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Cycloaddition Reactions of Alkoxy Alkynyl Fischer Carbene Complexes with *o*-Quinodimethanes (oQDMs)

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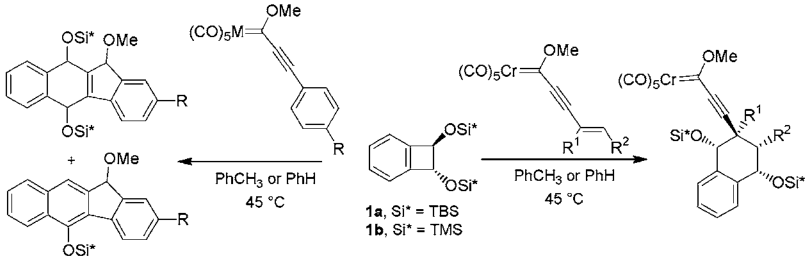
ABSTRACT



The reaction of *o*-quinodimethanes (oQDMs) with alkoxy alkynyl Fischer carbene complexes is highly dependent on the carbene complex. Thus, for arylalkynyl carbene complexes, the initial [4 + 2]-cycloadduct evolves opening a new entry to the benzo[*b*]fluorene skeleton, which is present in many natural products. However, for alkenylalkynyl carbene complexes, the reaction takes place through the double bond, instead of the triple bond, in an unprecedented fashion, leading to new functionalized alkynyl carbene complexes.

Cycloaddition reactions between 1,3-dienes and α,β-acetylenic Fischer carbene complexes have been extensively developed.[1] In these reactions, the initial [4 + 2] cycloadducts (which are, in fact, cyclohexenylcarbenes) can evolve, spontaneously or by warming, to form cyclopentadienes by a cyclopentannulation reaction, when the alkyne is substituted by an aryl[2] or an alkenyl[3] group.

However, the *o*-quinodimethane (oQDM, *o*-xylylene) system has remained elusive as a dienic antagonist of Fischer carbene complexes; this is probably due to the lack of methodologies for synthesizing oQDM derivatives that are compatible with carbene complexes.[4] The reversible conrotatory opening of the cyclobutene ring in benzocyclobutenes has been a widely used procedure for the generation of oQDM derivatives, although high temperatures are usually required.[5] However, it is known that electron-donating-substituted benzocyclobutenes exhibit outward opening even at temperatures below 0 °C. Also, very recently, Danishefsky has reported that *trans*-1,2-bis(trialkylsilyloxy)benzocyclobutenes can partake in intermolecular Diels−Alder cycloadditions with suitable carbodienophiles[6] and heterodienophiles[7]under remarkably mild conditions. In this regard, we have also prepared highly functionalized *trans*- and *cis*-1,2-

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(1) For recent reviews regarding the reactivity of Fischer alkynyl carbene complexes, see: (a) Aumann, R.; Nienaber, H. *Adv. Organomet. Chem.* **1997**, *41*, 163−242. (b) De Meijere, A.; Schirmer, H.; Duetsch, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3964−4002.

(2) (a) Barluenga, J.; Aznar, F.; Barluenga, S. *Chem. Commun.* **1995**, 1973−1974. For related transformations, see: (b) Barluenga, J.; Tomás, M.; Ballesteros, A.; Santamaría, J.; Suárez-Sobrino, A. *J. Org. Chem.* **1997**, *62*, 9229−9235. (c) Barluenga, J.; López, L. A.; Martínez, S.; Tomás, M. *Synlett* **1999**, 219−221. (d) Palomero, M. A. Ph.D. Dissertation, Universidad de Oviedo, Oviedo, Spain, 2002, pp 66−68.

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(4) For reviews regarding oQDMs chemistry, see: (a) Martín, N.; Seoane, C.; Hanack, M. *Org. Prep. Proced. Int.* **1991**, *23*, 237−272. (b) Chou, T. *Rev. Heteroatom Chem.* **1993**, *8*, 65−104. (c) Segura, J. L.; Martín, N. *Chem. Rev.* **1999**, *99*, 3199−3246.

(5) For recent reviews regarding benzocyclobutenes, see: (a) Michellys, P. Y.; Pellisier, H.; Santelli, M. *Org. Prep. Proced. Int.* **1996**, *28*, 545. (b) Mehta, G.; Cota, S. *Tetrahedron* **2001**, *57*, 625−659.

