



Titanocene(II)-promoted reaction of *gem*-dihalides possessing a terminal double bond. New intramolecular cyclopropanation

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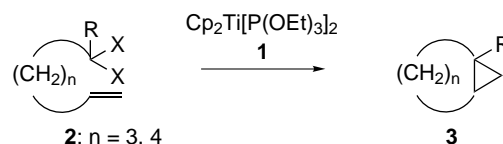
Abstract—The $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$ **1**-promoted intramolecular reaction of *gem*-dihalides possessing a terminal double bond is described. The treatment of 6,6- and 7,7-dihalo-1-alkenes with **1** produced bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane derivatives, respectively. © 2001 Elsevier Science Ltd. All rights reserved.

Recently we found that the treatment of diphenyl thioacetals having a terminal carbon–carbon double bond with $\text{Cp}_2\text{Ti}[\text{P}(\text{OEt})_3]_2$ **1** gave cycloalkenes via the ring-closing metathesis of the initially formed titanium–carbene complexes.¹ This new reaction is useful for the synthesis of a variety of nitrogen² and oxygen³ heterocycles. We also investigated the formation of the carbene complex-like organotitanium species by the reduction of *gem*-dihalides with **1** and found that these species are useful for the transformation of carbonyl compounds into highly substituted olefins.⁴ These results prompted us to investigate the reaction of *gem*-dihalides carrying a terminal double bond **2** with the low-valent titanium **1**. We found that, unlike the reaction of the thioacetals, bicyclo[3.1.0]hexane and bicyclo[4.1.0]heptane derivatives **3** were produced by the treatment of the corresponding *gem*-dihalides **2** with **1** (Scheme 1).

The starting materials **2** were easily prepared from the corresponding unsaturated carbonyl compounds by the method recently developed by us.⁵ First, the reaction of 6,6-dihalo-1-hexene derivatives was studied. When the *gem*-dichloride **2a** was treated with the low-valent titanium species **1** (3 equiv.) at 0°C for 1.5 h, the bicyclic cyclopropane **3a** was produced in 73% yield (entry 1, Table 1). Similarly, the reactions of several 6,6-dihalo-1-alkenes **2b–e** were performed and the cyclopropanes **3** were obtained in good yields (entries 2–5). The isolation of **3** by silica gel chromatography was sometimes

difficult owing to the contamination with trace amounts of olefinic byproducts. In such cases, the crude mixture was treated with hydrogen peroxide in acetic acid or *m*-chloroperbenzoic acid (MCPBA) before the isolation.

The following is a typical experimental procedure. To a THF (6.7 ml) solution of the titanocene(II) reagent **1**, prepared from titanocene dichloride (374 mg, 1.5 mmol), magnesium turnings (36 mg, 1.5 mmol), triethyl phosphite (0.52 ml, 3 mmol) and finely powdered molecular sieves 4 Å (150 mg),^{3b} was added a THF (10 ml) solution of 6,6-dibromo-4-phenyl-1-heptene (**2d**) (166 mg, 0.5 mmol) at 0°C under argon. After being stirred for 1.5 h, the reaction was quenched by addition of 1 M NaOH (30 ml). The insoluble materials were filtered off through Celite and washed with ether (10 ml). The layers were separated, and the aqueous layer was extracted with ether (2×20 ml). The combined organic extracts were dried over Na_2SO_4 . After removal of the solvent at atmospheric pressure, the residue was dissolved in AcOH (3 ml) and H_2O_2 (30%, 0.8 ml) was added to the solution with cooling (ca. 20°C). The reaction mixture was stirred for 6 h and diluted with water (20 ml). The organic materials were extracted with ether (2×20 ml) and dried (Na_2SO_4). The solvent was removed under atmospheric pressure, and the

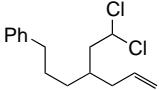
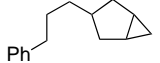
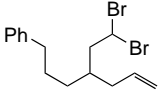
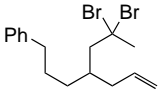
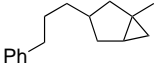
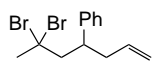
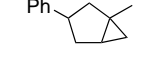
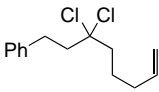
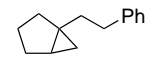
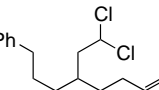
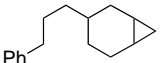
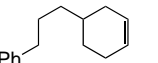
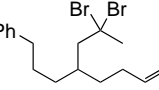
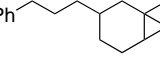
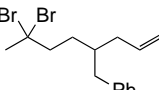
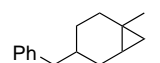
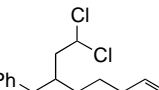
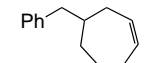


Scheme 1.

Keywords: cyclopropanation; dehalogenation; halogens and compounds; titanium and compounds.

