A Novel Type of Zirconium-Catalyzed or -Promoted Cyclization Reaction

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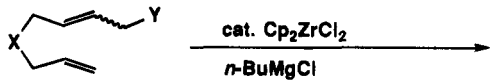
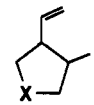
Summary: Intramolecular cyclization reactions of $YCH_2CH{=}CHCH_2XCH_2CH{=}CH_2$ *(X = CH_2, NPr, NPh; Y = PhO, MeO), which have a terminal double bond and an allylic ether moiety, were catalyzed by zirconocene dichloride (10–20 mol %) in the presence of n-BuMgCl. Cyclization products 2-methyl-1-vinylcyclopentane, 4-methyl-1-propyl-3-vinylpyrrolidine, and 4-methyl-1-phenyl-3-vinylpyrrolidine were obtained in 60–80% yields. Stoichiometric cyclization with* Cp_2ZrBu_2 *or* $(C_5H_3Me_2)_2ZrBu_2$ *at room temperature gave the same products in high yields after hydrolysis. When an excess of* Cp_2ZrBu_2 *was used, the stereoisomerization of cis product to trans isomer was observed.*

Intramolecular cyclization reactions using zirconium have been useful for organic synthesis and have been intensively studied.[1-6] However, zirconium-catalyzed intramolecular cyclization is very rare.[5] Recently we have reported zirconium-catalyzed or -mediated allylation reactions.[7] In order to extend the allylation reactions, we investigated a catalytic intramolecular cyclization reaction. In this paper we describe a novel type of zirconium-catalyzed or -promoted cyclization reaction.[8]

A typical procedure is as follows. To a mixture of zirconocene dichloride (0.059 g, 0.20 mmol) and *trans*-*N*-phenyl-*N*-allyl-4-phenoxy-2-butenylamine (**3b**; 0.28 g, 1.0 mmol) in THF (0.5 mL) at room temperature was added a THF solution of butylmagnesium chloride (1.05 M THF solution, 3 mmol). After it was stirred for 12 h, the reaction mixture was quenched with 3 N HCl. Treatment with 30% NaOH and the usual workup gave 4-methyl-1-phenyl-3-vinylpyrrolidine (**6**) (74% yield, a 63:37 mixture of cis and trans isomers).



1a: X = CH_2, Y = OPh, trans
1b: X = CH_2, Y = OMe, trans
2a: X = NPr, Y = OPh, cis
2b: X = NPr, Y = OPh, trans
3a: X = NPh, Y = OPh, cis
3b: X = NPh, Y = OPh, trans



(1)

4: X = CH_2
5: X = NPr
6: X = NPh

The results are shown in Table 1. Cyclization products were obtained in good yields. When the resulting mixture was treated with 20% DCl/D_2O, no deuterated products were detected. Elimination products **7**[9] were not formed. A zirconocene complex with butyl-substituted cyclopentadienyl ligands, $(C_5H_4Bu)_2ZrCl_2$, gave relatively higher yields than Cp_2ZrCl_2. The catalytic reaction of **8** did not afford the desired six-membered product **9**.[10] The stoichiometric cyclization reaction of **1–3** with Cp_2ZrBu_2 (Negishi reagent)[2c] gave the cyclization products **4–6**, respectively, in high yields after hydrolysis. Stereochemistry of the cyclized products was not strongly dependent on the structure of their starting materials. Interestingly, however, the cis:trans ratio of the products was dependent on the amount of Cp_2ZrBu_2 and the reaction time. First, the cis:trans ratio dramatically changed, for example, from 74:26 to 10:90 for **3b** when an excess of Cp_2ZrBu_2 was used. Second, the reaction of **3a** with 1.2 equiv of Cp_2ZrBu_2 gave **6** after hydrolysis in a ratio of 44:56 after 1 h. However, a longer reaction time (3 h) led to a ratio of 17:83. The stereoisomerization reaction must occur after cyclization reactions. Third, when **2b** was treated

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(10) A stoichiometric reaction gave **9** in low yield along with nona-1,8-diene.

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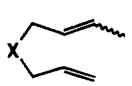
Table 1. Novel Zirconium-Catalyzed or -Promoted Cyclization Reactions

substrate	catalyst or reagent (*n*)	temp/ °C	time/h	product	yield[c]/ %	cis:trans
	Catalytic Reaction (*n* equiv of Cp_2ZrCl_2[a])					
1a	0.1	rt[e]	24	**4**	63	38:62
	0.2[b]	rt	12		84	39:61
1b	0.2	rt	3	**4**	68	31:69
2a	0.2	50	3	**5**	59	24:76
3a	0.2	rt	12	**6**	61	42:58
		rt	24		61	45:55
	0.2[b]	rt	24		78	44:56
3b	0.2	rt	12	**6**	74	63:37
	Stoichiometric Reaction (*n* equiv of Cp_2ZrBu_2)					
1a	1.2	rt	12	**4**	>98	28:72
1b	1.2	rt	6	**4**	89	8:92
2a	1.1	rt	6	**5**	97	33:67
2b	1.1	rt	6	**5**	>98	74:26
	1.1[d]	rt	6		94	92:8
3a	1.2	rt	1	**6**	96	44:56
	1.2	rt	3		72	17:83
3b	1.0	rt	6	**6**	78	74:26
	1.5	rt	6		50	10:90

