Synthetic Methods

DOI: 10.1002/ange.200501468

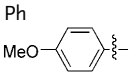
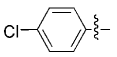
Lithium Benzocyclobuteneoxide as a Precursor of a Vinylogous Enolate: Solvent-Controlled Synthesis of Highly Functionalized Seven-Membered Benzocarbocycles**

José Barluenga, Patricia García-García, Manuel A. Fernández-Rodríguez, Enrique Aguilar, and Isabel Merino*

The role of Fischer carbene complexes (FCCs) as synthetic intermediates in organic chemistry is today perfectly established,[1] although new patterns of reactivity are still amenable. In this context, we have initiated an exploration of the reactivity of FCCs toward *ortho*-quinodimethanes[2] (*o*QDMs) and reported recently that the reaction of symmetric bistrialkylsilyloxy *o*QDMs, 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.[3] 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.[4] On the other hand, functionalized seven-membered benzocarbocycles are both important synthetic intermediates and key structural elements in various natural products and/or pharmacologically active compounds, such as terpenes, namely, (−)-presphaerene[5] and barbatusol;[6] alkaloids, for example, dragmacidin E;[7] (−)-colchicine, an antitumour agent;[8] nortriptyline and amitriptyline, which have antidepressant activities;[9] and hamigeran C, which is cytotoxic,[10] among others. We describe herein the preliminary results of the reaction of alkynyl FCCs with *o*QDM **1** prepared by Choy and Yang, thus leading to the preparation of highly functionalized seven-membered benzocarbocycles 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 *o*QDM **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 benzoheptacarbocycles[11] **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[a]	FCC	Metal	R	7	Yield [%][b]	8	Yield [%][b]
1	**3**	Cr	Ph	**7a**	8	**8a**	11
2	**4a**	W	Ph	**7a**	49	**8a**	16
3[c]	**4a**	W	Ph	**7a**	–	**8a**	50
4	**4b**	W		**7b**	71	**8b**	14
5	**4c**	W		**7c**	67	**8c**	30
6	**4d**	W		**7d**	52	**8d**	22
7	**4e**	W	*t*Bu	**7e**	50[d]	**8e**	5[d]

[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 ^{1}H NMR (300 MHz) spectroscopic analysis from a fraction enriched in **7e** after flash column chromatography.

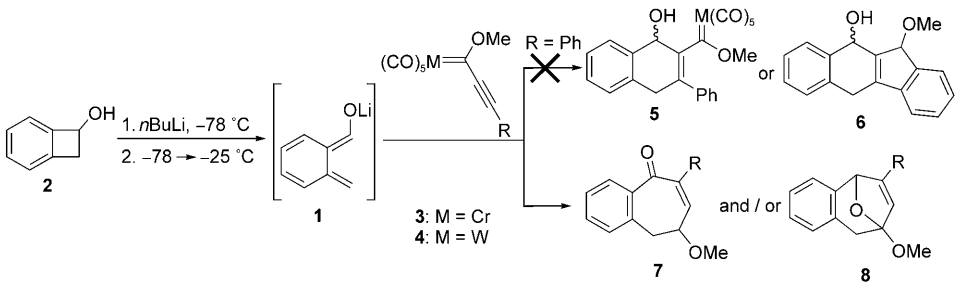
[*] Prof. Dr. J. Barluenga, P. García-García, Dr. M. A. Fernández-Rodríguez, Dr. E. Aguilar, Dr. I. Merino[+] Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al C.S.I.C. Universidad de Oviedo C/Julián Clavería, 8, 33006 Oviedo (Spain) Fax: (+34) 985-103-450 E-mail: barluenga@uniovi.es

[+] NMR spectroscopic studies.

[**] We thank the Ministerio de Ciencia y Tecnología (Spain; BQU2001-3853), the Consejería de Educación y Cultura del Principado de Asturias (PR-01-GE-11), and the Fundación Ramón Areces for financial support. We also appreciate the generous support given by Merck Sharp and Dohme. P.G.-G. is indebted to the Ministerio de Educación y Ciencia (Spain) for a MEC-FPU predoctoral fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim



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[12] 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 ($BuLi/ZnCl_2$) 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 benzoheptacarbocycles, 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).

