

# Synthetic Methods

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## Lithium Benzocyclobuteneoxide as a Precursor of a Vinylogous Enolate: Solvent-Controlled Synthesis of Highly Functionalized Seven-Membered Benzocarbo-cycles\*\*

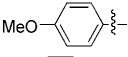
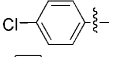
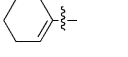
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The role of Fischer carbene complexes (FCCs) as synthetic intermediates in organic chemistry is today perfectly established,<sup>[1]</sup> although new patterns of reactivity are still amenable. In this context, we have initiated an exploration of the reactivity of FCCs toward *ortho*-quinodimethanes<sup>[2]</sup> (oQDMs) and reported recently that the reaction of sym-

metric bistrialkylsilyloxy oQDMs, readily generated by thermal ring opening of benzocyclobutenes, with alkynyl FCCs follows a tandem [4+2] cycloaddition/cyclopentannulation sequence that leads to benzo[*b*]fluorenes.<sup>[3]</sup> Choy and Yang have pointed out that the ring opening of metalated benzocyclobuteneoxides takes place at temperatures as low as –25 °C, thus confirming that such a process is favored by the presence of electron-donating groups on the cyclobutene ring.<sup>[4]</sup> On the other hand, functionalized seven-membered benzocarbo-cycles are both important synthetic intermediates and key structural elements in various natural products and/or pharmacologically active compounds, such as terpenes, namely, (–)-presphaerene<sup>[5]</sup> and barbatusol,<sup>[6]</sup> alkaloids, for example, dragmacidin E,<sup>[7]</sup> (–)-colchicine, an antitumour agent,<sup>[8]</sup> nortriptiline and amitriptiline, which have antidepressant activities,<sup>[9]</sup> and hamigeran C, which is cytotoxic,<sup>[10]</sup> among others. We describe herein the preliminary results of the reaction of alkynyl FCCs with oQDM **1** prepared by Choy and Yang, thus leading to the preparation of highly functionalized seven-membered benzocarbo-cycles which have not been previously accessed from FCCs.

In our initial experiment (Scheme 1), benzocyclobutenol **2** was deprotonated with *n*BuLi at –78 °C in THF and the reaction mixture was allowed to reach –25 °C to permit the formation of oQDM **1**; subsequently, chromium FCC **3** was added, and the reaction was monitored by TLC. However, rather than the expected [4+2] cycloadduct **5** or benzo[*b*]fluorene **6**, two benzoheptacarbo-cycles<sup>[11]</sup> **7a** and **8a** were isolated as a mixture in low yield, among other products (Table 1, entry 1). As far as we know, this reaction is the first example in which oQDM **1** acts as a four-carbon synthon in a formal [4+3] cycloaddition. We switched to the more stable tungsten FCC **4a** to find that the combined yield of the isolated products, [4+3] cycloadducts **7a** and **8a**, was improved to 65 % (entry 2) under similar reaction conditions. Other solvents (hexane, 1,2-dimethoxyethane, toluene, and dioxane) were then examined but produced either low-yielding mixtures of **7a** and **8a** or no identifiable products.

**Table 1:** Reaction of **1** with alkynyl carbene complexes **3** and **4** in THF.

Entry <sup>[a]</sup>	FCC	Metal	R	<b>7</b>	Yield [%] <sup>[b]</sup>	<b>8</b>	Yield [%] <sup>[b]</sup>
1	<b>3</b>	Cr	Ph	<b>7a</b>	8	<b>8a</b>	11
2	<b>4a</b>	W	Ph	<b>7a</b>	49	<b>8a</b>	16
3 <sup>[c]</sup>	<b>4a</b>	W	Ph	<b>7a</b>	–	<b>8a</b>	50
4	<b>4b</b>	W	MeO- 	<b>7b</b>	71	<b>8b</b>	14
5	<b>4c</b>	W	Cl- 	<b>7c</b>	67	<b>8c</b>	30
6	<b>4d</b>	W		<b>7d</b>	52	<b>8d</b>	22
7	<b>4e</b>	W	<i>t</i> Bu	<b>7e</b>	50 <sup>[d]</sup>	<b>8e</b>	5 <sup>[d]</sup>

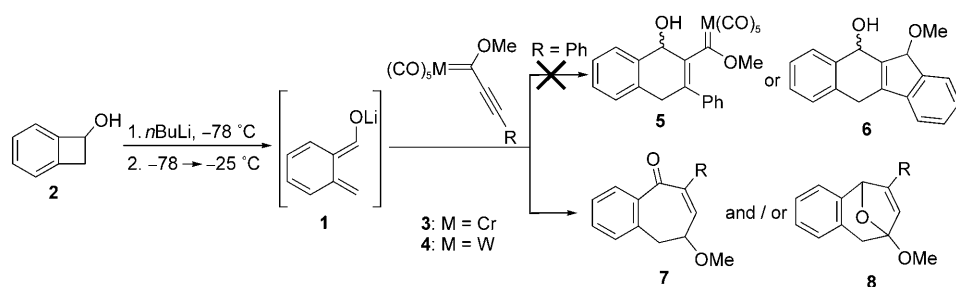
[a] All the reactions were carried out on a 0.5-mm scale for the carbene complex (0.033 M) with 1.5 equivalents of benzocyclobutenol (0.05 M). [b] Yields of isolated product based on the starting alkynyl carbene complexes. [c] Reaction performed in diethyl ether. [d] Products could not be separated; yield estimated by <sup>1</sup>H NMR (300 MHz) spectroscopic analysis from a fraction enriched in **7e** after flash column chromatography.

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**Scheme 1.** Reaction of **1** with alkynyl carbene complexes.

Interestingly, the reaction led exclusively to **8a** when performed in diethyl ether (entry 3). Such a strong solvent effect<sup>[12]</sup> prompted us to consider the possibility of increasing the yield through additives or by variation of the counterion. However, none of the following approaches led to improved results: the addition of different coordinating reagents (*N,N,N',N'',N'''*-pentamethyldiethylenetriamine (PMDTA), [12]crown-4, *N,N'*-dimethyl-*N,N'*-propyleneurea (DMPU)), the use of different bases (potassium hexamethyldisilazane (KHMDs), NaHMDS, EtMgBr), and transmetalation strategies (BuLi/ZnCl<sub>2</sub>) in both diethyl ether or THF.

Considering that at this point we had already created conditions that allowed for the selective formation of two differently functionalized benzoheptacarbo-cycles, we next tried to expand the scope of such transformations by examining of the nature of the substituents of the carbene complex. Thus, carbene complexes **4b–e** were treated with **1** in THF to obtain moderate to good yields of benzocycloheptenones **7** (Table 1, entries 4–7), which were accompanied by small amounts of benzocycloheptene ketals **8** that could be readily separated by flash column chromatography. The best yields were achieved when the R group was a *para*-substituted aromatic moiety (entries 4 and 5), although the reaction also took place selectively for alkenyl- and alkyl-substituted alkynyl FCCs **4d,e** (entries 6 and 7).

On the other hand, benzocycloheptene ketals **8** were obtained as the unique reaction products, as expected, when carbene complexes **4a–g** were treated with **1** in diethyl ether (Table 2; see also Table 1, entry 3). This reaction was much slower and usually required reaching either room temperature (Table 2, entries 2, 4, and 6) or reflux (entries 5 and 7) to proceed. Again, *para*-substituted alkynyl carbene complexes gave the best yields (entries 2 and 3). These reaction conditions tolerate alkenyl (entry 4), alkyl (entries 5 and 6), and silyl (entry 7) groups as substituents in the alkynyl FCC. We also observed that the yield may be improved by performing the reaction at a higher concentration with a higher excess of benzocyclobutenol (Table 2, entry 1 versus Table 1, entry 3).

As a basis for the mechanism, we propose that after the initial deprotonation of benzocyclobutenol **2** at  $-78^{\circ}\text{C}$ , the resulting lithium benzocyclobutenoxide opens to **1** by warming to  $-25^{\circ}\text{C}$  (Scheme 2). Subsequently, *o*QDM **1** would behave

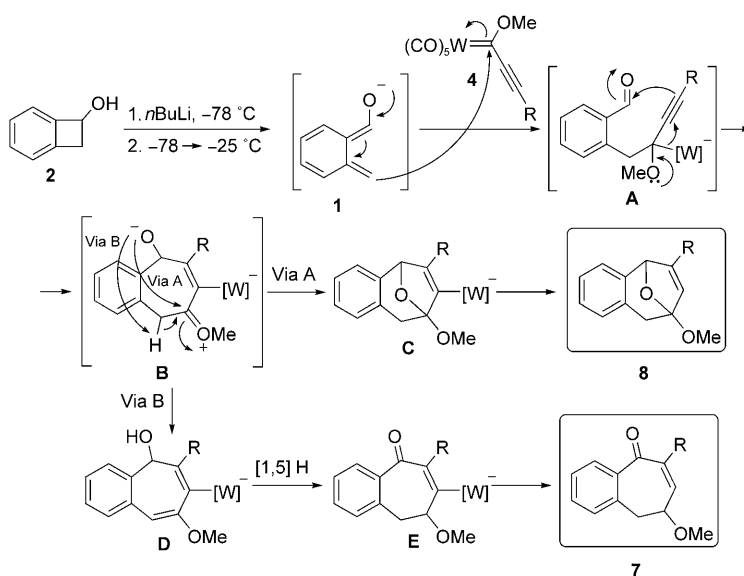
as a vinylogous enolate rather than a 1,3-diene, and a nucleophilic attack<sup>[13,14]</sup> on the carbene carbon of **4** would take place to form intermediate **A**. A 1,2-metal migration,<sup>[14]</sup> promoted by the methoxy group, would cause simultaneous ring closure to form intermediate **B**. The evolution of **B** could occur by two different routes: In the first (via A), an intramolecular nucleophilic attack would produce the metalated benzocycloheptene ketal **C**, which would account for the formation of **8**, whereas

in the second (via B), an intramolecular acid/base reaction would generate the metalated intermediate **D**, thus leading to **E** through a 1,5-hydrogen shift and finally to **7**.

**Table 2:** Reaction of **1** with tungsten alkynyl carbene complexes **4** in Et<sub>2</sub>O.

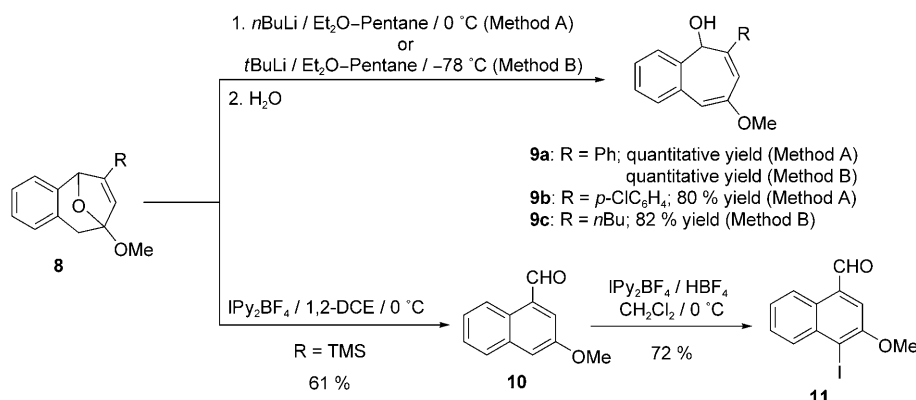
Entry <sup>[a]</sup>	FCC	R	<b>8</b>	Yield [%] <sup>[b]</sup>
1 <sup>[c]</sup>	<b>4a</b>	Ph	<b>8a</b>	70
2	<b>4b</b>		<b>8b</b>	56 <sup>[d]</sup>
3	<b>4c</b>		<b>8c</b>	86
4	<b>4d</b>		<b>8d</b>	55 <sup>[d]</sup>
5	<b>4e</b>	<i>t</i> Bu	<b>8e</b>	50 <sup>[e]</sup>
6	<b>4f</b>	<i>n</i> Bu	<b>8f</b>	25 <sup>[d]</sup>
7	<b>4g</b>	TMS	<b>8g</b>	38 <sup>[e]</sup>

