# ON THE REVERSIBILITY OF ALKENE CYCLOZIRCONATION

Douglass F. Taber*, James P. Louey and Julie A. Lim[1]

Department of Chemistry & Biochemistry, University of Delaware, Newark, DE 19716 USA

Summary: Diene 8, under cyclozirconation conditions, rapidly dimerizes to 10. This dimerization is reversible, slowly at room temperature and rapidly at 75°C. After equilibration, the dominant product is 12, the product of *intramolecular* cyclozirconation.

*Key words: carbocyclization, cyclometallation, cyclozirconation, diastereoselective, reversible, equilibrating*

In 1989, we (2) and Negishi (3) reported a powerful new method for ring construction, intramolecular diene cyclozirconation (1 -> 2 -> 3) (4,5). We are now involved in a general investigation of the scope and applicability of this cyclization. A key question is whether the observed products are being formed under kinetic or thermodynamic control. We now report that a cyclic alkene (8, **Scheme 1**) can participate in
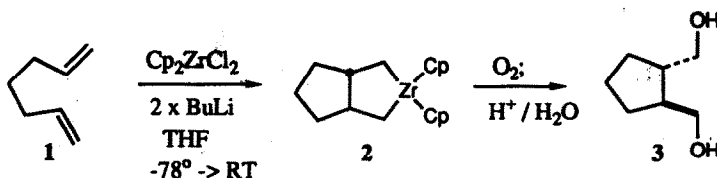


this reaction (6), that this particular intramolecular cyclozirconation proceeds with high diastereoselectivity, and that *intermolecular* alkene cyclozirconation is readily reversible (7, 8).

The starting diene for this investigation was prepared (**Scheme 1**) from the Diels-Alder adduct 6 (9, 10) of ethyl acrylate and 1, 3-cyclohexadiene. Alkylation from the less hindered face of the derived enolate provided 7 as the dominant diastereomer. Reduction then led to the stereochemically homogeneous alcohol 8.

To effect cyclozirconation, zirconocene dichloride (**Scheme 2**) was treated with three equivalents of n-BuLi (11, 12) at -5°C in toluene (13). The diene was then added, and the reaction mixture was stirred and allowed to come to room temperature. TLC analysis of the cyclozirconation reaction mixture indicated that 8 (TLC $R_f$ (20% EtOAc/petroleum ether) = 0.44) rapidly disappeared, and that a new material (TLC $R_f$ = 0.17) was formed. After two hours at room temperature, this product dominated in the reaction mixture. Acidic hydrolysis at this point, followed by silica gel chromatography, provided diol 10 (14), the product of intermolecular cyclozirconation (15).