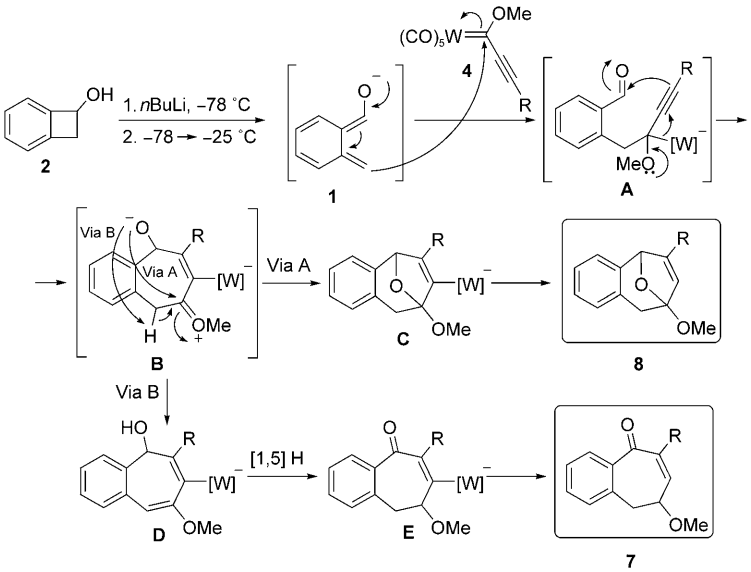
On the other hand, benzocycloheptene ketals **8** were obtained as the unique reaction products, as expected, when carbene complexes **4a–g** were treated with **1** in diethyl ether (Table 2; see also Table 1, entry 3). This reaction was much slower and usually required reaching either room temperature (Table 2, entries 2, 4, and 6) or reflux (entries 5 and 7) to proceed. Again, *para*-substituted alkynylaryl 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 °C, the resulting lithium benzocyclobutenoxide opens to **1** by warming to −25 °C (Scheme 2). Subsequently, *o*QDM **1** would behave as a vinylogous enolate rather than a 1,3-diene, and a nucleophilic attack[13,14] on the carbene carbon of **4** would take place to form intermediate **A**. A 1,2-metal migration,[14] 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_2O.

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

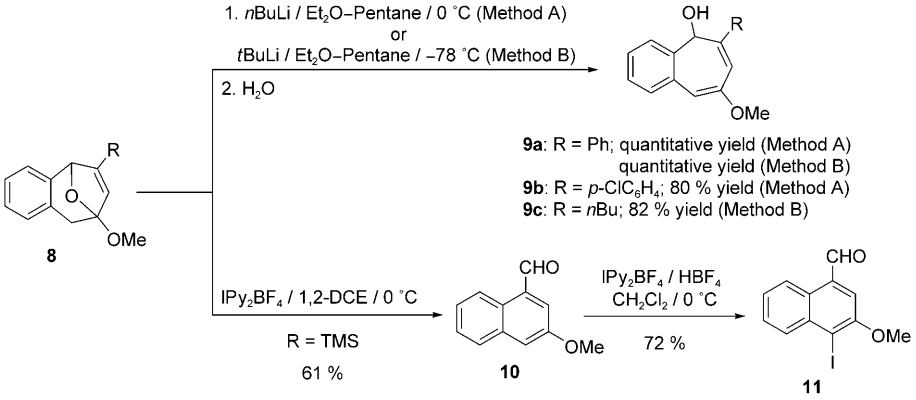
[a] All the reactions were carried out on a 0.5-mM scale for the carbene complex (0.033 M) with 1.5 equivalents of benzocyclobutenol (0.05 M), unless otherwise stated. [b] Yields of isolated product based on the starting alkynyl carbene complexes **4**. [c] Reaction carried out with 5 equivalents of 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 benzocarbocycles **7** and **8**.

