Stereoselective Cyclization via Zirconocene-Catalyzed Intramolecular Olefin Allylation

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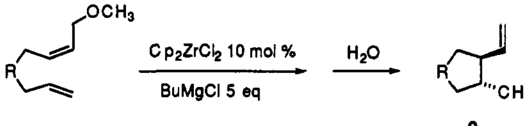
Summary: In the presence of excess butylmagnesium chloride and in diethyl ether at 25 °C, zirconocene dichloride is an effective catalyst precursor for the the stereoselective cyclization of nonconjugated dienes containing a terminal alkoxide substituent. The products are carbocyclic rings containing adjacent vinyl and methyl substituents with trans stereochemistry.

Metal-catalyzed cyclization reactions are becoming increasingly important as methods for the construction of carbocyclic and heterocyclic ring systems. We recently introduced a catalytic method for the cyclization of nonconjugated dienes to give bis(magnesiomethyl)-substituted carbocycles[1] using zirconocene complexes as catalysts.[2] The key step in this catalytic process involves the transmetalation of zirconacyclopentanes with alkylmagnesium reagents. In an effort to develop new patterns of substitution in the cyclized products, we have investigated other processes which would lead to catalytic reactions at zirconium centers. A number of reports in the recent literature describe the facile rearrangement of β-alkoxyzirconocene alkyls to form zirconium alkoxides and alkenes.[3] Such rearrangement reactions also occur with a variety of metallacycles bearing an alkoxy substituent β to the zirconium, including zirconacyclopropanes,[4] zirconacyclopropenes,[5] zirconacyclopentenes,[6,7] and zirconacyclopentanes,[8] and such sequences have been speculated to be important processes in stoichiometric and catalytic reactions. Herein we report our efforts to combine an intramolecular diene cyclization with alkoxy rearrangement and transmetalation to give a new catalytic cyclization of a diene containing an allylic ether.

Catalysts derived from zirconocene dichloride cyclize (Z)-1-methoxy-2,7-octadienes in the presence of a 4-fold excess of butylmagnesium chloride to yield cyclopentane rings containing adjacent vinyl and methyl groups with predominately trans stereochemistry. Reaction of 9-(1-propen-3-yl)-9-((Z)-4-methoxy-2-butenyl)fluorene with butylmagnesium chloride in diethyl ether at room temperature affords the *trans*-methylvinylcyclopentane in 82% isolated yield with greater than 95% diastereoselectivity (eq 1).



1 **2** (1)

If the reaction is worked up with D_2O rather than H_2O, no deuterium is incorporated, which suggests that the product of the catalytic reaction does not contain an alkylmagnesium functional group, in contrast to previous results.[1,2] The use of dibutylmagnesium[1a] or increasing the concentration of BuMgCl from 0.3 to 0.6 M did not result in the incorporation of an alkylmagnesium functional group in the products.

Several stoichiometric reactions were conducted to probe the mechanism of this catalytic cyclization. Reaction of diene **1** with an equal molar amount of dibutylzirconocene (generated from the reaction of Cp_2ZrCl_2 with 2 equiv of butyllithium at −78 °C) yielded the zirconocene alkyl alkoxide complex **6**,[9] which was characterized by NMR and elemental analysis and by hydrolysis (Scheme 1). Deuterolysis of **6** afforded the cyclic product **2-d**, which is deuterated at the methyl position. No intermediates could be detected when the reaction was monitored by ^{1}H NMR at room temperature. These results are consistent with the formation of a metallacyclopentane followed by

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[3] (a) Buchwald, S. L.; Nielsen, R. B.; Dewan, J. C. *Organometallics* **1988,** *7,* 2324–2328. (b) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989,** *30,* 5105–5108. (c) Karlsson, S.; Hallberg, A.; Gronowitz, S. *J. Organomet. Chem.* **1991,** *403,* 133–144.

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[6] Cuny, G. D.; Buchwald, S. L. *Organometallics* **1991,** *10,* 363.

