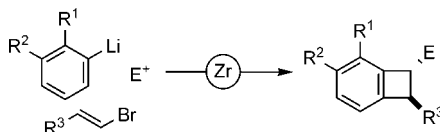


Zirconocene-Mediated Synthesis of
Cyclobutabenzenes[†]José Barluenga,* Jonás Calleja, María J. Antón, Lucía Álvarez-Rodrigo,
Félix Rodríguez, and Francisco J. FañanásInstituto Universitario de Química Organometálica “Enrique Moles”, Unidad
Asociada al CSIC, Universidad de Oviedo, Julián Clavería 8, 33006-Oviedo, Spain

barluenga@uniovi.es

Received July 21, 2008

ABSTRACT



A new, mild, one-pot method for the synthesis of cyclobutabenzenes by the zirconium-promoted cross-coupling reaction of aryllithium compounds and alkenyl bromides is reported. Formation of an arynezirconocene complex and its regioselective coupling with an alkenyl bromide are the key steps of the process. This method allows the regio- and diastereoselective synthesis of functionalized cyclobutabenzene derivatives from simple and easily available starting materials.

Cyclobutabenzenes (benzocyclobutanes) are very interesting compounds because of their structural features and important reactivity profile.¹ They serve as synthons for *o*-xylylenes upon thermal activation² and as building blocks for the synthesis of some natural products and drugs,³ and they are beginning to find application in polymer chemistry and material science.⁴ Although several methods have been described for the synthesis of functionalized cyclobutaben-

zenes in the last three decades, many of these methods involve (a) multistep routes, (b) unusual starting materials, (c) low overall yields, or (d) special apparatus.⁵

Since a few years ago, we have been involved in the development of a project regarding the reactivity of zirconocene complexes and heterosubstituted alkenes.⁶ In particular, we are interested in the reactivity of enol ethers and alkenyl halides.⁷ In this context, we found that cyclobutene derivatives could be obtained, under particular conditions, by the reaction of alkyne–zirconocene complexes and alkenyl bromides.⁸

Taking into account that aryne–zirconocene complexes could be considered as a particular class of alkyne–zirconocene complexes, we reasoned that cyclobutaben-

[†] Dedicated to John M. Birmingham, one of the pioneers in organozirconium chemistry, on the occasion of his 80th birthday.

(1) (a) Mychellys, P.-Y.; Pellissier, H.; Santelli, M. *Org. Prep. Proced. Int.* **1996**, 28, 545. (b) Segura, J. L.; Martin, N. *Chem. Rev.* **1999**, 99, 3199. (c) Mehta, G.; Kohta, S. *Tetrahedron* **2001**, 57, 625.

(2) For reviews, see: (a) Nemoto, H.; Fukumoto, K. *Tetrahedron* **1998**, 54, 5425. (b) Sadana, A. K.; Saini, R. K.; Billups, W. E. *Chem. Rev.* **2003**, 103, 1539.

(3) For recent examples, see: (a) Mychellys, P.-Y.; Maurin, P.; Toupet, L.; Pellissier, H.; Santelli, M. *J. Org. Chem.* **2001**, 66, 115. (b) Yamamoto, K.; Hentemann, M. F.; Allen, J. G.; Danishefsky, S. J. *Chem.—Eur. J.* **2003**, 9, 3242. (c) Matsuya, Y.; Masuda, S.; Itoh, T.; Murai, T.; Nemoto, H. *J. Org. Chem.* **2005**, 70, 6898. (d) Port, M.; Lett, R. *Tetrahedron Lett.* **2006**, 47, 4677.

(4) (a) Jiang, T.; Rigney, J.; Jones, M.—C. G.; Markoski, L. J.; Spilman, G. E.; Mielewski, D. F.; Martin, D. C. *Macromolecules* **1995**, 28, 3301. (b) Chino, K.; Takata, T.; Endo, T. *Macromolecules* **1995**, 28, 5947. (c) Klärner, F.—G.; Lobert, M.; Naatz, U.; Bandmann, H.; Boese, R. *Chem.—Eur. J.* **2003**, 9, 5036.