## Scheme 1
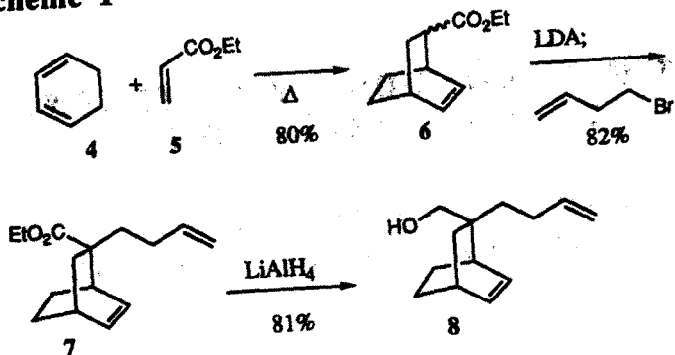


## Scheme 2
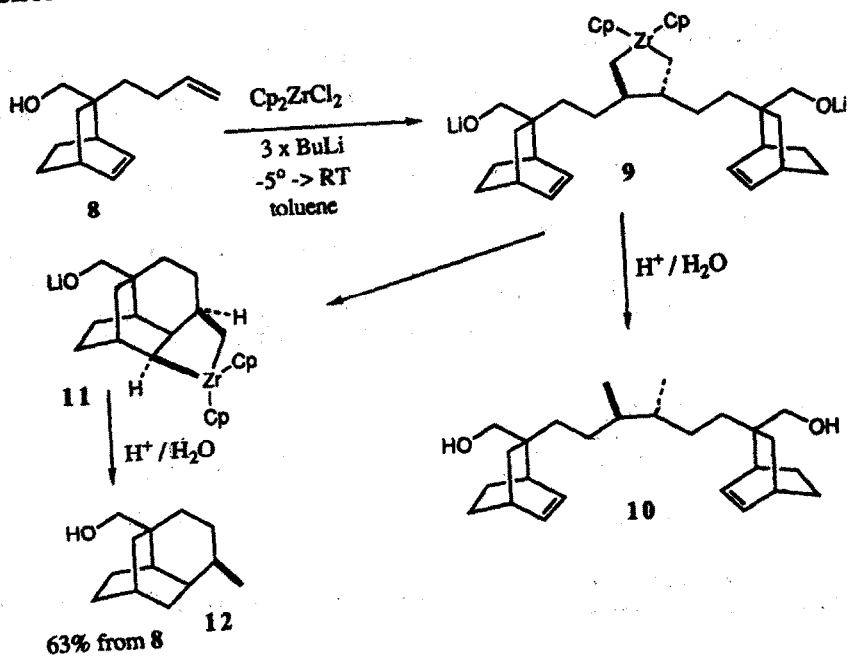
In the expectation that the intermolecular reaction might be reversible, the cyclozirconation of 8 was again attempted. After 19 hours at room temperature, a new spot (TLC $R_f$ = 0.36) had appeared. Quenching the reaction at this point, followed by silica gel chromatography, led to the isolation of this new substance, alcohol 12, the product of intramolecular cyclozirconation (16). In this run, 12 was isolated in 26% yield, along with a 37% yield of dimer 10.

In a third run, the reaction mixture, prepared in the same way, was maintained at 75°C for 1.5 h. TLC analysis at this time indicated that 12 had become the dominant product of the reaction. Quenching, followed by silica gel chromatography, provided 12 in 63% yield, accompanied by a 3% yield of 10.

At first inspection, intramolecular cyclozirconation of 8 might be expected to be particularly difficult. One of the cyclopentadienyl substituents of 11 (Scheme 2) is endocyclic, in a sterically very congested area. A key consideration, however, is that the carbon-zirconium bond length is about 2.3 angstroms. Thus, the zirconocene wedge sits somewhat away from the carbon skeleton, and there is room for the endocyclic cyclopentadienyl ring.

It should be noted that as the cyclization proceeds, only one diastereomer of the zirconacycle is possible. The scaffolding of the zirconacycle thus sets the relative configuration of the newly-formed methyl substituent, and the net transformation (8 to 12) is completely diastereoselective. Application of this inherent diastereoselectivity to natural product synthesis will be reported shortly (6).

**References and Notes:**

1.    Undergraduate research participant, University of Delaware.

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3.    Rousset, C.J.; Swanson, D.R.; Lamaty, F.; Negishi, E.-i. *Tetrahedron Lett.* 1989, *30*, 5105.

4.    For an earlier example of intramolecular cyclozirconation, see Yasuda, H.; Nagasuna, K.; Akita, M.; Lee, K.; Nakamura, A. *Organomet.* 1984, *3*, 1470.

5.    For more recent examples of alkene cyclozirconation, see (a) Mori, M.; Uesaka, N.; Shibasaki, M. *J. Chem. Soc., Chem. Commun.* 1990, 1222. (b) Dzhemiliv, U.M.; Ibragimov, A.G.; Morozov, A.B.; Muslukov, R.R.; Tolstikov, G.A. *Izv. Akad. Nauk SSSR, Ser. Khim.* 1991, 1607. (c) Takahashi, T.; Seki, T.; Nitto, Y.; Saburi, M.; Rousset, C.J.; Negishi, E.-i. *J. Am. Chem. Soc.* 1991, *113*, 6266. (d) Knight, K.S.; Waymouth, R.M. *J. Am. Chem. Soc.* 1991, *113*, 6268.

6.    For the intramolecular cyclozirconation of a cyclic alkene to form a pyrrolidine derivative, see Mori, M.; Uesaka, N.; Shibasaki, M. *J. Org. Chem.* 1992, *57*, 3519.

7. While this work was in progress, a demonstration of the reversibility of *intramolecular* alkene cyclozirconation appeared: Akita, M.; Yasuda, H.; Yamamoto, H.; Nakamura, A. *Polyhedron* **1991**, *10*, 1.