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Table 1. Reaction of *gem*-dihalides **2** with titanocene(II) **1**

Entry	<i>gem</i> -Dihalide 2	Temp / °C (Time / h)	Products (Yield / %; Ratio of isomers)
1		2a 0 (1.5)	 3a (73 ^a ; 89 : 11)
2		2b 0 (1)	3a (73 ^b ; 89 : 11)
3		2c 0 (1)	 3b (70 ^c ; 97 : 3)
4		2d 0 (1.5)	 3c (72 ^c ; 96 : 4)
5		2e 0 (1.5)	 3d (77 ^c)
6		2f rt (15)	 3e (20; 57 : 43)  4a (40)
7		2g rt (overnight)	 3f (68 ^c ; 63 : 37)
8		2h 0 (2)	 3g (68; 61 : 39)
9		2i rt (2) then reflux (1)	 4b (37 ^d)

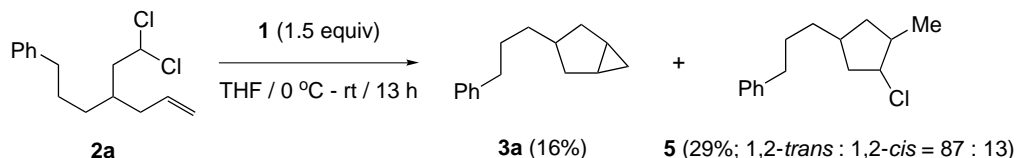
^aContaminated with 3-methyl-5-(3-phenylpropyl)-1-cyclopentene. The yield was corrected for the contaminant. ^bThe cyclopropane **3** was isolated after treatment of the crude mixture with MCPBA in dichloromethane. ^cThe cyclopropane **3** was isolated after treatment of the crude mixture with hydrogen peroxide in acetic acid. ^dContaminated with 3-benzyl-1,7-octadiene. The yield was corrected for the contaminant.

residue was purified by PTLC (hexane) to yield 63 mg (72%) of 1-methyl-3-phenylbicyclo[3.1.0]hexane (**3c**).

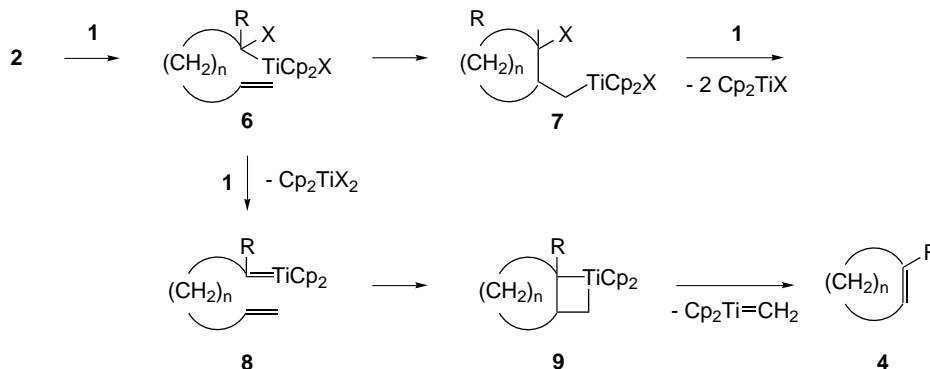
The mode of the reaction of 7,7-dihalo-1-heptene derivatives was largely dependent on the substituent at the carbon α to the halogen. Similarly to 6,6-dihalo-1-alkenes, the treatment of the dihalides bearing a substituent at 7-C position **2g** and **h** with the titanocene(II) species **1** selectively produced the cyclopropanes **3** in good yields (entries 7 and 8). Although the reaction of the *gem*-dichloride **2f** having no substituent at the 7-C position gave the cyclopropane **3e**, the major product was the cyclohexene **4a**. Further, we found that the

cycloalkene **4b** was obtained, and the corresponding cyclopropane was not produced by the reaction of 8,8-dichloro-1-octene derivative **2i** at an elevated temperature (entry 9).⁶

In connection with the mechanism of the Ziegler–Natta polymerization, intramolecular insertion of a terminal olefin into the titanium–carbon bond has been investigated. Alkenyltitanocene chlorides prepared by treating titanocene dichloride with the appropriate Grignard reagents cyclize to the corresponding (cycloalkylmethyl)titanocene chloride on treatment with ethylaluminum dichloride.⁷ This process is also promoted by



Scheme 2.



Scheme 3.

magnesium bromide or methylaluminumoxane.⁸ Although more study will be required before reliable reaction intermediates can be proposed, we tentatively assume that the present reaction proceeds via a similar olefin insertion process. We found that 1-chloro-2-methyl-4-(3-phenylpropyl)cyclopentane **5** was produced in 29% yield along with the cyclopropane **3a** and a substantial amount of the starting materials was recovered (41%) when the reaction of **2a** was performed using 1.5 equiv. of the low-valent titanium reagent **1** (Scheme 2). Therefore, the first step of the cyclopropane formation would be the cyclization of the α -halo alkyltitanium **6** to form the cyclic γ -halo alkyltitanium species **7**. The intramolecular reductive coupling of **7** with an additional equivalent of **1** affords the cyclopropane **3** (Scheme 3). If the titanium compound **6** is reduced with **1** prior to the cyclization, the ring-closing metathesis of the resulting carbene complex **8** proceeds via the formation of titanacyclobutane intermediate **9** to afford the cycloalkene **4**.

Synthesis of bicyclic cyclopropanes by intramolecular cyclopropanation has been extensively studied. The most widely employed method is the transition metal-catalyzed reaction of alkenyl diazo carbonyl compounds.⁹ Certain transition metal-carbene complexes are also used for this transformation.¹⁰ Titanium(II) species-promoted intramolecular reaction of ω -vinyl carboxylic esters under catalytic or stoichiometric conditions has been utilized for the preparation of bicyclic cyclopropanols.¹¹ Recently, Cohen et al. reported the synthesis of bicyclo[3.1.0] and [4.1.0] systems bearing an angular vinyl substituent by the tandem lithium-ene cyclization and thiophenoxide expulsion.¹² Since the alkenyl *gem*-dihalides are readily available from the corresponding unsaturated ketones or aldehydes, the present reaction provides a useful synthetic route to fused 5,3- and 6,3-systems.

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