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Titanocene- and Zirconocene-mediated Cyclization of Allyl Propargyl Ethers. Stereoselective Synthesis of 3-Methylenetetrahydrofurans

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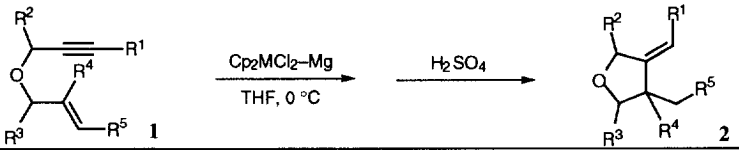
Abstract: Low-valent titanium and zirconium reagents *in situ* prepared from metallocene dichlorides (Cp_2MCl_2: M = Ti, Zr) and magnesium powder activated by 1,2-dibromoethane smoothly reacted with allyl propargyl ethers to afford 3-methylenetetrahydrofurans in good yields. It is noteworthy that the Cp_2Zr– and Cp_2Ti-mediated cyclizations proceed with inverse stereoselectivity.

The intramolecular reductive coupling of dienes, enynes, and diynes by low-valent group 4 metal reagents, prepared from Cp_2MCl_2 (M = Ti, Zr) and metal reductants (Na–Hg, Mg–$HgCl_2$) or alkyl metals (EtMgBr, BuLi), is a valuable method for the construction of carbocycles and N-containing heterocycles.[1,2] The method using alkyl metals is more preferable to that using metal reductants because the latter requires environmentally problematic Hg or $HgCl_2$ in addition to a large excess of Mg. In this sense, particularly the combination of Cp_2ZrCl_2 and two equiv. of BuLi (Negishi's method) is frequently utilized for the reductive cyclization.[3,4] However, the Cp_2ZrBu_2-mediated cyclization has some limitations with regard to applicable substrates, although the use of Cp_2TiCl_2/2EtMgBr improves the applicability.[5] We found that low-valent titanium and zirconium reagents could be easily and reproducibly prepared from Cp_2MCl_2 (M = Ti, Zr) and Mg powder activated by 1,2-dibromoethane,[6] and they were highly efficient in the *in situ* cyclization of allyl propargyl ethers, which are hardly employable in the Negishi method.[7,8] Here, we report that this method can be applied to various allyl propargyl ethers for the stereoselective synthesis of tetrahydrofurans.[9]

A general procedure for the present reductive cyclization is as follows.[10] Mg powder (40-50 mesh, 26.7 mg, 1.10 mmol) and a magnetic stirrer were put in a flask equipped with a dropping funnel containing Cp_2MCl_2 (M = Ti, 137 mg, 0.55 mmol; M = Zr, 219 mg, 0.75 mmol) under argon. THF (0.20 ml) and 1,2-dibromoethane (8.6 μl, 0.10 mmol) were added to Mg. After slow stirring for 30 min, the solvent was removed at reduced pressure to eliminate ethylene. To the activated Mg were added a freshly distilled allyl propargyl ether **1** (0.50 mmol). Then Cp_2MCl_2 was poured into the flask with the aid of THF (M = Ti, 5 ml; M = Zr, 10 ml). After stirring at 0 °C for the period described in Table 1, the resultant mixture was quenched with 20% H_2SO_4. Extraction with Et_2O and concentration *in vacuo* followed by purification by silica gel column chromatography afforded a 3-methylenetetrahydrofuran **2**.

As shown in Table 1, the reductive cyclization was the main reaction path in most cases, although the formation of alcohols by the reductive cleavage of C–O bond was observed to some extent. Generally, the Cp_2Zr-mediated reaction was completed in shorter time to give cyclized products in better yields than the Cp_2Ti-mediated reaction. In both Cp_2Ti- and Cp_2Zr-based systems, the allyl propargyl ether **1a** bearing a phenyl group at the acetylenic terminal was converted into the 3-methylenetetrahydrofuran **2a** with high

Table 1. Titanocene- and Zirconocene-Mediated Cyclization of Allyl Propargyl Ethers[a]



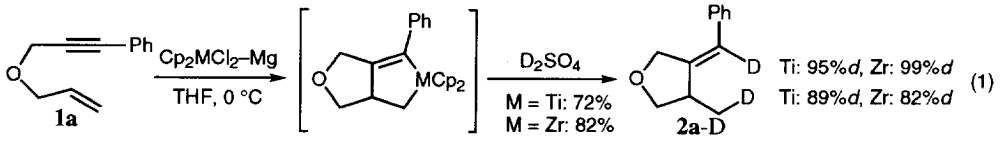
1 2

Entry	Allyl Propargyl Ether						M	Time (h)[b]	Isolated Yield (%)[b,c]	*cis* / *trans* [b,c,d]
	R^1	R^2	R^3	R^4	R^5					
1	Ph	H	H	H	H	**1a**	Ti	6	72	–
2							Zr	2	88	–
3	C_8H_{17}	H	H	H	H	**1b**	Ti	7	<49[e]	–
4							Zr	2	71	–
5	$SiMe_3$	H	H	H	H	**1c**	Ti	10	40	–
6							Zr	3	64	–
7	Ph	H	H	Me	H	**1d**	Ti	5	75	–
8							Zr	2.5	77	–
9	Ph	H	H	H	Me	**1e**	Ti	10	4	–
10							Zr	3.5	50	–
11	H	C_8H_{17}	H	H	H	**1f**	Ti	4	46	7 / 93
12							Zr	1.5 (6)	88 (94)	74 / 26 (76 / 24)
13	H	H	C_8H_{17}	H	H	**1g**	Ti	4	57	< 5 / 95
14							Zr	1.5	67	55 / 45
15	Ph	Me	H	H	H	**1h**	Ti	6	53	19 / 81
16							Zr	3	74	77 / 23
17	Ph	*t*-Bu	H	H	H	**1i**	Ti	3	80	< 5 / 95
18							Zr	2.5 (8)	75 (61)	89 / 11 (93 / 7)
19	Ph	H	Me	H	H	**1j**	Ti	5	62	< 5 / 95
20							Zr	3 (3)	88 (88)	56 / 44 (58 / 42)
21	Ph	H	*t*-Bu	H	H	**1k**	Ti	1.5	55	< 5 / 95
22							Zr	2	91	32 / 68