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bis(trialkylsilyloxy)benzocyclobutenes from Fischer carbene complexes and isocyanides[8] that can participate in intermolecular Diels−Alder reactions.

The benzo[*b*]fluorene tetracyclic nucleus is present in several naturally occurring compounds that display antibiotic properties (Figure 1). Biosynthetic studies have proved that *kinobscurinone* is an intermediate[9] for both *kinamycins* and *stealthins*. Besides being strongly active against Gram-positive bacteria,[10] some *kinamycins*, as well as structurally related *Lomaiviticin A*,[11] also have shown antitumor activity. *Stealthins*, on their hand, exhibit a potent free radical scavenger activity, which makes them potentially amenable for the treatment of diseases caused by oxygen-derived free radicals such as atherosclerosis or Parkinson's disease.[12]

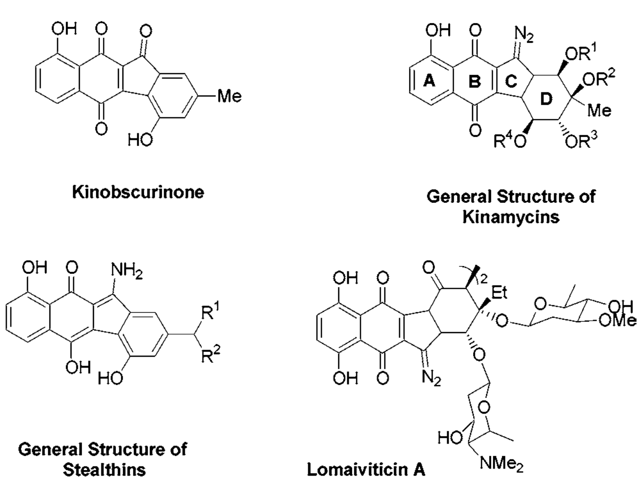
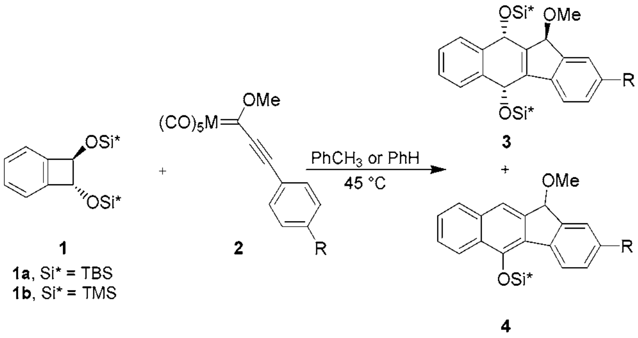


Figure 1. Naturally occurring compounds bearing the benzo[*b*]fluorene skeleton.

We hypothesized that the thermal reaction between oQDMs and α,β-acetylenic Fischer carbene complexes may follow a tandem [4 + 2]-cycloaddition/cyclopentannulation sequence leading to complex polycyclic structures. In this letter, we present the results we have obtained in this area.

Danishefsky's benzocyclobutenes **1**[6] were initially treated with alkoxy arylalkynyl Fischer carbene complexes **2** in benzene or toluene at 45 °C. The reaction was monitored by TLC until the disappearance of the carbene spot (3−7 h). After workup, dihydrobenzo[*b*]fluorenes **3** and benzo[*b*]fluorenes **4** were isolated in the yields listed in Table 1.

Table 1. Cycloaddition Reactions of Alkoxy Arylethynylcarbenes **2** with Benzocyclobutene **1**-Derived OQDMs



entry	1	Si*	2	M	R	3	yield[a]	4	yield[a]
1	**1a**	TBS	**2a**	Cr	H	**3a**	73	**4a**	25
2	**1b**	TMS	**2a**	Cr	H	**3b**	9	**4b**	80
3	**1a**	TBS	**2b**	W	H	**3a**	35	**4a**	55
4	**1a**	TBS	**2c**	Cr	OMe	**3c**	65	**4c**	5

[a] Isolated yield after chromatography based on starting carbene **2**.