[a] All the reactions were carried out on a 0.5-mm scale for the carbene complex (0.033 M) with 1.5 equivalents of benzocyclobutenol (0.05 M), unless otherwise stated. [b] Yields of isolated product based on the starting alkynyl carbene complexes **4**. [c] Reaction carried out with 5 equivalents of benzocyclobutenol (0.33 M). [d] It was necessary to reach room temperature for the reaction to proceed. [e] It was necessary to reach reflux for the reaction to proceed. TMS = trimethylsilyl.



**Scheme 2.** Proposed mechanism for the formation of seven-membered benzocarbo-cycles **7** and **8**.

Our preliminary results into the reactivity of benzocycloheptene ketals **8** indicate that it is possible to break the heteroatom bridge of **8** by treatment with *n*BuLi or *t*BuLi to form benzocycloheptadienols **9** in good to excellent yields (Scheme 3); therefore, this breakage acts as a direct entry to a



**Scheme 3.** Chemical transformations of benzocycloheptene ketals **8**. IPy<sub>2</sub>BF<sub>4</sub> = bis(pyridine)-iodonium(i) tetrafluoroborate, 1,2-DCE = 1,2-dichloroethene.

third type of functionalized seven-membered benzocarbocycle. On the other hand, we also observed that ring contraction<sup>[15]</sup> takes place in **8g** (R = TMS) upon treatment with IPy<sub>2</sub>BF<sub>4</sub><sup>[16]</sup> to give **10** in 61 % yield. This apparently simple compound has now been prepared for the first time;<sup>[17]</sup> thus, by using this approach the difficulties that derived from both the electronic nature and the relative position of its substituents have been overcome. Naphthyl aldehyde **10** could be iodinated with IPy<sub>2</sub>BF<sub>4</sub> in acidic medium at the C4 position of the naphthalene skeleton to form **11** in 72 % yield (Scheme 3), thus expanding the possibilities for further transformations.

In summary, we have established a new and direct route to seven-membered functionalized benzocarbocycles from tungsten alkynyl FCCs. In this transformation, oQDM **1** prepared by Choy and Yang behaves as a vinylogous enolate which acts for the first time as a four-carbon component in a formal [4+3] cycloaddition. The outcome of the reaction is solvent controlled: selective formation of benzocycloheptenones **7** can be achieved in THF, whereas exclusive synthesis of benzocycloheptene ketals **8** occurs in diethyl ether. The latter compounds can be readily transformed in benzocycloheptadienols **9** by a base-promoted opening of the cyclic ketal moiety. Access to the previously unknown 3-methoxy-1-naphthylcarbaldehyde (**10**) is obtained by a ring contraction of cyclic ketal **8g** promoted by IPy<sub>2</sub>BF<sub>4</sub>. The exploration of transition-metal-catalyzed (Cu, Rh) nucleophilic ring openings<sup>[18]</sup> of ketals **8** is currently underway and the results will be reported in due course.

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**Keywords:** carbene ligands · carbocycles · cycloaddition · enolates · solvent effects

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