© 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

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_2BF_4 = 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[15] takes place in **8g** (R = TMS) upon treatment with IPy_2BF_4[16] to give **10** in 61% yield. This apparently simple compound has now been prepared for the first time;[17] 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_2BF_4 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_2BF_4. The exploration of transition-metal-catalyzed (Cu, Rh) nucleophilic ring openings[18] of ketals **8** is currently underway and the results will be reported in due course.

Received: April 28, 2005

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

[1] Selected recent reviews: a) J. Barluenga, M. A. Fernández-Rodríguez, E. Aguilar, *J. Organomet. Chem.* **2005**, *690*, 539–587; b) M. Gómez-Gallego, M. J. Mancheño, M. A. Sierra, *Acc. Chem. Res.* **2005**, *38*, 44–53; c) J. Barluenga, J. Santamaría, M. Tomás, *Chem. Rev.* **2004**, *104*, 2259–2283; d) J. W. Herndon, *Coord. Chem. Rev.* **2004**, *248*, 3–79; e) J. Barluenga, J. Flórez, F. J. Fañanás, *J. Organomet. Chem.* **2001**, *624*, 5–17; f) K. H. Dötz, C. Jakel, W. C. Haase, *J. Organomet. Chem.* **2001**, *617–618*, 119–132; g) A. J. Fletcher, S. D. R. Christie, *J. Chem. Soc. Perkin Trans. 1* **2001**, 1–13; h) M. A. Sierra, *Chem. Rev.* **2000**, *100*, 3591–3638; i) A. de Meijere, H. Schirmer, M. Duestsch, *Angew. Chem.* **2000**, *112*, 4124–4162; *Angew. Chem. Int. Ed.* **2000**, *39*, 3964–4002. Books; j) *Metal Carbenes in Organic Synthesis* (Ed.: K. H. Dötz) in *Topics in Organometallic*, *Vol. 13 Chemistry*, Wiley, New York, **2004**; k) *Carbene Chemistry: From Fleeting Intermediates to Powerful Reagents* (Ed.: G. Bertrand), Marcel Dekker, New York, **2002**; l) F. Zaragoza Dörwald in *Metal Carbenes in Organic Synthesis*, Wiley-VCH, Weinheim, **1999**.

[2] a) G. Mehta, S. Cota, *Tetrahedron* **2001**, *57*, 625–659; b) J. L. Segura, N. Martín, *Chem. Rev.* **1999**, *99*, 3199–3246; c) P. Y. Michellys, H. Pellisier, M. Santelli, *Org. Prep. Proced. Int.* **1996**, *28*, 545–608; d) T. Chou, *Rev. Heteroat. Chem.* **1993**, *8*, 65–104; e) N. Martín, C. Seoane, M. Hanack, *Org. Prep. Proced. Int.* **1991**, *23*, 237–272.

[3] J. Barluenga, M. A. Fernández-Rodríguez, E. Aguilar, *Org. Lett.* **2002**, *4*, 3659–3662.

[4] W. Choy, H. Yang, *J. Org. Chem.* **1988**, *53*, 5796–5798.

[5] a) J. Lee, J. Hong, *J. Org. Chem.* **2004**, *69*, 6433–6440; b) F. Cafieri, P. Ciminiello, C. Santacroce, E. Fattorusso, *Phytochemistry* **1983**, *22*, 1824–1825.

[6] a) G. Majetich, Y. Zhang, T. L. Feltman, S. Duncan, Jr., *Tetrahedron Lett.* **1993**, *34*, 445–448; b) E. R. Koft, *Tetrahedron* **1987**, *43*, 5775–5780; c) A. Kelecom, *Tetrahedron* **1983**, *39*, 3603–3608.

[7] R. J. Capon, F. Rooney, L. M. Murray, E. Collins, A. T. R. Sim, J. A. P. Rostas, M. S. Butler, A. R. Carroll, *J. Nat. Prod.* **1998**, *61*, 660–662.

[8] a) H.-G. Capraro, A. Brossi in *The Alkaloids, Vol. 23* (Ed.: A. Brossi), Academic Press, New York, **1984**, pp. 1–70; b) A. Brossi, *J. Med. Chem.* **1990**, *33*, 2311–2319; c) O. Boye, A. Brossi in *The Alkaloids, Vol. 41* (Ed.: A. Brossi, G. A. Cordell), Academic Press, New York, **1992**, pp. 125–176.