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[9] Characterization data for complex **6**: ^{1}H NMR (300 MHz, C_6D_6) δ 1.09–1.23 (m, 2 H), 1.90 (dd, 3 H, J = 11, 12 Hz), 2.25–2.45 (m, 5 H), 2.5–2.6 (m, 1 H), 2.15–2.25 (m, 1 H), 3.21 (s, 3 H), 5.28–5.32 (m, 2 H), 5.75 (s, 5 H), 5.66 (s, 5 H), 5.7–5.89 (m, 1 H), 7.15–7.3 (m, 4 H), 7.45–7.7 (m, 4 H); ^{13}C NMR (75 MHz, C_6D_6) δ 42.21 ($-CH_2-$) 48.74 ($-CH_2-$), 51.07 ($-CH_2-$), 53.41 ($-CH_2-$), 58.12 (quaternary), 57.17, 61.95, 110.81 (Cp $-CH-$), 111.00 (Cp $-CH-$), 114.83 ($-CH_2$), 120.16 ($-CH-$), 120.34 ($-CH-$), 123.30 ($-CH-$), 123.38 ($-CH-$) 127.18 ($-CH-$), 128.1 ($-CH-$), 128.3 ($-CH-$), 140.04 ($-C-$), 140.22 ($-C-$), 143.09 ($-CH-$), 156.82 ($-C-$), 157.11 ($-C-$). Anal. Calcd: C, 72.25; H, 6.30; Zr, 17.82. Found: C, 72.67; H, 6.43; Zr, 18.02.

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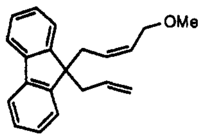
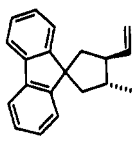
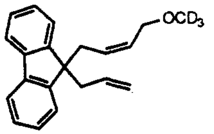
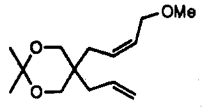
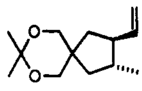
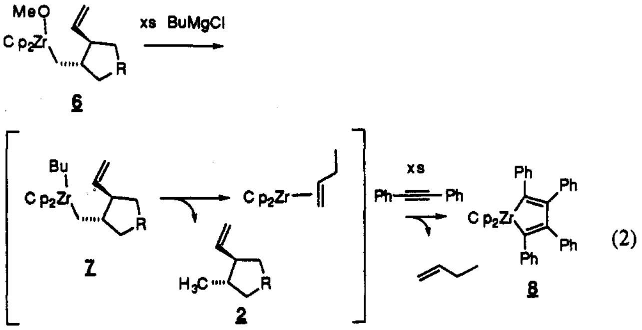
Table 1. Cyclization of Allylic Diene Ethers

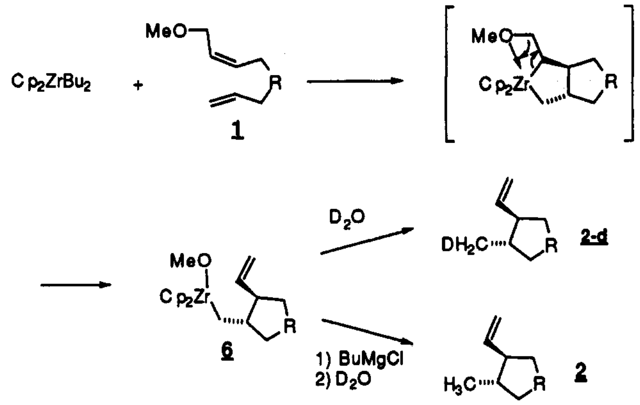
entry no.	diene	Mg reagent	solvent	workup	product	yield %	stereochem trans:cis
1	 **1**	BuMgCl	Et_2O	H_2O, H^+	 **2**	82	95:5
2	1	BuMgCl	Et_2O	D_2O, D^+	2	85	95:5
3	1	Bu_2Mg	Et_2O	D_2O, D^+	2	88	95:5
4	1	BuMgCl	THF	D_2O, D^+	2	60	95:5
5	 **3**	BuMgCl	Et_2O	H_2O, H^+	2	80	95:5
6	 **4**	BuMgCl	Et_2O	H_2O, H^+	 **5**	77	85:15

rapid β-alkoxide elimination to give the zirconocene alkyl alkoxide complex **6**.[10] Reaction of **6** with 2 equiv of butylmagnesium chloride followed by deuterolysis yielded the completely perprotiated product. Treatment of **6** with excess butylmagnesium chloride in the presence of diphenylacetylene affords the known tetraphenylzirconacyclopentadiene **8**[11] and the cyclized product **2** (eq 2).

