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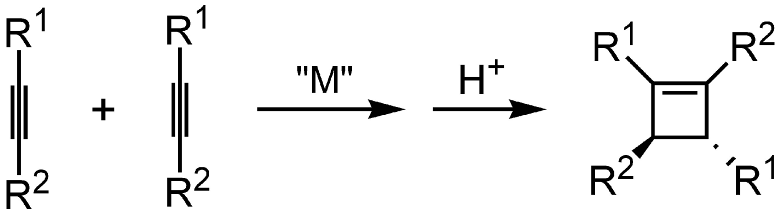
J. Am. Chem. Soc., **2005**, 127 (11), 3662-3663• DOI: 10.1021/ja042636m • Publication Date (Web): 22 February 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

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Published on Web 02/22/2005

Highly Regio- and Stereoselective Synthesis of Tetrasubstituted Cyclobutenes via Cyclodimerization of Alkynes Mediated by Zirconium

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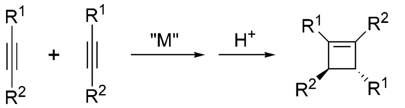
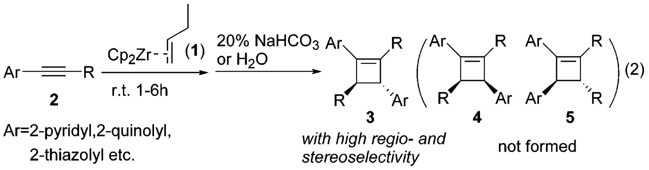
Transition-metal-mediated inter- or intramolecular cyclodimerization of alkynes has received considerable attention during the last several decades, which, in most cases, results in the formation of η^4-cyclobutadiene metal complexes.[1] A great deal of work has been done in this area with regards to mechanistic and synthetic aspects. The synthetic approaches for alkyne cyclodimerization mainly include (i) reactions of alkynes with metal carbonyl derivatives,[2] (ii) reactions of alkynes with coordination complexes and inorganic salts,[3] and (iii) syntheses via precursors derived indirectly from alkynes.[4] Among various reagents, Co complexes are the most widespread owing to their high capacity for cyclizing functionalized alkynes.[2] However, so far, the triple bond moiety of alkynes used in cyclodimerization reactions has only been incorporated in products as double bonds, and there has been no example in which one of the triple bonds is reduced to a single bond, that is, the formation of cyclobutene derivatives, as shown in eq 1. Although, Lewis acid[5a−d] or transition-metal[5e−f]-promoted [2 + 2] cycloadditions of alkenes and alkynes or alkyne/alkene cross coupling via metallacyclopentenes[6] to give cyclobutenes have been reported. In this paper, we report the first example of zirconium-induced regioselective cyclodimerization of alkynes, which afforded a new access to highly regio- and diastereoselective tetrasubstituted cyclobutenes.



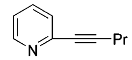
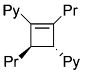
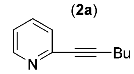
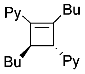
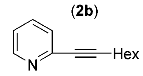
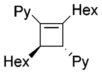
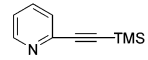
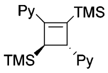
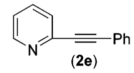
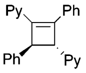
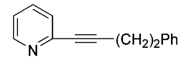
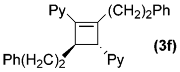
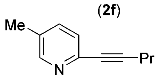
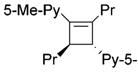
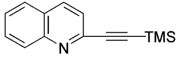
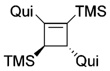
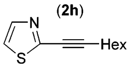
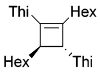
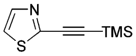
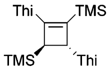
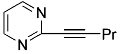
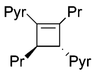
(1)

Zirconocene coupling route using dialkylzirconocenes, Cp_2ZrBu_2 or Cp_2ZrEt_2, has proven to be a powerful methodology for oxidative coupling of alkynes.[7] The thus formed zirconacyclopentadienes are very useful intermediates in organic synthesis. However, there is no report of direct cyclodimerization of two alkynes in this system. During the course of our study on the reaction of "Cp_2Zr" with heteroaryl-substituted acetylenes, we found, interestingly, that cyclobutene derivatives **3** were formed in good to high yields after hydrolysis by alkali solution or water (eq 2).



