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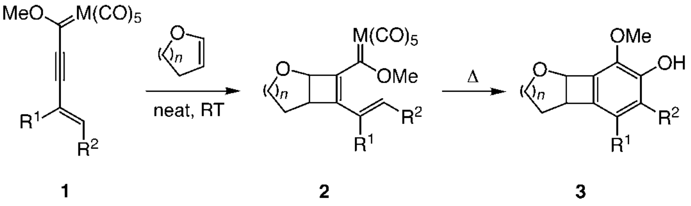
Eight-Membered Carbocycles from a Dötz-Like Reaction**

José Barluenga,* Fernando Aznar, and
M. Angel Palomero

The reaction of Fischer carbene complexes with alkynes can lead, under appropriate conditions, to a diverse array of structures.[1] The most important and widely used among these reactions is the well-known Dötz benzannulation,[2] which affords *p*-alkoxyphenol derivatives by successive insertion of one molecule of alkyne and one CO ligand in an α,β-unsaturated carbene, and subsequent electrocyclic ring closure.[1] Although reaction of chromium arylcarbene complexes with alkynes can produce more than fifteen different types of organic compounds as side products,[1a,c] alkenylcarbenes yield benzannulated products with greater fidelity.[3] The formation of cyclopentadiene derivatives from the coupling of acetylenes and vinylcarbenes has been observed in a few cases.[4] On the other hand, compounds such as cyclopentenones,[5] heterocycles,[6] or spirocycles,[7] have been achieved when (2-amino-1-vinyl)carbenes were used.[8] The presence of additional unsaturation, either in the starting carbene or in the alkyne, allows entry to new types of structures, usually polycycles.[9] However, as far as we know, the reaction of dienyl carbenes and alkynes has never been reported.[10]

One of the current interests in our research group focuses on the preparation and synthetic applications of 1-metalla-1,3,5-hexatrienes. In this context, we have recently described the synthesis of stable dienyl complexes **2** by [2+2] cycloaddition of alkynyl carbenes **1** and enol ethers (Scheme 1).[11] The complexes **2** were unreactive at room temperature, but gave benzannulation products when heated. Cyclopentadiene derivatives, which usually result from 1-metalla-1,3,5-hexatrienes, were not observed, not even as side products. We assumed that this different behavior was due to the presence of the cyclobutene ring. In order to ascertain whether the unusual reactivity of **2** could be extended to other processes,



Scheme 1. M = Cr, W; *n* = 1, 2.

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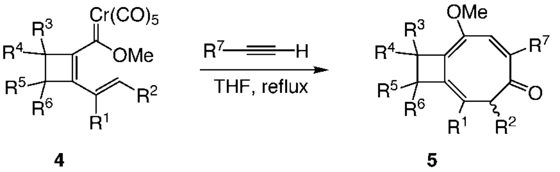
we decided to check their reaction with alkynes. Herein we report preliminary results of the study of the coupling of cyclobutene-containing metallatrienes and alkynes.

When dienyl carbene complexes **4** were treated with three equivalents of a terminal alkyne in THF and warmed to reflux, the corresponding cyclooctatrienones **5** (Scheme 2) were obtained in moderate yields (Table 1). The reaction proceeded in a regioselective fashion and led, owing to the newly created stereogenic center, to a mixture of diastereoisomers. This process can be viewed as a variation of the Dötz reaction, since both an alkyne and CO are inserted. However, the additional double bond present in the starting complex participates in the subsequent electrocyclic ring closure, giving rise to eight-membered carbocycles. Although Fischer carbene complexes have proven to be useful starting materials for the preparation of up to seven-membered carbocycles,[1a,c] this is, as far as we know, the first time that reactions of these complexes have resulted in the formation of an eight-membered carbocyclic ring.



Scheme 2.

Table 1. Preparation of eight-membered carbocycles **5**.