(5) Jakiela, D. J.; Helquist, P.; Jones, L. D. *Organic Syntheses*; Wiley: New York, 1990; *Collect. Vol.* 7, p 326, and references therein.

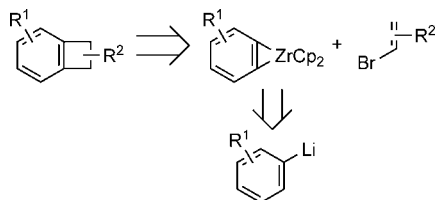
(6) Barluenga, J.; Rodríguez, F.; Álvarez-Rodrigo, L.; Fañanás, F. J. *J. Chem. Soc. Rev.* **2005**, 34, 762.

(7) (a) Barluenga, J.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J.; Sordo, T. L.; Campomanes, P. *Angew. Chem., Int. Ed.* **2007**, 46, 2607. (b) Barluenga, J.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Org. Lett.* **2007**, 9, 3081. (c) Barluenga, J.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, 45, 6362. (d) Barluenga, J.; Fernández, A.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Synlett* **2005**, 2513. (e) Barluenga, J.; Álvarez-Rodrigo, L.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2004**, 43, 3932. (f) Barluenga, J.; Rodríguez, F.; Álvarez-Rodrigo, L.; Zapico, J. M.; Fañanás, F. J. *Chem.—Eur. J.* **2004**, 10, 109.

(8) Barluenga, J.; Rodríguez, F.; Álvarez-Rodrigo, L.; Fañanás, F. J. *Chem.—Eur. J.* **2004**, 10, 101.

zene derivatives could be easily available from simple aryllithium compounds and alkenyl bromides as depicted in Scheme 1. Details on the development of this strategy are given in this paper.

Scheme 1. Proposal for the Zirconocene-Mediated Synthesis of Cyclobutabenzene Derivatives



We initiated our study with the reaction of different aryllithium compounds **1** with zirconocene methyl chloride and bromoalkenes **2** using THF as solvent. Thus, after heating the mixture at 80 °C in a sealed tube during 14 h the reaction was quenched with H₂O to obtain the functionalized cyclobutabenzene derivatives **3a–g** (Scheme 2 and

Scheme 2. Synthesis of Cyclobutabenzenes **3a–g** from Aryllithium Compounds **1** and Alkenyl Bromides **2** Mediated by Zirconocene

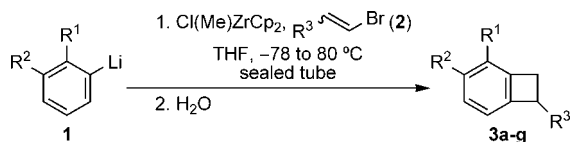


Table 1). These compounds **3a–g** were obtained in all cases as single regioisomers. We only observed the formation of that isomer in which the R¹ group is far away from the R³ group.

Table 1. Cyclobutabenzene Derivatives **3a–g** from Aryllithium Compounds **1** and Bromoalkenes **2** Mediated by Zirconocene

1	R ¹	R ²	2	R ³	3	yield ^a (%)
1a	Me	H	2a ^b	Me	3a	76
1b	Et	H	2a ^b	Me	3b	72
1c	OMe	H	2a ^b	Me	3c	60
1c	OMe	H	2b ^c	Dec ^d	3d	70
1d	Ph	H	2a ^b	Me	3e	65
1d	Ph	H	2c ^c	Bn	3f	79
1e	–(CH ₂) ₄ –	H	2a ^b	Me	3g	62

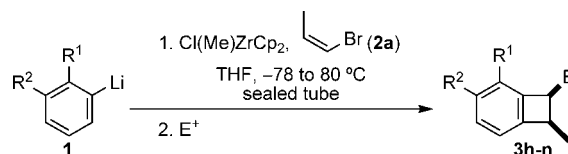
^a Isolated yield based on starting **1**. ^b *cis*-Isomer. ^c *trans*-Isomer. ^d Dec = decyl.