Alkynes bearing various heteroaromatic groups **2a**−**k** were synthesized by sonogashira coupling of heteroaryl bromides with 1-alkynes in high yields.[8] A typical procedure for alkyne coupling is as follows. To a solution of Cp_2ZrBu_2, which was prepared from Cp_2ZrCl_2 (1.1 mmol) and 2 equiv of BuLi (2.2 mmol, 1.6 M solution in hexane) in THF at −78 °C, was added alkyne **2a** (2 mmol). The mixture was warmed to room temperature and stirred for 1 h. After the resulting golden-yellow solution was quenched by 20% $NaHCO_3$, *trans*-**3a** was formed in 78% yield. The representative results are given in Table 1. In all cases, the ring-closure products of **3a**−**k** were obtained in high regio- and stereoselectivity, in which the substituents of alkynes connected to each other in a head-to-tail pattern and only *trans*-**3** were observed. The cis isomer **4** and the regioisomer **5** were not detected. The stereochemical assignments of the cycloadducts **3** are supported by ^1H NMR coupling constants, as well as X-ray crystallographic analysis. Trans-3,4-disubstituted cyclobutenes are readily characterized by a small coupling constant ($^3J_{HH}$ = 0−2.1 Hz) between the four-membered ring protons. X-ray crystallography of **3e** bearing

Table 1. Selective Formation of Tetrasubstituted Cyclobutenes via Alkyne Cyclodimerization

Entry	Ar—≡—R	Temp/Time	Product[a]	Yield[b]
1	 (**2a**)	r.t. 1h	 **(3a)**	78 (71)
2	 (**2b**)	r.t. 1h	 **(3b)**	78 (65)[c]
3	 (**2c**)	r.t. 1h	 **(3c)**	82 (65)
4	 (**2d**)	r.t. 3h	 **(3d)**	80 (56)
5	 (**2e**)	r.t. 6h	 **(3e)**	40 (21)[d]
6	 (**2f**)	r.t. 1h	 **(3f)**	50 (45)
7	 (**2g**)	r.t. 1h	 **(3g)**	88 (73)
8	 (**2h**)	r.t. 3h 50°C, 6h	 **(3h)**	80 (65)
9	 (**2i**)	r.t. 1h	 **(3i)**	56 (49)[e]
10	 (**2j**)	r.t. 3h 50°C, 12h	 **(3j)**	34 (24)
11	 (**2k**)	r.t. 3h 50°C, 1h	 **(3k)**	28 (23)

[a] Qui = 2-quinolyl, Thi = 2-thiazolyl, Pyr = 2-pyrimidyl. [b] NMR or GC yields. Isolated yields are given in parentheses. [c] (1*E*,3*Z*)-1,3-Di(2-pyridyl)-2-butyl-1,3-octadiene was obtained in 5% yield. [d] Dienes of **7** and **8** were obtained in a combined yield of 38%. [e] (1*E*,3*Z*)-1,3-Di(2-thiazolyl)-2-hexyl-1,3-decadiene was obtained in 17% yield.

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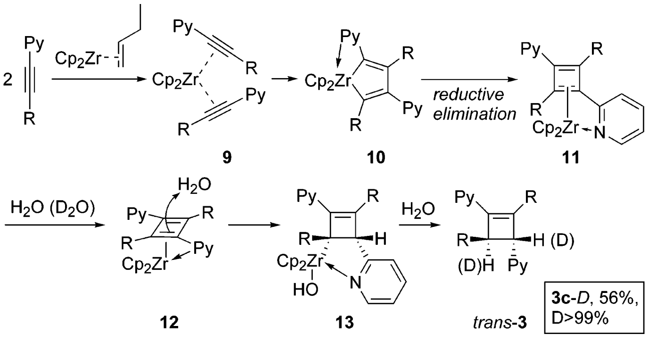
Scheme 1



