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Naphthalenes, Isoquinolines, and a Benzazocine from Zirconocene–Copper-Mediated Coupling of Benzocyclobutadiene with Nitriles and Alkynes

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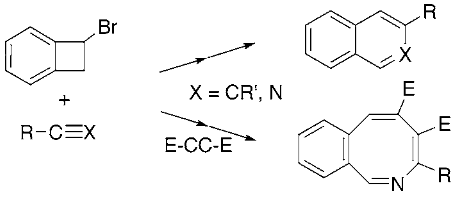
ABSTRACT



Commercially available 1-bromobenzocyclobutene is a potentially useful synthon particularly with the application of organometallic methodology. Here we show that it is readily converted into Cp_2Zr(benzocyclobutadiene), which couples with alkynes or nitriles giving five-membered zirconacycles. Treatment of these alkyne- or nitrile-derived zirconacycles with CuCl yields substituted naphthalenes, isoquinolines, or in the presence of MeO_2C–CC–CO_2Me, a 2-benzazocine containing an eight-membered ring.

Reactions mediated by transition metals have played an important role in synthetic methodology during the last quarter century.[1] Zirconocene complexes have attracted much interest in this regard.[2] Recently, transmetalation of zirconacycles onto Cu and Ni have opened new avenues in carbon−carbon and carbon−heteroatom bond coupling chemistry.[3]

Benzocyclobutenes are useful synthons in organic chemistry.[4] Application of organometallic methodology could greatly expand their usefulness. To this end, we recently reported the zirconocene complex, Cp_2ZrMe(1-benzocyclobutenyl) **2**, readily prepared from commercially available 1-bromobenzocyclobutene **1**, its thermolysis to yield the novel complex $Cp_2Zr(\eta^2$-benzocyclobutadiene$)(PMe_3)$ **3**, and the reactions of **3** with alkynes, nitriles, and isocyanides to give zirconacycles fused to the benzocyclobutene (Scheme 1).[5]

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[1] *Organometallics in Synthesis*, 2nd ed.; Schlosser, M., Ed.; Wiley: New York, 2002.

[2] Recent reviews: (a) Negishi, E. In *Organometallics in Synthesis*, 2nd ed.; Schlosser, M., Ed.; Wiley: New York, 2002; Chapter 8, pp 925−1002. (b) Majoral, J.-P.; Igau, A.; Cadierno, V.; Zablocka, M. *Top. Curr. Chem.* **2002**, *220*, 53−77. (c) Takahashi, T.; Kotora, M.; Hara, R.; Xi, Z. F. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2591−2602. (d) Negishi, E.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755−769. (e) Majoral, J.-P.; Igau, A. *Coor. Chem. Rev.* **1998**, *176*, 1−16. (f) Majoral, J. P.; Meunier, P.; Igau, A.; Pirio, N.; Zablocka, M.; Skowronska, A.; Bredeau, S. *Coord. Chem. Rev.* **1998**, *178−180* (part 1), 145−167. (g) Avarvari, N.; Rosa, P.; Mathey, F.; Le Floch, P. *J. Organomet. Chem.* **1998**, *567*, 151−155. (h) Whitby, R. J. *Transition Met. Org. Synth.* **1997**, 133−165. (i) Fillery, S. F.; Gordon, G. J.; Luker, T.; Whitby, R. J. *Pure Appl. Chem.* **1997**, *69*, 633−638. (j) Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burkalov, V. V.; Rosenthal, U. *Synlett* **1996**, 111−118. (k) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696−1701.

[3] (a) Leading references: Liu, Y.; Zhong, Z.; Nakajima, K.; Takahashi, T. *J. Org. Chem.* **2002**, *67*, 7451−7456. (b) Takahashi, T.; Li, Y.; Ito, T.; Xu, F.; Nakajima, K.; Liu, Y. *J. Am. Chem. Soc.* **2002**, *124*, 1144−1145. (c) Takahashi, T.; Tsai, F.-Y.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059−5067. (d) Takahashi, T.; Li, Y.; Stepnicka, P.; Kitamura, M.; Liu, Y.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 576−582.

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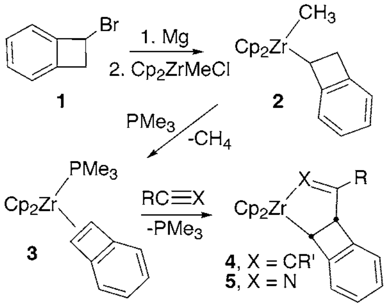
Scheme 1



We now report that when these zirconacycles are treated with 2 equiv of CuCl, naphthalenes[6] **6**−**8** and isoquinolines[7] **9** and **10** are obtained and, if dimethylacetylenedicarboxylate (DMAD) is added to the reaction of **5** (R = *t*-Bu), benzazocine[8,9] **11** is formed in 57% isolated yield based on **5** (Scheme 2). Isolated yields of the naphthalene and isoquinolines, based on **4** or **5**, are given in Table 1. Detailed procedures for these reactions and following reactions and compound characterization data can be found in Supporting Information.