Some conclusions can be extracted from analysis of Table 1. The reaction takes place with either chromium or tungsten carbene complexes in high combined yields although, in the latter case, the reaction is slower (7 h) and silanol elimination is favored leading to **4a** as the major product. When silyloxybenzocyclobutenes **1a** are warmed together with chromium carbene complexes, it is possible to exert control over the reaction, as the sole products detected by TLC and 300 MHz ^{1}H NMR in the crude residue are dihydrobenzo[*b*]fluorenes **3**. However, partial silanol elimination occurs during column chromatrography purification thus originating benzo[*b*]fluorenes **4**, while compounds **3** are still isolated as the main products. Silanol elimination also takes place very easily during the workup when the oQDM is generated from TMS-oxybenzocyclobutene **1b**, even when reacted with chromium carbene complexes (Table 1, entry 2).

The scope of the reaction was examined by treating benzocyclobutene **1a** with sterically hindered alkoxy carbene **5**, amino carbene **6**, or methyl 3-phenylpropionate **7**. However, in the conditions described before or in refluxing benzene, **1a** does not react with any of those substrates; it dimerizes instead to form **8**. The last case is one more example that corroborates the fact that metal carbene-substituted alkynes are better dienophiles than the analogous esters.

The proposed mechanism is initiated by a thermally driven conrotatory ring opening of benzocyclobutenes **1** to generate the corresponding oQDMs smoothly, which would react in a [4 + 2] fashion with Fischer alkynyl carbene complexes **2**, to form cycloadducts **I**, which were not detected. A nucleophilic attack of the aryl ring on the carbene carbon of

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(7) Hentemann, M. F.; Allen, J. G.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1937−1940.

(8) (a) Barluenga, J.; Aznar, F.; Palomero, M. A. *Chem. Eur. J.* **2002**, *8*, in press. (b) However, the oQDM precursors prepared in ref 8a do not react with alkoxy alkynyl Fischer carbene complexes: Barluenga, J.; Aznar, F.; Palomero, M. A. Unpublished results.

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(10) (a) Omura, S.; Nakagawa, A.; Yamada, H.; Hata, T.; Furusaki, A.; Watanabe, T. *Chem. Pharm. Bull.* **1971**, *19*, 2428−2430. (b) Isshiki, K.; Sawa, T.; Nagawaga, H.; Matsuda, N.; Hattori, S.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1989**, *42*, 467−469. (c) Arya, D. P.; Jebaratnam, D. J. *J. Org. Chem.* **1995**, *60*, 3268−3269.

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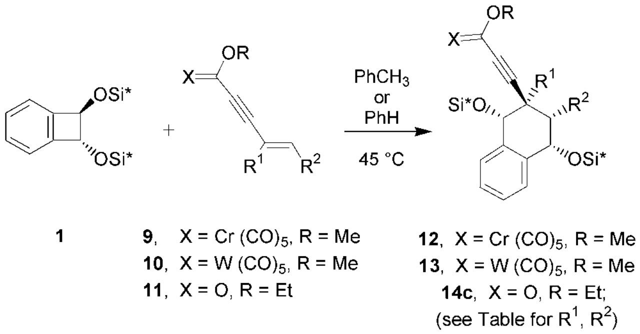
I, as was proposed by Aumann for the cyclopentannulation reactions of metallatrienes,[3b,13] would lead to intermediate **II**, which suffers elimination of the metallic fragment to produce **III**. A 1,5-hydrogen sigmatropic rearrangement promoted by the rearomatization of the aryl ring leads to the formation of compounds **3**. Finally, in situ or silica gel-catalyzed trialkylsilanol elimination accounts for the obtainment of benzo[*b*]fluorenes **4**.

The elucidation of the structure of the cycloadducts was achieved by the usual techniques (COSY, HMQC, HMBC). NOESY experiments (400 MHz) served to ascertain the regiochemistry of the silanol elimination when benzo[*b*]fluorenes **4** are formed (NOESY performed on **4a**) and the relative configuration for dihydrobenzo[*b*]fluorenes **3** (NOESY performed on **3c**), which was found to be trans between the methoxy and both silyloxy groups, as depicted above and as expected for steric reasons.