Noteworthy, this process supposes an easy functionalization of two adjacent positions of the initial aromatic ring

and the reaction of both of the C_{sp}² of the alkenyl bromide. This transformation is accomplished through non conventional reactions of the starting materials: functionalization of an aromatic C–H bond, substitution of a bromine atom in an alkenyl bromide or a formal and net [2 + 2] cycloaddition reaction between an aryllithium reagent and an alkenyl bromide.

To expand the synthetic possibilities of this reaction, we carried out a set of experiments adding different electrophiles at the end of the reaction. Thus, the reaction of aryllithium compounds **1** and zirconocene methyl chloride followed by treatment with bromoalkene **2a** and further reaction with appropriate electrophiles led to the formation of the new cyclobutabenzene derivatives **3h–n** substituted at the 7- and 8-positions (Scheme 3 and Table 2). Notably, products **3h–n**

Scheme 3. Synthesis of Cyclobutabenzenes **3h–n** from Aryllithium Compounds **1**, Alkenyl Bromide **2a**, and Electrophiles



were obtained as single regio- and *cis*-diastereoisomers. Those examples where the reaction with the electrophile implies the formation of a new carbon–carbon bond should be remarked (reactions with phenyl iodide, allyl chloride, and 2-cyclohexenone as electrophiles).

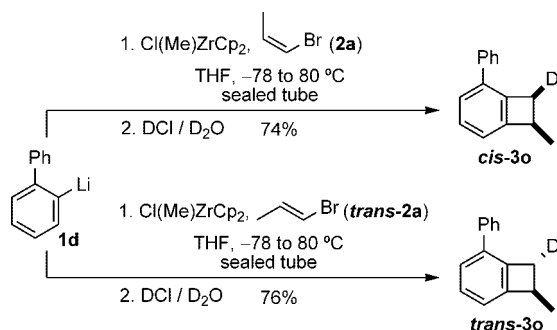
Table 2. Cyclobutabenzenes **3h–n** from Aryllithium Compounds **1**, Alkenyl Bromide **2a**, and Electrophiles

1	R ¹	R ²	E ⁺	E	3	yield ^a (%)
1a	Me	H	allyl chloride ^b	allyl	3h	76
1a	Me	H	2-cyclohexenone ^c	3-oxocyclohexyl	3i	74 ^d
1c	OMe	H	D ₂ O	D	3j	64
1c	OMe	H	allyl chloride ^b	allyl	3k	62
1c	OMe	H	PhI ^e	Ph	3l	75
1f	H	H	D ₂ O	D	3m	75
1f	H	H	allyl chloride ^b	allyl	3n	72

^a Isolated yield based on starting **1**. ^b CuCl (5 mol %) was also added. The reaction was stirred at 60 °C for 6 h. ^c CuCl (5 mol %), LiCl (1 equiv) and TMSCl (2 equiv) were also added. The reaction was stirred at 60 °C for 6 h. ^d 4: 1 mixture of diastereoisomers. Isomers at the stereogenic center of the cyclohexyl moiety. ^e CuCl (1.5 equiv), LiCl (1 equiv), and Pd(PPh₃)₄ (5 mol %) were also added. The reaction was stirred at 60 °C for 6 h.

To gain further insight into the mechanism of formation of cyclobutabenzenes **3**, we performed the reaction of organolithium **1d** with zirconocene methyl chloride, and we treated the reaction mixture with both **2a** (*cis*-isomer) and *trans*-**2a** followed by addition of a solution of DCl in D₂O (Scheme 4). As expected, the reaction with **2a** led to *cis*-**3o** in high yield. However, the reaction with *trans*-**2a** exclu-