Scheme 2

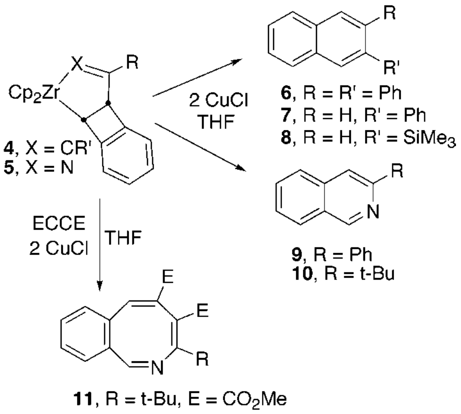


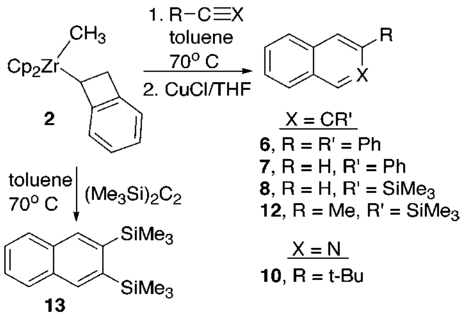
Table 1. Isolated Yields for Naphthalenes and Isoquinolines

compound	6	7	8	9	10	12	13
method of Scheme 2	94%	90%	89%	85%	89%		
method of Scheme 3	78%	72%	75%		61%	70%	85%

While the reactions in Scheme 2 give high yields of the naphthalenes, isoquinolines, and benzazocine, the procedure from commercially available 1-bromobenzocyclobutene involves multiple workups and the critical η^2-benzocyclobutadiene complex, formed by methane elimination from **2**, must be stabilized with trimethylphosphine prior to the insertion reactions. We have therefore worked to shorten the procedure and eliminate the use of trimethylphosphine. This can be achieved by trapping the η^2-benzocyclobutadiene complex by immediate cycloaddition of the alkynes and nitriles and by adding CuCl to the reaction mixture.

A smooth reaction occurs when benzocyclobutenyl complex **2** is heated with diphenylacetylene and the coupled product **4** is formed directly. Addition of THF and 2 equiv of CuCl to the reaction mixture gives 2,3-diphenylnaphthalene **6** in 78% isolated yield (Scheme 3 and Table 1).

Scheme 3



A similar procedure with the alkynes, RCCH (R = $SiMe_3$ and Ph), and $Me_3Si{-}CC{-}Me$ gives the corresponding

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(4) Mehta, G.; Kotha, S. *Tetrahedron* **2001**, *57*, 625−659.

(5) Ramakrishna, T. V. V.; Lushnikova, S.; Sharp, P. R. *Organometallics* **2002**, *21*, 5685−5687.

(6) Recent naphthalene syntheses: (a) Yasukawa, T.; Satoh, T.; Miura, M.; Nomura, M. *J. Am. Chem. Soc.* **2002**, *124*, 12680−12681. (b) Edwards, A. J.; Willis, A. C.; Wenger, E. *Organometallics* **2002**, *21*, 1654−1661. (c) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650−12651. (d) Duan, Z.; Nakajima, K.; Takahashi, T. *Chem. Commun.* **2001**, 1672−1673. (e) Yoshikawa, E.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2000**, *39*, 173−175. (f) Iwasawa, N.; Shido, M.; Maeyama, K.; Kusama, H. *J. Am. Chem. Soc.* **2000**, *122*, 10226−10227. (g) Pena, D.; Pérez, D.; Guitián, E.; Castedo, L. *J. Am. Chem. Soc.* **1999**, *121*, 5827−5828.

(7) Recent isoquinoline syntheses: (a) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557−3560. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437−3444. (c) Abdou, W. M.; Fahmy, A. F. M.; Kamel, A. A.-A. *Eur. J. Org. Chem.* **2002**, 1696−1701. (d) Tsutsui, H.; Narasaka, K. *Chem. Lett.* **2001**, 526−527. (e) Prauda, I.; Reiter, J. *J. Heterocycl. Chem.* **2001**, *38*, 199−204. (f) Prauda, I.; Kovesdi, I.; Trinka, P.; Reiter, J. *J. Heterocycl. Chem.* **2001**, *38*, 403−414. (g) Hussain, H.; Kianmehr, E.; Durst, T. *Tetrahedron Lett.* **2001**, *42*, 2245−2248. (h) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973−2976. (i) Campos, P. J.; Caro, M.; Rodriguez, M. A. *Tetrahedron Lett.* **2001**, *42*, 3575−3577. (j) Ameur Meziane, M. A.; Royer, S.; Bazureau, J. P. *Tetrahedron Lett.* **2001**, *42*, 1017−1020. (k) Ishii, H.; Imai, Y.; Hirano, T.; Maki, S.; Niwa, H.; Ohashi, M. *Tetrahedron Lett.* **2000**, *41*, 6467−6471. (l) Hoshina, H.; Kubo, K.; Morita, A.; Sakurai, T. *Tetrahedron* **2000**, *56*, 2941−2951. (m) Brun, E. M.; Gil, S.; Mestres, R.; Parra, M. *Synthesis* **2000**, 273−280.