We treated next benzocyclobutenes **1** with alkenyl-substituted alkynyl chromium carbene complexes **9**, bearing in mind that these reactions should proceed by a tandem double cycloaddition−cyclopentannulation.[3b] However, to our surprise, carbene complexes **9** reacted with oQDMs in a Diels−Alder fashion through the double bond, instead of the triple bond, producing new tetrahydronaphthylalkynyl chromium carbene complexes **12**. This result was totally unexpected as, prior to our experiments, carbene complexes **9** had only shown this behavior in one case, leading to the corresponding [4 + 2]-cycloadduct as the minor product.[3b] Similarly, tetrahydronaphthylalkynyl tungsten carbene complex **13** was obtained when tungsten carbene complex **10** was heated in the presence of **1a**. Carbene complexes **12** (**13**) were isolated in good yields (Table 2) as single diastereomers, with the exception of carbene **12d** for which a 4:1 diastereomeric mixture was observed.

Table 2. [4 + 2]-Cycloaddition Reactions of Alkoxy Alkenylethynylcarbenes **9** and Ester **10** with Benzocyclobutene **1**-Derived OQDM78s



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9, X = Cr (CO)$_5$, R = Me
10, X = W (CO)$_5$, R = Me
11, X = O, R = Et

12, X = Cr (CO)$_5$, R = Me
13, X = W (CO)$_5$, R = Me
14c, X = O, R = Et;
(see Table for R^1, R^2)

entry	1	dienophile	R^1	R^2	time	product	yield[a]
1	**1a**	**9a**	Me	Ph	2 h	**12a**	70
2	**1a**	**9b**	−(CH$_2$)$_3$−		3 h	**12b**	95
3	**1a**	**9c**	−(CH$_2$)$_4$−		3 h	**12c**	78
4	**1a**	**9d**	H	Ph	2 h	**12d**	80[b]
5	**1b**	**9b**	−(CH$_2$)$_3$−		2 h	**12e**	50
6	**1a**	**10**	−(CH$_2$)$_4$−		3 h	**13**	86
7	**1a**	**11**	Me	Ph	3 days	**14c**	<10[c]

[a] Isolated yield after chromatography based on starting dienophile. [b] Obtained as a diastereomeric mixture in a 4:1 ratio [determined by ^{1}H NMR (300 MHz)] (see text for the relative configuration of **12d**). [c] Compound not isolated; data estimated by ^{1}H NMR (300 MHz) of the crude mixture.

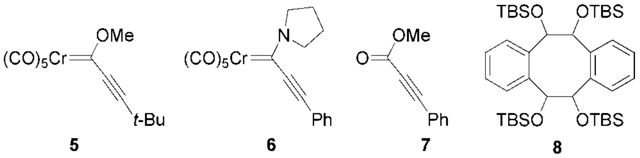

Figure 2.

Again, the reaction was tested with the analogous ester **11**. In this case, only less than a 10% of cycloaddition product **14c** could be estimated as a mixture of diastereomers by ^{1}H NMR (300 MHz) of the crude residue after 3 days of warming at 45 °C. Presumably, the lesser reactivity of the ester **11** as dienophile and the rapid dimerization of the oQDM, as pointed out before, account for this low amount of cycloadduct.

Compounds **12** (**13**) gave spectroscopically consistent data, and their relative configuration was assigned to be the one depicted above by NOESY correlations (400 MHz). In most cases, the only compound detected was the diastereomer that comes from an exo-selective approach of the double bond of carbenes **9** (**10**) to the oQMDs (Figure 3a). However, for carbene **12d** the major diastereomer observed was the result of the endo-selective approach (Figure 3b).

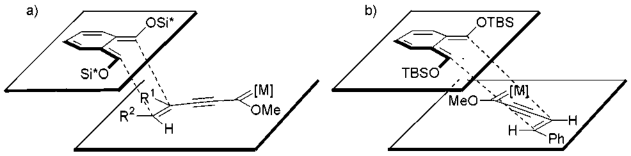

Figure 3. (a) Preferred exo-selective transition state for the cycloaddition reaction of oQDMs and carbene complexes **9a**−**c** and **10**. (b) Preferred endo-selective transition state for the cycloaddition reaction with carbene complex **9d**.