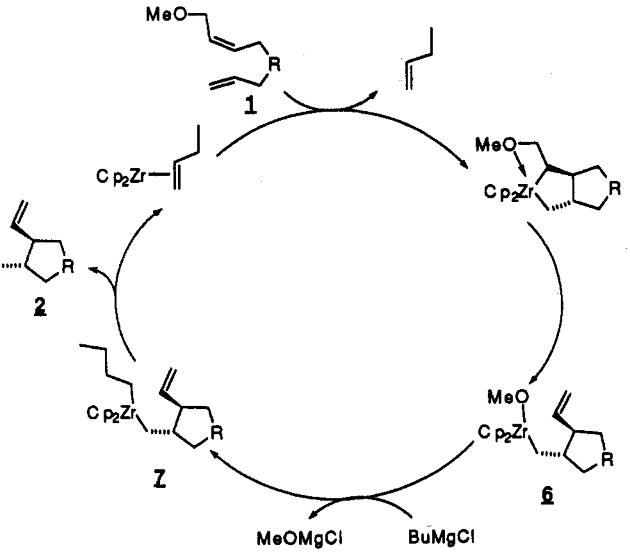


The results of the stoichiometric investigations suggest that transmetalation of **6** with BuMgCl yields the dialkylzirconium intermediate **7**, which rapidly eliminates to give the product **2** and the zirconocene–butene adduct, which can be trapped with diphenylacetylene to give tetraphenylzirconacyclopentadiene. Apparently, elimination of the product from **7** to give the butene adduct is more rapid than subsequent transmetalation which would lead to a alkylmagnesium-containing cyclized product.[1,2]

Scheme 1



Scheme 2. Catalytic Cycle for the Cyclization of Allylic Diene Ethers



On the basis of the stoichiometric experiments and previous work,[1,2,8] a reasonable mechanism for the catalytic reaction can be proposed (Scheme 2) in which the active catalyst is generated from dibutylzirconocene by elimination of butane to form a zirconocene–butene adduct. Displacement of butene by the diene produces a zirconacyclopentane,[12] which undergoes a β-alkoxide elimination to form the zirconium alkyl alkoxide **6**. Transmetalation

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[10] An alternative mechanism involving complexation of the allyl ether and rearrangement of the resultant metallacyclopropane to form a zirconocene allyl alkoxide, which could then undergo a metallo-ene reaction, is considered less likely but has not been experimentally ruled out. Such a mechanism would be similar to that observed for later transition metal catalyzed metallo-ene processes. (a) Felkin, H.; Umpleby, D. J.; Hagaman, E.; Wenkert, E. *Tetrahedron Lett.* **1972**, *13*, 2285. (b) Oppolze, W.; Gaudin, J.-M. *Helv. Chim. Acta* **1987**, *70*, 1477–1481. (c) Oppolzer, W.; Gaudin, J.-M.; Berkinshaw, T. N. *Tetrahedron Lett.* **1988**, *29*, 4705–4708. (d) Oppolzer, W.; Bedoya-Zurita, M.; Switzer, C. Y. *Tetrahedron Lett.* **1988**, *29*, 6433–6436.

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of the alkoxide followed by elimination of the cyclized product **2** regenerates the zirconocene–butene adduct.

To rule out that **2** could be formed by elimination of the cyclized fragment directly from **6**,[13] cyclization of a substrate perdeuterated at the methoxy position (Table 1), entry 5) was examined. This substrate yielded no deuterium incorporation at the methyl position in the cyclized product, indicating that the elimination reaction likely proceeds through the dialkylzircononocene intermediate **7**.

In summary, we have demonstrated a new zirconium-catalyzed cyclization reaction in which alkoxy dienes undergo cyclization and fragmentation on a zirconium center to afford *trans*-1-vinyl-2-methyl carbocycles. This process achieves a transformation that is similar to metallo-ene reactions that have been studied for later transition metals but appears to proceed by a different mechanism.[10] Thus, these reactions are complementary to the metallo-ene reactions in that different selectivities are to be expected. Further studies are currently underway to explore the scope, mechanism, and application of this reaction.

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Supplementary Material Available: Text giving synthetic details and characterization data for the compounds discussed in this paper (7 pages). Ordering information is given on any current masthead page.

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[13] Buchwald has demonstrated facile methane elimination from zirconocene methyl amido and zirconocene methyl thiolate complexes to yield the corresponding zirconocene imine and thioaldehyde adducts: (a) Buchwald, S. L.; Wannamaker, M. W.; Watson, B. T. *J. Am. Chem. Soc.* **1989**, *111*, 776. (b) Buchwald, S. L.; Wannamaker, M. W.; Watson, B. T.; Dewan, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 4486. (c) Buchwald, S. L; Nielsen, R. B. *J. Am. Chem. Soc.* **1988**, *110*, 3171. Buchwald, S. L; Nielsen, R. B.; Dewan, J. C. *J. Am. Chem. Soc.* **1987**, *109*, 1590.