(8) Azocine review: Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131−9166.

(9) Recent azocine syntheses: (a) Hamamoto, H.; Anilkumar, G.; Tohma, H.; Kita, Y. *Chem. Commun.* **2002**, 450−451. (b) Gil, L.; de Freitas Gil, R. P.; dos Santos, D. C.; Marazano, C. *Tetrahedron Lett.* **2000**, *41*, 6067−6069. (c) Taylor, E. C.; Dowling, J. E.; Bhatia, B. *J. Org. Chem.* **1999**, *64*, 441−446. (d) Nicolaou, K. C.; Namoto, K. *Chem. Commun.* **1998**, 1757−1758. (e) Torisawa, Y.; Soe, T.; Katoh, C.; Motohashi, Y.; Nishida, A.; Hino, T.; Nakagawa, N. *Heterocycles* **1998**, *47*, 655−659. (f) Vedejs, E.; Galante, R. J.; Goekjian, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 3613−3622. (g) Winkler, J. D.; Stelmach, J. E.; Axten, J. *Tetrahedron Lett.* **1996**, *37*, 4317−4318. (h) Yoneda, R.; Sakamoto, Y.; Oketo, Y.; Harusawa, S.; Kurihara, T. *Tetrahedron* **1996**, *52*, 14563−14576. (i) Donati, D.; Fusi, S.; Ponticelli, F. *Tetrahedron Lett.* **1996**, *37*, 5783−5786.

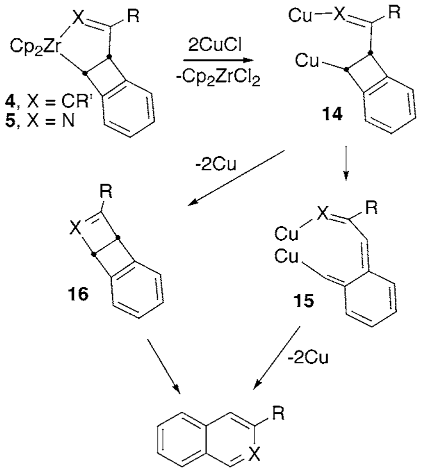
naphthalenes **7**, **8**, and **12**, respectively (Scheme 3). Interestingly, the bulky acetylene, $Me_3Si-CC-SiMe_3$, which does not react with **3**, does react with **2** and yields directly the naphthalene, 2,3-bistrimethylsilylnaphthalene **13** *without* addition of CuCl. The mechanism involved in this transformation remains to be clarified.

The shortened procedure gives the naphthalenes in 70−85% isolated yield based on **2** (Table 1). Reaction of **2** with *t*-BuCN and Ph-CN were carried out in a similar fashion (Scheme 3). *t*-BuCN gives isoquinoline **10** in 61% yield, but PhCN gives only traces of 3-phenylisoquinoline **9**.

Attempts to further shorten the procedure by eliminating the isolation of **2** have not yet been successful. Complex **2** only forms cleanly in THF, yet the thermolysis of **2** proceeds cleanly only in toluene.

A proposed pathway for the CuCl reactions is shown in Scheme 4 and is initiated by transmetalation from Zr to Cu to give intermediate **14**. Opening of the four-membered ring may then occur to give **15** from which Cu elimination gives the naphthalene or isoquinoline. Alternatively, this sequence could be reversed with Cu elimination from **14** giving Dewar structure **16**, which then opens. Since species such as **16** are known to be reasonably stable at ambient temperatures,[10] **15** is favored. Azocine formation can then occur by coupling of the second alkyne with **14** or **15**. It should be noted that naphthalenes and isoquinolines have previously been prepared from benzocyclobutenes and alkynes or nitriles but by a different nonmetal-mediated pathway involving benzocyclobutene ring opening followed by cycloaddition of the alkyne or nitrile to the reactive ring-opened product.[11]

Scheme 4



In conclusion, we have demonstrated that Cp_2ZrMe(1-benzocyclobutenyl), **2**, is a reactive and useful reagent in benzocyclobutene chemistry. This usefulness is based on metal-mediated processes, including insertion, coupling, transmetalation, and reductive elimination, and has resulted in new methods for the formation of substituted naphthalenes, isoquinolines, and benzazocines. It is anticipated that **2** and its derivatives will be useful in the synthesis of a number of interesting new natural and unnatural products. Further results will be reported in due course.

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Supporting Information Available: Detailed descriptions of experimental procedures and compound characterization data and references. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] (a) Miki, S.; Ema, T.; Shimizu, R.; Nakatsuji, H.; Yoshida, Z. *Tetrahedron Lett.* **1992**, *33*, 1619−1620. (b) Grimme, W. *Chem. Ber.* **1978**, *111*, 2563−2570.

[11] (a) Fitzgerald, J. J.; Michael, F. E.; Olofson, R. A. *Tetrahedron Lett.* **1994**, *35*, 9191−9194. (b) Andersen, N. G.; Maddaford, S. P.; Keay, B. A. *J. Org. Chem.* **1996**, *61*, 2885−2887. (c) Craig, D.; Robson, M. J.; Shaw, S. J. *Synlett* **1998**, 1381−1383.