The reactivity of these new alkynyl carbene complexes **12** is currently being investigated. Preliminary tests indicate that, as expected, treatment with pyridine *N*-oxide causes the oxidation of the carbene moiety thus producing the analogous esters **14** (Scheme 2). Also, the reaction of **12b** with methyllithium produces a new enyne **15**, while the bubbling of dimethylamine through a solution of the same carbene leads to the corresponding amino carbene complex

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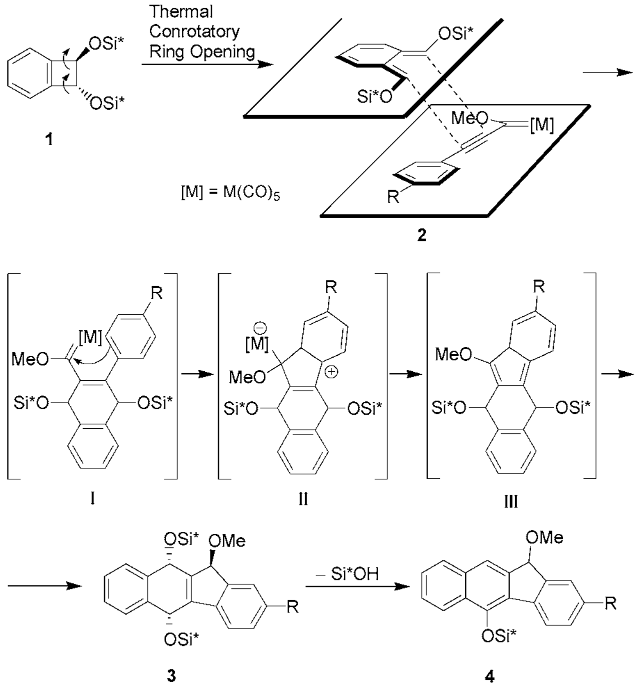
(13) (a) Aumann, R.; Heinen, H.; Hinterding, P.; Strater, N.; Krebs, B. *Chem. Ber.* **1991**, *124*, 1229−1236. (b) Aumann, R.; Heinen, H.; Dartmann, M.; Krebs, B. *Chem. Ber.* **1991**, *124*, 2343−2347. (c) Aumann, R.; Meyer, A. G.; Fröhlich, R. *Organometallics* **1996**, *15*, 5018−5027.

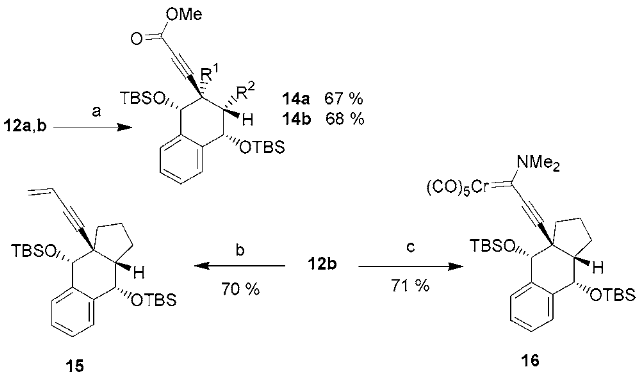
Scheme 1



16. In all cases, the nucleophilic reagent attacks the carbene carbon and no products arising from the addition to the triple bond were detected, probably due to steric reasons.

In conclusion, oQDMs, generated thermally from *trans*-bis(trialkylsilyloxy)benzocyclobutenes, react with alkoxy arylethynyl Fischer carbene complexes to form benzo[*b*]fluorene derivatives by a tandem cycloaddition−cyclopentannulation sequence. This tetracyclic skeleton is present in several naturally occurring compounds with interesting biological properties, and efforts toward their synthesis are currently being taken. On the other hand, the reaction of the same oQDMs with alkoxy alkenylethynyl carbene complexes takes place unexpectedly at the double bond to form new alkoxy alkynyl complexes. Preliminary results indicate that nucleophiles react with the carbene carbom atom of these new alkynyl carbenes in a 1,2-addition process instead of the alternatively possible 1,4-addition process. Work to expand the scope of the reactivity of these new carbenes is also under way.

Scheme 2[a]



[a] Reagents and conditions: (a) Pyridine *N*-oxide, THF, rt. (b) (i) MeLi (1.2 equiv), THF, −78 °C; (ii) SiO_2, −78 °C. (c) Me_2NH, Et_2O, rt.

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

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