2-pyridyl and a phenyl substituent confirmed the cyclobutene structure and clearly showed the trans configuration of **3e**. Structure assignment of silyl-containing product **3d** is supported through the X-ray crystallographic analysis of its bis(1-methyl)pyridium salt **6** prepared by the reaction of **3d** with methyl iodide. Furthermore, COSY NMR experiments and 2D heteronuclear multiple bond coherence (HMBC) techniques performed on **3a** provided additional support for the regiochemistry of the alkyl-substituted products. 2-Pyridylalkynes bearing an alkyl or trimethylsilyl group were smoothly transformed into *trans*-cyclobutenes in 50−88% yield (entries 1−4, 6, and 7). In contrast, the phenyl-substituted alkyne gave a lower (40%) yield of **3e** (entry 5), along with the formation of two regioisomers of linear butadiene derivatives, namely, (1*E*,3*E*)-1,4-di(2-pyridyl)-2,3-diphenyl-1,3-butadiene (**7**) and (1*Z*,3*Z*)-1,4-diphenyl-2,3-di(2-pyridyl)-1,3-butadiene (**8**) in 16 and 22% yields, respectively, perhaps due to the steric hindrance caused by the phenyl group. Employing 2-quinolylalkyne **2h** also proceeded well to give **3h** in 80% yield. When alkynes bearing a 2-thiazolyl or 2-pyrimidyl group were subjected to the reactions, the corresponding products were obtained in 28−56% yield (entries 9−11). It should be noted that using 2-thienylalkyne, 3-pyridylalkyne, or aryl/alkyl alkyne failed to give cyclobutenes; instead, butadienes were formed as sole products (see Supporting Information). These results indicated that the nitrogen-containing heterocycle group is necessary, and that the nitrogen atom must locate at the right position in which it might coordinate to the metal more efficiently.

On the basis of the above results and the known chemistry of cyclobutadiene metal complex, we tentatively propose a mechanism as depicted in Scheme 1, which involves the following. (i) Oxidative coupling of the two complexed alkynes affords unsymmetrically substituted zirconacyclopentadiene **10**, in which a pyridyl group may coordinate with zirconium through its nitrogen atom. The high regioselectivity may be caused by a cooperation of steric and electronic effects. (ii) Reductive elimination of **10** gives N-donor-stabilized η^2-cyclobutadiene complex[9] **11**. To account for the trans selectivity of **3**, an external electrophilic attack of water at the face opposite the metal on coordinated alkene is suggested. The protonation occurred at the carbon atom in the α-position to the pyridine ring to give **13**,[10] which affords *trans*-**3** by a second protonation. Although the attempted isolation of the zirconium intermediate has not been successful, the deuteration experiment of the reaction mixture of **2c** provided evidence in support of the intermediacy of the η^2-cyclobutadiene complex. The dideuterated compound *trans*-**3c**−D was formed in 56% yield with >99% deuterium incorporation. More interestingly, it was found that quenching the reaction mixture using bulky weak acid, such as (+)-camphoric acid, could afford the cis isomer of **3**. In the case of **2c**, the cis/trans isomers were obtained in a ratio of 4.2:1 with a combined isolated yield of 54%, which turned out to be easily separated by column chromatography. Ligand-induced reductive elimination in zirconium chemistry has been demonstrated.[6b,11] Thus, it is reasonable to assume that it is the interaction between Zr and the nitrogen atom, which locates in the close environment of the metal, that promotes reductive elimination of **10** to **11**. However, formation of an η^4-cyclobutadienezirconium complex as an intermediate could not be ruled out. It is interesting to note that although a variety of transition-metal systems are capable of cyclizing two alkynes, the newly formed cyclobutadienes are typically not readily released from complexes.[1] The method presented here provided a new mode of alkyne cyclodimerization, in which the decomplexation of the intermediacy of a coordinated zirconium group appears to be fairly easy.

In summary, a zirconium-induced cyclodimerization of heteroaryl-substituted alkynes has been described, which provides a facile synthesis of tetrasubstituted cyclobutenes with high regio- and diastereoselectivity. This method also enhances the synthetic utility of zirconocene-induced coupling reaction of alkynes. Further research is currently underway to establish the detailed mechanism and to clarify the factors leading to cyclization of two alkynes.

Acknowledgment. We thank the National Natural Science Foundation of China (Grant No. 20402019), Chinese Academy of Science, and the Science and Technology Commission of Shanghai Municipality for financial support. We also thank Professor Houming Wu for 2D NMR determination.

Supporting Information Available: Experimental details and spectroscopic characterization of all isolated compounds, and CIF files giving crystallographic data of **3e**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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JA042636M