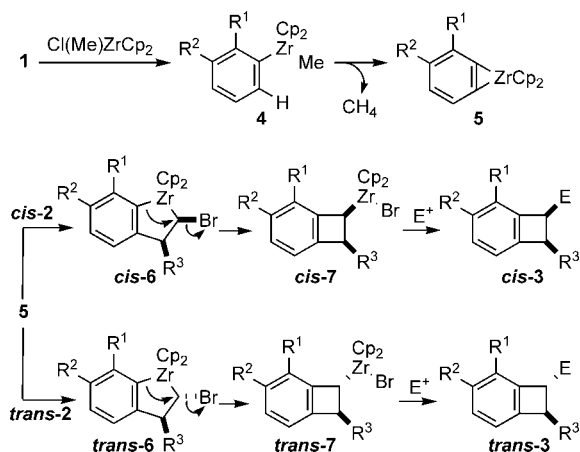
Scheme 4. Cyclobutabenzenes *cis*-**3o** and *trans*-**3o** by the Zirconocene-Mediated Reaction of Aryllithium **1d** with Bromoalkenes **2a** and *trans*-**2a**, Respectively



sively led to *trans*-**3o**. The structure of these products was assigned on the basis of different NMR studies including HSQC-NOESY experiments performed on *trans*-**3o** and the totally hydrogenated compound **3e**.

All these results allow us to propose the mechanism shown in Scheme 5 for the formation of cyclobutabenzenes **3**. In

Scheme 5. Proposed Mechanism of Formation of Benzocyclobutenes **3**



first place, the transmetalation reaction of the organolithium compounds **1** and the zirconocene methyl chloride leads to the formation of the new aryl–zirconocene complex **4**. These complexes are known to evolve through a β -abstraction of

a hydrogen atom to furnish the aryne–zirconocene complex **5** and a molecule of methane.⁹ The insertion reaction of the corresponding alkenyl bromide **2** and complex **5** generates the intermediates *cis*-**6** or *trans*-**6** depending on the structure of the alkenyl bromide **2**. It is important to note that the insertion process is doubly regioselective: insertion occurs at the zirconium–carbon bond of **5** which is far away from the R^1 group. Also, the double bond of the alkenyl bromide **2** is oriented during the insertion step so that the bromine atom is close to the zirconocene moiety. An intramolecular migratory insertion process is proposed to explain the formation of the cyclobutene core observed in the final products.¹⁰ This reaction leads to *cis*-**7** from *cis*-**6** and *trans*-**7** from *trans*-**6**.

Regarding the diastereoselectivity of the reaction, it should be noted that the migratory insertion process leading to *cis*-**7** or *trans*-**7** occurs with inversion of the configuration of the carbon initially substituted by the bromine atom ($\text{S}_\text{N}2$ like process). Finally, the reaction of intermediate *cis*-**7** or *trans*-**7** with the corresponding electrophile leads, after the hydrolysis step, to the final benzocyclobutane derivatives *cis*-**3** or *trans*-**3** respectively (Scheme 5).

In summary, we have developed a new zirconocene-mediated method for the selective synthesis of cyclobutabenzene derivatives through a three-component one-pot coupling reaction of an aryllithium compound, an alkenyl bromide, and an electrophile. The method is broad in scope, and it offers the option of varying the substituents of both the aryl moiety and the cyclobutene ring. This method implies nonconventional transformations of simple starting materials, providing an elegant synthesis of highly functionalized cyclobutabenzenes not easily available by other procedures. The key steps of the process are the formation of an aryne–zirconocene complex and a doubly regioselective insertion reaction of an alkenyl bromide.

Acknowledgment. Financial support for this work was provided by the Ministerio de Educación y Ciencia of Spain (CTQ2007-61048/BQU and predoctoral grants to L.A.-R. and J.C.).

Supporting Information Available: Experimental procedures and characterization data. Copies of ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL801652H

(9) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047.

(10) For an excellent account on zirconium-mediated migratory insertion processes, see: (a) Dixon, S.; Whitby, R. J. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; p 86. See also: (b) Kasatkin, A.; Whitby, R. J. *Tetrahedron* **2003**, *59*, 9857.