8. The interconversion of titana-, zircona-, and hafnacyclopentanes with the corresponding bis-alkene adducts, known for some years, has been explored systematically by Negishi and Takahashi: (a) McDermott, J. X.; Wilson, M.E.; Whitesides, G.M. *J. Am. Chem. Soc.* **1976**, *98*, 6529. (b) Erker, G.; Engel, K.; Dorf, U.; Atwood, J.L.; Hunter, W.E. *Angw. Chem. Int. Ed. (Eng.)* **1982**, *21*, 914. (c) Erker, G.; Czisch, P.; Kruger, C.; Wallis, J. *Organometallics* **1985**, *4*, 2059. (d) Erker, G.; Dorf, V.; Rheingold, A.L. *Organometallics* **1988**, *7*, 138. (e) Takahashi, T.; Tamaru, M.; Saburi, M.; Uchida, Y.; Negishi, E.-i. *J. C. S. Chem. Commun.* **1989**, 852. (f) Takahashi, T.; Fujimori, T.; Seki, T.; Saburi, M.; Uchida, Y.; Rousset, C.J.; Negishi, E.-i. *J. C. S. Chem. Commun.* **1990**, 182. (g) Negishi, E.-i.; Swanson, D.R.; Takahashi, T. *J. C. S. Chem. Commun.* **1990**, 1254.

9. Seka, R.; Tramposch, O. *Chem. Berichte* **1942**, *75*, 1379.

10. Ester 6, b.p.$_{0.5\ mm}$ (bath) = 100-110°C, was prepared in 65% yield by heating a 1:1 mixture of 1,3-cyclohexadiene and ethyl acrylate containing a little methylene blue in a sealed tube at 180°C for 18 h.

11. For the first report of reduction of zirconocene dichloride with n-BuLi, see Negishi, E.-i.; Cederbaum, F.E.; Takahashi, T. *Tetrahedron Lett.* **1986**, *27*, 2829.

12. An extra equivalent of n-BuLi was included to deprotonate the alcohol of 8.

13. We have found toluene to give consistently better yields than THF in the cyclozirconation reaction.

14. **Dimeric diol 10:** ^{1}H NMR: 6.28, dd, J=6.9 Hz, 7.5 Hz, 2H; 6.18, dd, J=6.9 Hz, 7.5 Hz, 2H; 3.55, d, J=11.0 Hz, 2H; 3.46, d, J=11.0 Hz, 2H; 2.47-2.36, m, 4H; 1.92-1.73, m, 4H; 1.50-0.71, m, 26H. ^{13}C NMR: u: 66.9, 41.3, 37.5, 34.7, 28.1, 23.9, 21.5 d: 134.9, 132.8, 35.4, 30.3, 15.0. IR (cm$^{-1}$): 3318, 2938, 2860, 1672, 1461, 1377, 1025, 737, 695. MS (m/z, relative intensity): 289 (30), 175 (17), 161 (15), 149 (24), 147 (29), 135 (38), 133 (12), 123 (15), 121 (33), 109 (15). HRMS calculated for m+1 $C_{26}H_{43}O_2$ 387.3257 observed 387.32891.

15. For previous examples of alkene cyclozirconation, see (a) Schock, L.E.; Marks, T.J. *J. Am. Chem. Soc.* **1988**, *110*, 7701. (b) Swanson, D.R.; Rousset, C.J.; Negishi, E.-i.; Takahashi, T.; Seki, T.; Saburi, M.; Uchida, Y. *J. Org. Chem.* **1989**, *54*, 3521.

16. **Tricyclic alcohol 12:** ^{1}H NMR: 3.48, d, J=10.7 Hz, 1H; 3.26, d, J=10.7 Hz, 1H; 1.80-0.86, m, 17H; 0.82, d, J=6.4 Hz, 3H. ^{13}C NMR: u: 71.2, 41.8, 35.5, 34.8, 26.3, 25.9, 25.6, 22.8 d: 38.4, 35.3, 34.0, 24.8, 18.6. IR (cm$^{-1}$): 3360, 2924, 2860, 1384, 1039, 1004. MS (m/z, relative intensity): 194 (1.2), 176 (1.1), 164 (13), 163 (100), 147 (2.4), 121 (8.4), 107 (12), 105 (2.4), 95 (13), 93 (10). HRMS calculated for $C_{13}H_{22}O$ 194.16706, observed 194.1647.