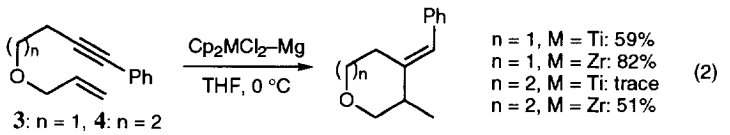
[a]See the text for the general reaction conditions. [b]The results of the reaction at –20 °C are indicated in parentheses. [c]The geometry of an olefinic moiety and the relative configuration between the substituents on the ring were assigned on the basis of NOE analysis. [d]The ratio was determined by 270 MHz ^{1}H NMR analysis. [e]The product contained a small amount of unidentified compounds.

efficiency compared with the substrate bearing an octyl or a trimethylsilyl group (entries 1-6). The Cp_2Zr-based system is effective in the cyclization of the methallyl and crotyl ethers, **1d** and **1e** (entries 8, 10), while the Cp_2Ti-mediated cyclization of **1e** resulted in failure because of the reductive cleavage of the C–O bond (entry 9). In order to investigate both the limitations and stereoselectivities of the present method, we employed the allyl propargyl ethers **1f** and **1g**, which are terminal acetylenes and have an octyl group at the allylic and propargylic position, respectively (entries 11-14). These substrates underwent the reductive cyclization without difficulty. This result is noteworthy since the Cp_2M (M=Ti, Zr)-mediated cyclization of 1,6-enynes has been known to have no tolerance for a terminal alkyne.[1b,11-13] In addition, interestingly, the Cp_2Ti- and Cp_2Zr-mediated cyclizations exhibited inverse stereoselectivity to each other.[14] The former proceeded with high *trans*-selectivity, but the latter with moderate to low *cis*-selectivity. Similar

stereochemical outcomes were obtained in the reactions of other substrates **1h-j** substituted at the allylic or propargylic position (entries 15-20). The selectivity depended on the bulkiness of the substituent. The change of methyl to a *t*-butyl group at the propargylic position improved the selectivity in both Cp_2Ti- and Cp_2Zr-based systems. However, the presence of a *t*-butyl group at the allylic position reduced the *cis*-selectivity in the Cp_2Zr-based system (entry 22). The Cp_2Zr-mediated cyclization at lower temperature slightly enhanced the *cis*-selectivity. The formation of titana- and zirconacyclopentene could be confirmed by quenching the reaction mixture obtained from **1a** with D_2SO_4 in place of H_2SO_4 (eq. 1).



The present method is applicable to the synthesis of 6- and 7-membered cyclic ethers. The Zr-based system again revealed higher efficiency than the Ti-based system in both cases of the enynes **3** and **4** (eq. 2).



In the Cp_2ZrCl_2–Mg-mediated cyclization of allyl propargyl ethers, the reductive cleavage of C–O bonds was a minor path as mentioned above. The result is a sharp contrast to that obtained by the Negishi method. For example, the reaction of the allyl propargyl ether **1a** with Cp_2ZrBu_2 afforded 3-phenyl-2-propyn-1-ol in 45% yield along with a small amount of **2a** (6%). The fast C–O bond cleavage seemed to be attributed to the presence of an alkene ligand in the reducing agent generated from Cp_2ZrBu_2, that is, a Cp_2Zr–1-butene complex. To confirm this hypothesis, the Cp_2ZrCl_2–Mg promoted reaction of **1a** was carried out in the presence of 1-hexene. However, the result indicated that 1-hexene did not induce the reductive cyclization.

In conclusion, we have disclosed that the reagents generated from Cp_2MCl_2 (M = Ti, Zr) and activated Mg powder can be utilized for the reductive cyclization of a wide range of allyl propargyl ethers. The present method tolerates substrates having a terminal alkyne moiety. We have also shown that the Cp_2Zr- and Cp_2Ti-mediated cyclizations proceed with inverse stereoselectivity.

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8. Enynes bearing a siloxy group at the allylic position can be successfully cyclized with Cp_2ZrCl_2/2BuLi. See ref. 3c and 3e. Recently, the Cp_2Zr-mediated cyclization of dienes containing an aryl allyl ether to chromans has been reported . Bird, A. J.; Taylor, R. J. K.; Wei, X. *Synlett,* **1995**, 1237-1238.
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10. The conditions (the equivalents of Mg and Cp_2MCl_2 to the substrate, the concentration of reactants, and reaction temperature) were optimized in the cyclization of **1a**. The increased amount (0.75 mmol) of Cp_2TiCl_2 slightly reduced the yield of **2a**. In the Cp_2ZrCl_2/Mg system, the concentration of reactants, that is the volume of THF, depended on the efficiency of the cyclization. The use of 5 ml of THF per 1 mmol of **1a** resulted in 65% yield of **2a** owing to the reductive cleavage of the C–O bond.
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14. A similar stereochemical outcome has been observed in the Cp_2Ti- and Cp_2Zr-mediated cyclizations of 5-siloxy-1-decen-6-yne. However, the low overall yield of the cyclized products in the Cp_2Ti-based system implies the possibility that a *cis*-titanacycle is being formed as the major product and then decomposes in a subsequent step.[3c]

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