
9	Cr	Me	 **2c**	 **7c**	57[d]
10	Cr	Ph			61[d]
11	W	Me			63[d]
12	W	Ph			60[d]
13	Cr	Me	 **4a**	 **7d**[e]	81
14	Cr	Ph			75
15	W	Me			68
16	W	Ph			66
17	Cr	Me	 **4b**	 **7e**	71
18	Cr	Ph			70
19	W	Me			63
20	W	Ph			65
21	W	Me	 **8a**	 **7f**	52
22	W	Ph			53
23	W	Me	 **8b**	 **7g**	65
24	W	Ph			62

[a] Isolated yield based on the starting carbene complex. [b] 78% conversion in the cycloaddition reaction. [c] 68% conversion in the cycloaddition reaction. [d] After hydrolysis of the reaction crude. [e] Structure confirmed by X-ray diffraction.

The metathesis reaction can also be initiated by [3+2] and [4+2] cycloadditions. Thus, when carbenes **1a**–**d** were stirred in the presence of 2 equiv of nitrones **4** at rt, the corresponding intermediate cycloadducts were detected. Subsequent heating for 2 h provided, finally, the naphthoisoxazola derivatives **5d**,**e** in good yields (entries 13–20). A similar reaction protocol was used with cyclopentadiene and Danishefsky's diene. Again, the final products were the phenanthrene derivatives (**8f**, **8g**) coming from a cycloaddition/metathesis process (entries 21–24).

Computational and Mechanistic Considerations. To gather some insight into the mechanisms of these processes that might explain the different behavior of carbenes featuring terminal or disubstituted olefins, we carried out computational DFT calculations for the tungsten series starting from the model systems **A** (**A1**, R = H; **A2**, R = Me; and **A3**, R = Ph) that feature the conformational restrictions imposed by a four-membered ring.[7−9]

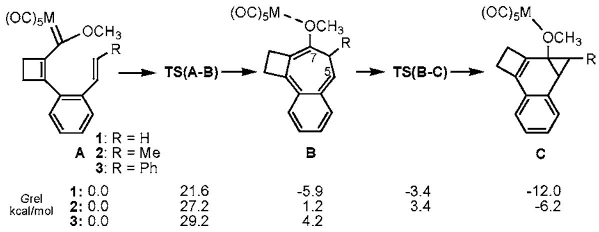


Figure 2. Calculated reaction pathway for the cyclopropanation.

According to our calculations, the formation of cyclopropane **C** occurs through two consecutive electrocyclic processes from the tungsten pentacarbonyl complex **A**.

In a first step, cycloheptatriene **B** is formed through an 8π-electrocyclization with participation of the carbene carbon and release of the metal fragment, which remains complexed to the methoxy group. Then, a 6π-electrocyclization takes place to produce the homonaphthalene **C**. The first step was found to be rate limiting, while the formation of the cyclopropane features a very low-energy barrier as a result of the proximity of C5 and C7 in the intermediate **B**, and the recovery of the aromaticity of the benzene ring.

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(6) Some representative examples of metathesis processes of Fischer carbene complexes with electron-rich olefins: (a) Fischer, E. O.; Dötz, K. H. *Chem. Ber.* **1972**, *105*, 3966. (b) Dorrer, B.; Fischer, E. O.; Kalbfus, W. *J. Organomet. Chem.* **1974**, *81*, C20. (c) Murray, C. K.; Yang, D. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1990**, *112*, 5660. (d) Barluenga, J.; Aznar, F.; Martín, A. *Organometallics* **1995**, *14*, 1429. (e) For details of strained olefin metathesis see: Katz, T. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3010 and references therein.

(7) Calculations were carried out with the Gaussian03 package of programs (see the Supporting Information for the complete reference).

(8) Geometry optimizations were carried out employing the LANL2DZ ECP for W and Cr and the 6-31G(d) basis set for the rest of the atoms. Single point energy calculations at the stationary points were carried out employing the 6-311++G** basis set for the light elements and again the LANL2DZ basis set for the metals. Solvation free energy was calculated employing the SRCF PCM model. See the Supporting Information for further details.

(9) For some selected examples on DFT calculations on group 6 Fischer carbene complexes see: (a) Gleichmann, M. M.; Dötz, K. H.; Hess, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10551. (b) Cases, M.; Frenking, G.; Durán, M.; Solá, M. *Organometallics* **2002**, *21*, 4182. (c) Fernández, I.; Cossío, F. P.; Arrieta, A.; Lecea, B.; Mancheño, M. J.; Sierra, M. A. *Organometallics* **2004**, *23*, 1065. (d) Fernández, I.; Sierra, M. A.; Mancheño, M. J.; Gómez-Gallego, M.; Cossío, F. P. *Chem.-Eur. J.* **2005**, *11*, 5988. (e) Fernández, I.; Cossío, F. P.; Sierra, M. A. *Organometallics* **2007**, *26*, 3010 and references cited therein.

