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Unexpected Thermal Benzannulation of 1,3,5-Metallahexatrienes: Synthesis of *o*-Alkoxyphenol-Containing Polycycles

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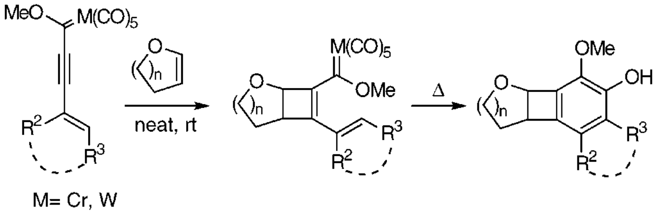
ABSTRACT



A new synthesis of *o*-methoxyphenol-containing polycyclic systems is described. Cyclobutene-containing 1,3,5-metallahexatrienes, obtained by [2 + 2] cycloaddition of cyclic enol ethers and chromium or tungsten alkynyl carbene complexes, undergo unexpected thermal benzannulation to provide access to a wide range of *o*-methoxy-substituted aromatic alcohols.

Fischer carbene complexes are useful starting materials for the preparation of different size ring systems.[1] Thus, in recent years, there has been a large number of publications showing the wide range of both monocyclic and polycyclic compounds prepared using these complexes. Among the reactions of Fischer carbene complexes, the benzannulation reaction, first described by Dötz in 1975,[2] has become the most studied and important reaction, showing many applications in synthetic organic chemistry.[1a,b,e,f] On the basis of the cycloaddition of an alkyne to a carbene complex, this reaction enables the synthesis of *p*-alkoxyphenol derivatives and also cyclopentadienes as side products, both in a regioselective fashion. These six- or five-membered rings are formed when the intermediate metallatriene undergoes a CO insertion or a direct cyclization, respectively. Metallatrienes obtained by other routes show a similar reaction pattern, affording in most cases five-membered rings.[3]

We have recently reported that 2-amino-1,3-butadienes react with α,*β*-acetylenic carbene complexes of group VI (especially chromium and tungsten) to afford different kinds of polycyclic systems.[4] In the particular case when vinyl-substituted alkynyl carbene complexes are used, the initially formed 1,3,5-metalatriene **3** undergoes a cascade double or triple tandem ([4 + 2] cycloaddition−cyclopentannulation) process to afford polycycles **4a** or **4b**, in which six or nine C−C bonds and five or seven stereogenic centers, respectively, have been created (Scheme 1).

Encouraged by these results, we decided to expand the applicability of this process by using other different metallatriene systems to study its scope and synthetic possibilities. The propensity of alkyl, silyl, and phenyl acetylenic carbene complexes to participate in [2 + 2] cycloaddition reactions with enol and silyl enol ethers,[5] to afford cyclobutenyl derivatives, has been previously described in the literature. We envisioned that the application of this methodology by using vinyl-substituted alkynyl carbenes would lead to the kind of metallatrienes we wanted to study.

Herein we report the preliminary results of the studies directed toward the synthesis of nonaromatic metallatrienes bearing a cyclobutene ring and the subsequent synthesis of polycycles containing *o*-methoxy-substituted phenols, which is achieved by thermal cyclization of the former substrates.

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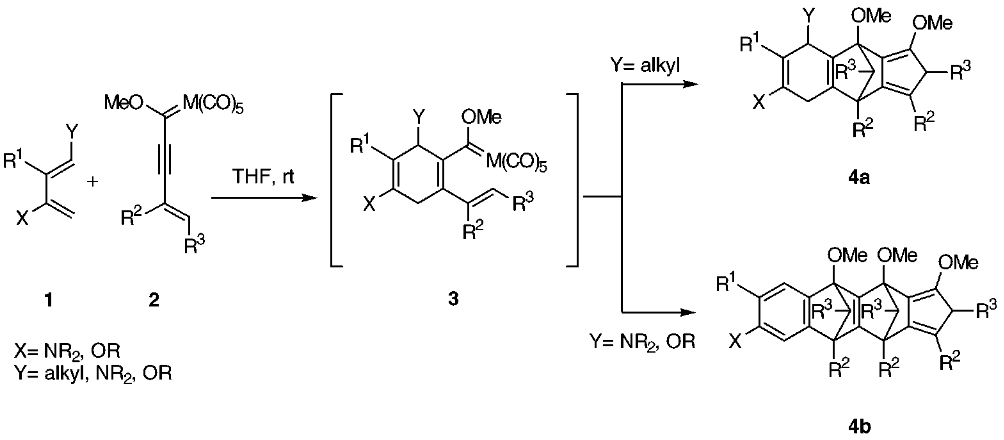
Scheme 1



The [2 + 2] cycloaddition reaction between cyclic enol ethers **5** and chromium or tungsten carbene complexes **2** was performed at room temperature under a nitrogen atmosphere using 10 equiv of **5** as solvent (Scheme 2). As indicated in Table 1, moderate to good yields of cycloadducts **6** were obtained, especially when 2,3-dihydrofuran was used (entries b and c). These compounds were isolated, in most of the cases, as stable solids at room temperature after column chromatography.[6] Reaction times were typically long, being significantly longer for six-membered-ring enol ethers (entries e−j). The stereoselectivity in the formation of the fused cycles was determined to be *cis* by NOE experiments of compound **6h**.