[a] The catalytic reaction was carried out in the presence of *n* equiv of Cp_2ZrCl_2 and 3.0 equiv of *n*-BuMgCl in THF. [b] $(C_5H_4Bu)_2ZrCl_2$ was used as a catalyst instead of Cp_2ZrCl_2. [c] Combined yield of cis and trans isomers. For stoichiometric reactions, products were obtained after hydrolysis. [d] $(C_5H_3Me_2)_2ZrBu_2$ was used as a reagent instead of Cp_2ZrBu_2. [e] rt = room temperature.

with 1.1 equiv of a zirconium complex with dimethylated cyclopentadienyl rings, $(C_5H_3Me_2)ZrBu_2$, the product **5** was formed in 94% yield (cis:trans = 92:8). However,



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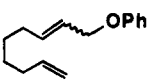

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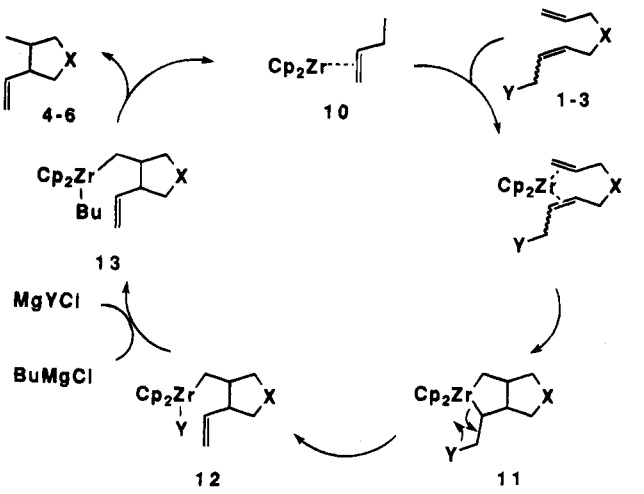
an excess of $(C_5H_3Me_2)ZrBu_2$ does not lead to the stereoisomerization. This is in contrast to the reaction with Cp_2ZrBu_2.

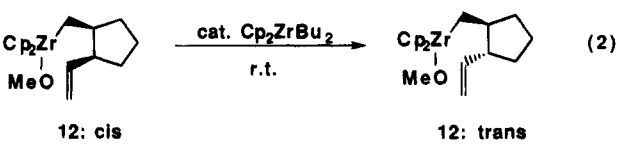
The zirconium-containing stoichiometric reaction product **12** was spectroscopically characterized.[11] The ^1H NMR spectrum of the trans isomer of **12** (X = CH_2; Y = OMe) showed two singlets at 5.72 and 5.77 ppm assignable to Cp protons and one methyl signal for the OMe group at 3.67 ppm. The ^{13}C NMR also indicated two resonances at 110.17 and 110.58 ppm assigned to Cp carbons and a resonace for the methyl group of OMe at 61.63 ppm. A similar type of zirconocene complex prepared from a zirconocene–ethylene complex and allylic ethers has been characterized by our group.[7] The reaction of **12** (X = CH_2; Y = OMe; cis:trans = 47:53) with a catalytic amount of Cp_2ZrBu_2 was monitored by ^1H NMR spectroscopy. Interestingly, the stereoisomerization reaction of **12** (cis isomer) occurred to give its trans isomer (eq 2;cis:trans = 4.96; at room temperature for 30 min). The total amount of cis and trans isomers was constant during the reaction. Treatment of the cyclization product **6** (cis:trans = 74:26) with 5 mol % of Cp_2ZrBu_2 also showed similar isomerization to give predominantly the trans isomer (cis:trans = 13:87, 95% yield) after 8 h. Although we must await further investigations to elucidate the mechanism of this stereoisomerization reaction, the reaction possibly involves

(11) **12** (X = CH_2; Y = OMe): ^1H NMR (C_6D_6,Me_4Si) δ 0.9–1.2 (m, 3H), 1.5–2.1 (m, 7H), 3.67 (s, 3H), 5.09–5.25 (m, 2H), 5.72 (s, 5H), 5.77 (s, 5H), 5.8–6.1 (m, 1H); ^{13}C NMR (C_6D_6, Me_4Si) δ 23.85, 32.78, 35.81, 44.26, 51.48, 57.83, 61.63, 110.17, 110.58, 113.19, 144.24.

Scheme 1



a positional isomerization of the terminal double bond and regeneration of the terminal double bond via abstraction of allylic hydrogen by a Zr(II) species. In catalytic reactions, since only a small amount of zirconocene complex was used, this type of isomerization does not affect the cis:trans ratio.



A plausible mechanism for the catalytic cyclization reaction involves (i) the replacement of butene on zirconium by **1**–**3**, (ii) a bicyclization and a sequential elimination of the alkoxy group[5c,7,12] from **11** to form **12**, (iii) transmetalation by BuMgCl, and (iv) a β-hydrogen abstraction from a Bu group on zirconium to regenerate the zirconocene–butene complex **10**. Actually, the reaction of **12** (X = CH_2; Y = OMe) with 1.2 equiv of BuMgCl in the presence of PMe_3 gave the butene complex stabilized with PMe_3 in 76% yield. β-Hydrogen abstraction from a Bu group in **13** was more favorable than that from the cyclized moiety.[13]

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Supplementary Material Available: Text giving experimental details for the cyclization reactions and the stereoisomerization reaction (4 pages). Ordering information is given on any current masthead page.

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