The activation free energy for the rate-limiting step is greatly influenced by the size of the substituent of the double bond. For **A1**, which features a terminal double bond, the activation free energy was determined to reach 21.5 kcal·mol^{-1}, a reasonable barrier for a rt or moderate temperature process. For the methyl-substituted system **A2** we obtained a higher activation barrier of 27.2 kcal·mol^{-1}, while for **A3**, which features a bulkier phenyl substituent, an even higher barrier of 29.2 kcal·mol^{-1} was calculated. The destabilization of **TS(A2-B2)** and **TS(A3-B3)** when compared with **TS(A1-B1)** can be understood considering the steric interaction between the substituent of the olefin and the CO ligands of the metal. Thus, the transformation of **A2** into **B2** and **A3** into **B3** features high free energy barriers and is unlikely to take place at room temperature. In fact, complexes of types **A2** and **A3** are stable and can be isolated.

Naphthalene **F** must be formed through a ring-closing metathesis reaction. For this process to occur, dissociation of a carbonyl ligand to form tetracarbonyl complex **D** is necessary. Then, complex **D** must undergo a conformational interconversion (not calculated) to the more stable complex **E**, in which the olefin occupies the vacant coordination site at the metal. Finally, tetracarbonyl complex **E** suffers the metathesis reaction to produce directly the naphthalene derivative **F** and release the metal carbene **G**. Noteworthy, the metallacyclobutene **TS(E-F)** was identified as a transition state and not an intermediate in the metathesis reaction.[10] The elementary step features a relatively high activation energy of 25 kcal·mol^{-1}. On the other hand, the overall process is very exergonic, due to the formation of an aromatic naphthalene derivative.

Under the experimental conditions, the dissociation of the CO ligand can be regarded as an irreversible process, because the released CO ligand leaves the solution and is no longer available to revert to the pentacarbonyl complex. Therefore, the different reactivity of **A1** when compared with **A2** and **A3** relies on the different activation free energy of the electrocyclization to form **B** when compared with the dissociation of a CO ligand to give **D**.[11] At rt, the substituted **A2** and **A3** systems do not evolve, due to the high-energy barrier required to undergo cyclization or dissociation of a CO ligand. At higher temperature, CO dissociation occurs preferentially, leading ultimately to the metathesis product, naphthalene **F**.

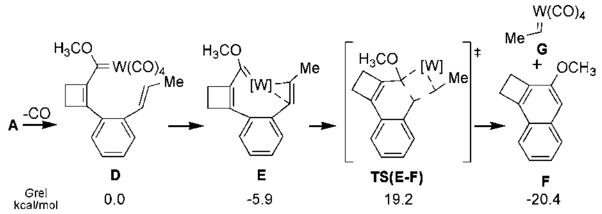

Figure 3. Calculated reaction pathway for the metathesis.

Thus, the computational modeling proposes a two-step cyclopropanation reaction, which features a novel cycloheptaannulation as the rate determining step for the formation of the homonaphthalenes from terminal olefins. This process is disfavored with substituted olefins, due to the steric interactions between the metal pentacarbonyl moiety and the substituent of the olefin. Then the CO dissociation must be favored, triggering the metathesis process, which gives rise to the naphthalenes.

In summary, we have presented two new types of cascade processes with alkynyl Fischer carbene complexes, triggered by cycloaddition reactions. These reactions led to molecules with high structural complexity from readily available starting materials in one single operation, and showed once again the ability of Fischer carbene complexes to participate in cascade reactions.

Acknowledgment. Financial support of this work by the DGI and a FPU predoctoral fellowship for F.A. are gratefully acknowledged. We wish to thank Dr. Dimas Suárez (Universidad de Oviedo) for helpful discussions regarding the computational calculations.

Supporting Information Available: Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for compounds **1**, **3**, **5**, and **7**, computational details, energy tables, Cartesian coordinates, and 3D models for all the calculated species. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] Similar results have been previously reported for metathesis reactions of simpler tungsten carbene complexes: Tlenkopatchev, M.; Fomine, S. *J. Organomet. Chem.* **2001**, *630*, 157.

[11] We obtained a value of 33 kcal·mol^{-1} for the bond dissociation potential energy for the CO ligand. However, to determine the activation free energy of the CO dissociation in solution is not straightforward, due to the overestimation of the entropic contributions in ligand dissociation reactions. See: Sumimoto, M.; Iwane, N.; Takahama, T.; Sakaki, S. *J. Am. Chem. Soc.* **2004**, *126*, 10457. For this reason, a free energy comparison between both reaction pathways has not been attempted. See the Supporting Information for further details.