Scheme 2

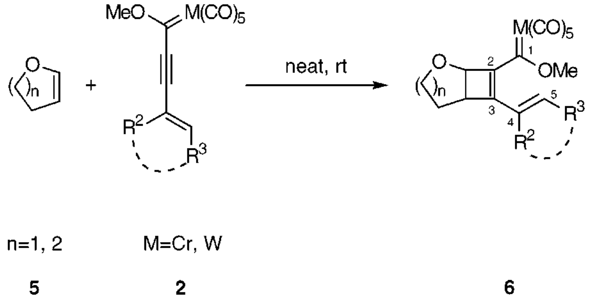
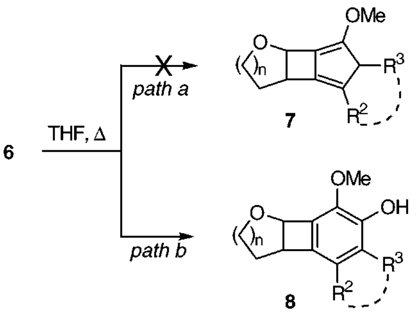


Table 1. [2 + 2] Cycloadditions To Yield Cyclobutenyl Complexes **6**

entry	*n*	M	R^2	R^3	*t*	% yield
a	1	W	Me	Ph	3 d	64
b	1	W	$-CH_2CH_2CH_2-$		12 h	85
c	1	Cr	$-CH_2CH_2CH_2-$		4 h	93
d	1	Cr	$-CH_2CH_2CH_2CH_2-$		12 h	58
e	2	W	Me	H	5 h	79
f	2	Cr	Me	Ph	5 d	40
g	2	Cr	H	Ph	6 d	45
h	2	W	$-CH_2CH_2CH_2-$		4 d	53
i	2	Cr	$-CH_2CH_2CH_2-$		6 d	75
j	2	Cr	$-CH_2CH_2CH_2CH_2-$		3 d	40
k	2	Cr	Me	$-CH_2OAll$	2 d	79

Scheme 3



Given that the aim of our project was the synthesis of cyclopentanulated derivatives from metallatrienes, and since the new metallatrienes were unreactive at room temperature, we decided to promote their reactivity by increasing the temperature. However, the heating of a solution of **6** in THF under reflux did not give the expected products **7** (Scheme 3, path a), derived from a cyclopentannulation process, but rather the *o*-methoxyphenols **8** (Scheme 3, path b) (Table 2). Their formation involves a CO insertion followed by cyclization, which can be assumed to be a variation of the Dötz reaction, in which *o*-hydroquinones are obtained instead

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(1) For reviews on the synthetic applications of Fischer carbene complexes, see: (a) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 587. (b) Wulff, W. D. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol. 12, p 469. (c) Hegedus, L. S. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol. 12, p 549. (d) Doyle M. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon Press: New York, 1995; Vol. 12, p 387. (e) Harvey, D. F.; Sigano. D. M. *Chem. Rev.* **1996**, *96*, 271. (f) Zaragoza Dörwald, F. *Metal Carbenes in Organic Synthesis*; Wiley-VCH: 1999.

(2) Dötz, K. H. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 644.

(3) Aumann, R.; Nienaber, H. *Adv. Organomet. Chem.* **1997**, *41*, 163.

Table 2. Synthesis of Polycyclic Systems **8**

entry	complex	t[a] (h)	% yield of **8**[a]
a	**6a**	12	89
b	**6b**	9	77[b]
c	**6c**	4	56[b]
d	**6d**	6	46
e	**6e**	9	79
f	**6f**	12	60
g	**6g**	7 (12)	56 (32)
h	**6h**	9 (20)	59 (58)[c]
i	**6i**	8 (12)	72 (26)[c]
j	**6j**	9 (12)	69 (44)
k	**6k**	3	77

[a] Data in parentheses correspond to reactions carried out without N_2 purge. [b] **8b** and **8c** are the same compound. [c] **8h** and **8i** are the same compound.

of the usual *p*-hydroquinone derivatives. This result is certainly surprising since, as far as we know, thermal benzannulation reactions of alkoxy metallatrienes have not been described before.[7] A possible explanation for the different behavior observed between metallatrienes **3** and **6** could be rationalized in terms of their geometries. We have proposed that the cyclopentannulation of compounds **3** takes place through an initial nucleophilic attack of the terminal double bond to the carbene carbon atom (Scheme 1).[4] In the case of metallatrienes **6**, however, this interaction is not likely to occur since the distance between carbons C_1 and C_5 is considerably longer than that for systems **3**.[8] Moreover, that fact could justify the stability of the metallatrienes **6** at room temperature and, also, the formation of the more favored six-membered rings upon thermal treatment of **6**. It is worth pointing out that a similar photochemically driven process, leading to analogous phenol derivatives, has been reported previously.[9] However, in those examples all the substrates employed bore, at least, one aromatic double bond in the metallatriene backbone. The thermal reaction was also tested, but a complex mixture of products was usually obtained.

A range of solvents can be used in the benzannulation reaction, although the best results were obtained in THF. Interestingly, when complexes **6** were heated under a purge of nitrogen, shorter reaction times were needed, providing better yields of phenols **8** (Table 2, entries g−j). We believe that the nitrogen purge facilitates the formation of a tetracarbonyl species by the elimination of CO. Otherwise, when the same reactions were carried out under a CO atmosphere, the initial carbene complex was recovered unaltered. These results support the idea that the key step of the reaction is the release of a CO ligand in the metallatriene **6**, followed by CO insertion (in the intermediate tetracarbonyl complex) and electrocyclic closure of the resulting dienyl ketene. The benzannulation process takes place under mild conditions, in reasonable reaction times, and with moderate to good yields. These results, as well as the broad range of possibilities of substitution in the substrate, indicate that this process is a good method for synthesis of polycycles **8**.[10]

Furthermore, both processes, [2 + 2] cycloaddition and benzannulation, can be carried out without purification of the metallatriene **6**. For instance, compound **8i** was synthesized in a 48% overall yield by simple removal of the excess of enol ether, once the cycloadduct **6i** was formed, followed by addition of THF and heating.[11]

In conclusion, we have reported the synthesis of novel cyclobutene-containing 1,3,5-metallahexatrienes. These systems undergo thermal benzannulation instead of the expected cyclopentannulation reaction, providing a good method for producing polycyclic systems **8**, which contain an *o*-methoxyphenol moiety in their structure. This is, as far as we know, the first time that such thermal behavior has been observed in pentacarbonyl alkoxy 1,3,5-metallahexatrienes.

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

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(6) Compounds **6** were prepared according to literature procedures.[5a] Selected data for **6c**: mp = 89−91 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.72−2.03 (m, 4H), 2.19−2.49 (m, 4H), 3.40 (dd, $J = 7.9, 3.3$ Hz, 1H), 3.75−3.91 (m, 1H), 4.13 (t, $J = 8.2$ Hz, 1H), 4.73 (s, 3H), 5.61 (d, $J = 3.3$ Hz, 1H), 6.37 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.6 (CH_2), 27.1 (CH_2), 33.1 (CH_2), 33.2 (CH_2), 44.1 (CH), 65.5 (CH_3), 66.5 (CH_2), 80.1 (CH), 136.9 (C), 138.4 (C), 142.9 (CH), 146.1 (C), 216.2 (C), 223.8 (C), 334.3 (C); IR (CH_2Cl_2) $\nu = 2057, 1942\ cm^{-1}$. Anal. Calcd for $C_{18}H_{16}CrO_7$: C, 54.54; H, 4.07. Found: C, 59.48; H, 4.18.

(7) A thermal benzannulation of a 1,4,5-η^3-dienylcarbene to yield phenols has been observed: Barluenga, J.; Aznar, F.; Gutiérrez, I.; Martín, A.; García-Granda, S.; Llorca-Baragaño, M. A., submitted for publication.

(8) Simple molecular mechanics modeling showed that the difference between the distances C_1-C_5 in metallatrienes **3** and **6** is about 0.7 Å (molecular mechanics calculations were carried out using the MM2 force field; data for the pentacarbonyl chromium carbene moiety were taken from an X-ray structure of a similar compound and kept fixed along the minimization).

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(10) **General Procedure for the Preparation of Polycycles 8.** A solution of complex **6c** (0.20 g, 0.5 mmol) in THF (25 mL) was refluxed under a nitrogen purge. The reaction was stopped when TLC revealed total comsumption of the starting material; the solution was then diluted with 50 mL of hexane and exposed to sunlight and air for 12 h. Purification by flash chromatoghaphy with hexane:ether:dichloromethane (6:1:1) afforded **8c** (89 mg, 77%) as a white solid: mp = 155−157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 1.70−1.88 (m, 2H), 2.09 (hept, $J = 7.2$ Hz, 2H), 2.71 (t, $J = 7.2$ Hz, 2H), 2.83 (t, $J = 7.2$ Hz, 2H), 3.63−3.70 (m, 1H), 3.93 (dd, $J = 7.8, 3.6$ Hz, 1H), 4.01 (s, 3H), 4.10 (t, $J = 8.0$ Hz, 1H), 5.44 (s, 1H), 5.58 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.0 (CH_2), 28.8 (CH_2), 28.9 (CH_2), 29.4 (CH_2), 47.7 (CH), 58.1 (CH_3), 66.8 (CH_2), 80.5 (CH), 124.2 (C), 130.3 (C), 132.0 (C), 132.9 (C), 140.0 (C), 140.7 (C); HRMS calcd for $C_{14}H_{16}O_3$ 232.1099, found 232.1096; LRMS (EI) *m*/*z* 232 (75), 217 (100), 189 (27), 171 (7), 128 (8), 91 (5). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.38; H, 6.95. Found: C, 72.32; H, 6.94.

(11) When the reaction was performed without removal of the excess of olefin, a complex mixture of products was obtained.