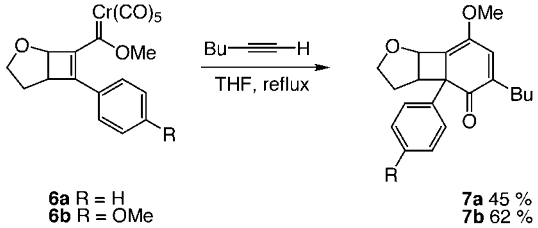
Compound	R1	R2	R3	R4	R5	R6	R7	d.r.[a]	Yield [%][b]
5a	-(CH$_2$)$_3$-		H	-O(CH$_2$)$_2$-		H	Ph	1.2:1	71
5b	-(CH$_2$)$_3$-		H	-O(CH$_2$)$_2$-		H	Bu	3:1	70
5c	-(CH$_2$)$_3$-		H	-O(CH$_2$)$_2$-		H	CH$_2$OTBS[f]	1.3:1	59
5d	Me	Ph	H	-O(CH$_2$)$_2$-		H	Bu	5:1	57
5e	Me	Ph	H	-O(CH$_2$)$_2$-		H	TMS[g]	1.4:1	63[c,d]
5f	-(CH$_2$)$_4$-		MeO	Me	H	H	Bu	15:1	53[e]
5g	-(CH$_2$)$_4$-		MeO	MeO	MeO	MeO	Bu	–	52

[a] Determined by integration of the ^{1}H NMR signals in the crude reaction mixture. [b] Yield of isolated products by flash chromatography. [c] Diastereoisomers could not be separated by chromatography. [d] 20% of the product was isolated as the Cr(CO)$_3$ complex. [e] Only the major diastereoisomer was isolated. [f] TBS = *tert*-butyldimethylsilyl. [g] TMS = trimethylsilyl.

The photochemically driven reaction of metallatriene **4a** and 1-hexyne was also tested. We found that both the yield and the diastereoselectivity obtained were comparable to those of the thermal process. The structure of the new compounds was elucidated on the basis of their COSY and HMBC NMR spectra. To date, it has not been possible to determine the relative stereochemistry between the created stereocenter and the ones preexisting in the starting dienyl complex.

Carbocycles **5** could also be prepared in a tandem one-pot process from the vinyl-substituted alkynyl chromium carbenes **1** (Scheme 1).[12] Upon refluxing the starting complexes with three equivalents of 2,3-dihydrofuran and three equivalents of the corresponding alkyne in THF, the desired products were obtained in slightly lower yields compared to those of the stepwise reactions.[13]

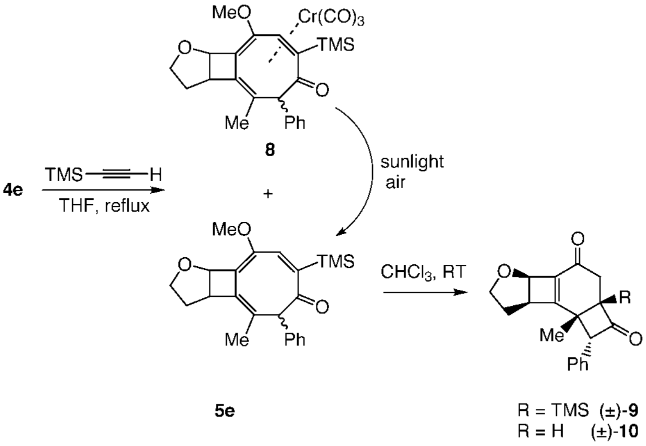
With these data in hand, we decided that it would be interesting to extend this novel reaction to carbenes **6**, in which the terminal double bond is part of an aromatic ring. As shown in Scheme 3, these systems reacted in the fashion expected for single alkenyl complexes, affording the corresponding benzannulation products **7** in moderate yields.



Scheme 3.

The formation of **5** can be explained by means of a mechanism in which the first steps are identical to those of the Dötz reaction. The sequential insertion of an alkyne and a CO molecule gives rise to a trienylketene complex intermediate which undergoes an eight-electron electrocyclic ring closure, instead of the expected six-electron electrocyclization, to afford the Cr(CO)$_3$-complexed carbocycles. The decomplexation of the metal–tricarbonyl moiety provides the final products. We believe that the presence of a four-membered ring introduces geometric restraints in the intermediate, which promote the eight-electron ring closure. However, when the terminal double bond is contained within an aromatic ring, as in compounds **6**, the geometrically disfavored six-electron electrocyclization of the intermediate is preferred, yielding the cyclohexadienones **7**. This is presumably due to the high energetic cost that would be required to break the aromaticity of the ring.

This mechanistic proposal is partially supported by the isolation of one of the reaction intermediates, the Cr(CO)$_3$-complexed cyclooctatrienone **8** (Scheme 4).[14] Treatment of **4e** with trimethylsilylacetylene affords **8**, together with a mixture of both diastereoisomers of **5e**. The former com-



Scheme 4.

pound was purified by flash chromatography, and its structure was assigned by COSY and HMBC experiments. This compound could be quantitatively converted into the metal-free carbocycle **5e** by exposure to air and sunlight.

Most of the compounds **5** are unstable in solution leading in a few hours to complex and unidentifiable mixtures of products. However, compound **5e** gave a single diastereoisomer of polycyclic system **9**, in 90% yield, upon standing in $CHCl_3$ for ten days (Scheme 4). Longer reaction times led to the release of the trimethylsilyl (TMS) group, and thus to the formation of **10** (92% yield). These products are evidently derived from the six-electron electrocyclization of the starting trienyl system **5e** and the hydrolysis of the resulting enol ether. The single diastereoisomer of **9** can best be explained as arising from epimerization of the α-carbonyl stereocenter in **5e** and the stereoselective cyclization of one of the epimeric ketones.

In conclusion, we have reported the first Dötz-like reaction between conjugated dienyl carbene chromium complexes and terminal alkynes to afford eight-membered carbocycles. We have also studied the ring closure of one of the mentioned systems to yield new polycyclic compounds.

Experimental Section

A solution of dienyl carbene **4** (1 mmol) and of the alkyne (3 mmol) in THF (15 mL) was refluxed, under a nitrogen atmosphere, until analysis by thin-layer chromatography revealed total consumption of the starting complex. The reaction mixture was diluted with hexane (20 mL) and exposed to sunlight and air in order to oxidize the metallic species to the corresponding organic compounds. Filtration through a pad of Celite and flash chromatography provided carbocycles **5**.

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Combinatorial Solid-Phase Synthesis of Multivalent Cyclic Neoglycopeptides[**]

Valentin Wittmann[*] and Sonja Seeberger

Dedicated to Professor Horst Kessler

The molecular recognition of carbohydrates by carbohydrate-binding proteins (lectins) is the basis of numerous intercellular recognition processes.[1] High-affinity lectin ligands are of considerable medicinal interest in the diagnosis and manipulation of such processes.[2] Individual carbohydrate epitopes (normally mono- to pentasaccharides) are, however, mostly bound by lectins with only low affinity (dissociation constants in the milli- to micromolar range) and in part broad specificity.[3] Since many membrane-associated lectins have several binding sites or occur in oligomeric or clustered form,[4] the creation of multivalent carbohydrate derivatives is a promising approach to arrive at effective lectin ligands.[5, 6]

Several strategies have been described to achieve the formation of a sufficient number of individual interactions necessary for high avidity of a multivalent ligand. Glycopolymers,[7] for example, are able to cover large areas of cell surfaces and bridge several membrane-located lectins ("statistical" multivalency). Small oligovalent carbohydrate derivatives (miniclusters)[6] on the other hand bind preferentially to several binding sites of a single (oligomeric) lectin proximate

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