[9] M. Williams, E. A. Kovaluk, S. P. Arneric, *J. Med. Chem.* **1999**, *42*, 1481–1500.

[10] a) K. Wellington, R. Cambie, P. Rutledge, P. Bergquist, *J. Nat. Prod.* **2000**, *63*, 79–85; b) R. Cambie, A. Lai, M. Kernan, *J. Nat. Prod.* **1993**, *58*, 940–942.

[11] The identity of all the new compounds was ascertained unequivocally by NMR spectroscopic experiments, including COSY, HMQC, HMBC, and NOESY for selected compounds (see the Supporting Information); an X-Ray structure elucidation for **8a** was also obtained: P. García-García, F. Andina, M. A. Fernández-Rodríguez, E. Aguilar, in preparation.

[12] Solvent-controlled processes that involve FCCs in the synthesis of five-membered carbocycles have been recently highlighted:

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim

a) F. Zaragoza Dörwald, *Angew. Chem.* **2003**, *115*, 1372 – 1374; *Angew. Chem. Int. Ed.* **2003**, *42*, 1332 – 1334; b) J. Barluenga, S. López, J. Flórez, *Angew. Chem.* **2003**, *115*, 241 – 243; *Angew. Chem. Int. Ed.* **2003**, *42*, 231 – 233.

[13] a) The nucleophilic attack of lithium enolates derived from methyl ketone takes place at the carbene carbon of α,β-unsaturated FCCs: J. Barluenga, J. Alonso, F. J. Fañanás, J. Borge, S. García-Granda, *Angew. Chem.* **2004**, *116*, 5626 – 5629; *Angew. Chem. Int. Ed.* **2004**, *43*, 5510 – 5513, and references cited therein; on the other hand, substituted lithium enolates add to α,β-unsaturated FCCs in the fashion of a Michael addition; see, for example: b) I. Merino, Y. R. S. Laxmi, J. Flórez, J. Barluenga, J. Ezquerra, C. Pedregal, *J. Org. Chem.* **2002**, *67*, 648 – 655.

[14] 1,2-Metal migrations have been invoked in related transformations: a) J. Barluenga, M. Tomás, E. Rubio, J. A. López-Pelegrín, S. García-Granda, P. Pertierra, *J. Am. Chem. Soc.* **1996**, *118*, 695 – 696; this rearrangement could be monitored by NMR spectroscopic analysis: b) J. Barluenga, M. Tomás, A. Ballesteros, J. Santamaría, R. J. Carbajo, F. López-Ortiz, S. García-Granda, P. Pertierra, *Chem. Eur. J.* **1996**, *2*, 88 – 97.

[15] Iodine-promoted ring contractions in seven-membered rings have been previously observed in our group: J. Barluenga, F. González-Bobes, J. M. González, *Angew. Chem.* **2002**, *114*, 2668 – 2670; *Angew. Chem. Int. Ed.* **2002**, *41*, 2556 – 2558.

[16] IPy_2BF_4 (Py = pyridine) is commercially available from either Novabiochem or Aldrich; for recent applications, see: a) J. Barluenga, F. González-Bobes, M. C. Murguía, S. R. Ananthoju, J. M. González, *Chem. Eur. J.* **2004**, *10*, 4206 – 4213; for a brief overall review of early applications, see: b) J. Barluenga, *Pure Appl. Chem.* **1999**, *71*, 431 – 436.

[17] Structurally related compounds, such as 3-hydroxy-1-naphthylcarbaldehyde, have been previously prepared; see: K. Chamontin, V. Lokshin, V. Rossollin, A. Samat, R. Guglielmetti, *Tetrahedron* **1999**, *55*, 5821 – 5830.

[18] a) M. Lautens, K. Fagnou, S. Hiebert, *Acc. Chem. Res.* **2003**, *36*, 48 – 58; b) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169 – 196; c) P. A. Evans, D. K. Leahy, *J. Am. Chem. Soc.* **2002**, *124*, 7882 – 7883.

 © 2005 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim