Formation of Cyclopropanes by the Reductive Coupling of 1,3-Dihalides Promoted by Titanocene(II) Species

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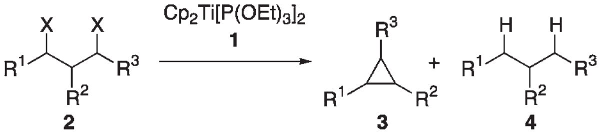
The treatment of various 1,3-dihalides including the ones bearing an ester group with the titanocene(II) species produced cyclopropanes in good yields. The reaction of dihalides possessing two secondary halogens proceeded stereoselectively to afford *trans*-isomers as major products.

The reductive coupling of 1,3-dihalides is an attractive way for the construction of three-membered rings and various reagents have been investigated for this transformation. Magnesium,[1] sodium,[2] and zinc[3] metals are employed for the synthesis of unfunctionalized cyclopropanes. The reductive couplings mediated by cobalt[4] and nickel[5] complexes and $LiAlH_4$[6] have been studied. Cyclization of primary 1,3-dihalides with alkyllithium[7] or a Grignard reagent-$FeCl_3$ system[8] has also been reported.

In spite of these extensive studies, the reductive coupling of conformationally mobile 1,3-dihalides to form 1,2-disubstituted cyclopropanes including its stereoselectivity has not been fully studied yet. Kochi and Singleton studied the reductive coupling of *meso*- and *dl*-2,4-dibromopentane with ethylenediaminechromium(II) reagent and found that there is no stereospecificity and stereoselectivity in cyclopropane formation.[9] The lack of selectivity was also observed in the formation of cyclopropane by the nickel-salen complex mediated electrochemical reduction of two diastereomers of 2,4-dibromopentane.[10]

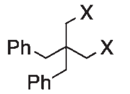
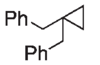
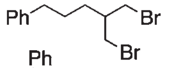
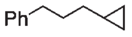
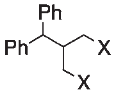
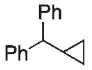
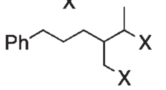
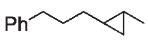
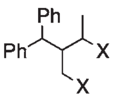
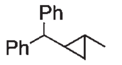
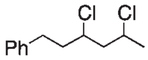
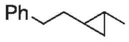
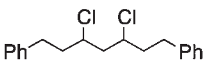
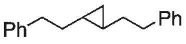
Recently we reported the titanocene(II) $Cp_2Ti[P(OEt)_3]_2$ **1**-promoted intramolecular cyclopropanation of ω,ω-dihalo-1-alkenes, in which a γ-haloalkyltitanium intermediate is suggested to be formed and its intramolecular substitution affords a three-membered ring.[11] In connection with the mechanism of this reaction, we were intrigued with the reductive coupling of 1,3-dihalides **2** with the titanocene(II) reagent **1**. In this communication, we describe preliminary results of the formation of cyclopropanes **3** by the treatment of various types of 1,3-dihalides **2** with **1** and its stereoselectivity (Scheme 1).

The treatment of 2,2-dibenzyl-1,3-dichloropropane **2a** with 1.5 equiv of titanocene(II) species **1** at room temperature for 2 h gave the cyclopropane **3a** in 61% yield along with a substantial amount of starting material (34%). When the reaction was carried out using 3 equiv of **1**, the cyclopropane **3a** was produced in high yield (Table 1, Entry 1). The corresponding dibromide **2b** also can be employed for the present reaction giving **3a** in comparable yield (Entry 3). In a similar manner, the reactions of various dihalides **2** were performed, and the corresponding cyclopropanes **3** were obtained in good to high yields with small amounts of the dehalogenated hydrocarbons **4**.[12]



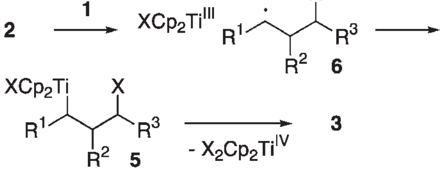
Scheme 1.

Table 1. Cyclization of 1,3-dihalides **2**

Entry	1,3-Dihalides **2** (Ratio of isomers)	Temp / °C (Time / h)	Product[a] (Yield / %; *trans* : *cis*)[b]
1	 **2a**: X = Cl	rt (2)	 **3a** (93)
2	**2b**: X = Br	rt (3)	**3a** (84)
3	**2b**	0 (3)	**3a** (87)
4	 **2c**	0 (3)	 **3b** (75)
5	 **2d**: X = Cl	rt (3)	 **3c** (81)
6	**2e**: X = Br	0 (3)	**3c** (87)
7	 **2f**: X = Cl (59 : 41)	rt (3)	 **3d** (83; 62 : 38)
8	**2g**: X = Br (51 : 49)	rt (3)	**3d** (70; 62 : 38)
9	 **2h**: X = Cl[c]	rt (3)	 **3e** (83; 80 : 20)
10	**2i**: X = Br (97 : 3)	0 (3)	**3e** (85; 73 : 27)
11	 **2j** (61 : 39)	rt (3)	 **3f** (66; 77 : 23)
12	 **2k** (81 : 19)	rt (3)	 **3g** (85; 92 : 8)
13	**2k** (61 : 39)	rt (3)	**3g** (86; 91 : 9)
14	**2k** (49 : 51)	rt (3)	**3g** (84; 92 : 8)

[a] Contaminated with **4** (2-7%). The yield was corrected for the contaminant. [b] Determined by NMR analysis. [c] Single isomer.

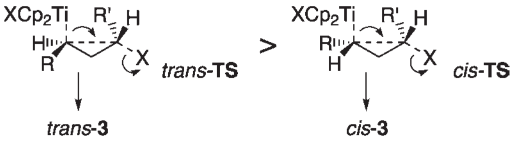
When 1,2-disubstituted cyclopropanes are produced, the *trans*-isomers are formed preferentially. Considering the stereoisomeric purity of the starting materials and products, it is obvious that this reaction is not stereospecific. Kochi and Singleton noted that the lack of stereospecificity in the reductive coupling of 2,4-dibromopentane with the chromium(II) complex is due to the formation of γ-halo radical intermediate.[9] Therefore it is reasonable to assume that the present reaction also proceeds via the formation of γ-haloalkyltitanium intermediate **5** through



Scheme 2.

atom transfer process,[13] which involves a radical intermediate **6** as shown in Scheme 2. Intramolecular nucleophilic substitution of **5** affords cyclopropane **3** and titanocene dichloride.[14,15]

Grubbs and coworkers studied the formation of cyclopropanes by cleavage of titanacyclobutane with iodine and concluded that the cyclization of the intermediate γ-iodoalkyltitanocene iodide proceeds by a stereospecific intramolecular S_N2 process, with retention at the α-carbon attached to the titanium atom and inversion at the γ-carbon.[16] If the present reaction follows a similar pathway, the stereochemistry is established during the formation of γ-haloalkyltitanium **5**. However alternative mechanism, in which *trans*-stereoselectivity is dependent on the steric non-bonding interaction between the alkyl substituents in the transition state of cyclization **TS** (Scheme 3), should also be considered because the formation of **5** with a high degree of diastereoselectivity is unlikely. Such process involves the equilibrium between the two diastereomers of **5** through a radical intermediate **6**, and *trans*-**3** is preferentially produced via the transition state *trans*-**TS**, which has less steric interaction.



Scheme 3.

The present reductive coupling showed the tolerance to ester group. The treatment of dihaloesters **2l** and **2m** with **1** at 0 °C and then at room temperature gave the ethyl cyclopropanecarboxylates **3h** and **3i**, respectively (Scheme 4, Table 2). In these cases, the formation of rearrangement products **7a** and **7b** was observed. The ratio of rearrangement product **7** to cyclopropane **3** increased when the reaction was initiated at room temperature (Entry 3). Since it was confirmed that the cyclopropane **3i** was not transformed into the β-methylene ester **7b** by the treatment with the titanocene(II) reagent, **7** would be formed directly from the γ-halotitanium intermediate **5**.

In summary, we have found that the titanocene(II) species **1** is useful for the stereoselective reductive coupling of 1,3-dihalides. Further application of the titanocene(II) reagent for the reduction of organic halides is currently in progress.

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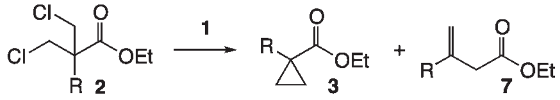

Scheme 4.

Table 2. Preparation of ethyl cyclopropanecarboxylates

Entry	1,3-Dihalides **2**	Temp/°C (Time/h)	Products (Yield/%)	
1	**2l**: R = $Ph(CH_2)_2$	0(1) then rt (2)	**3h**(71)	**7a**(9)
2	**2m**: R = $PhCH_2$	0(1) then rt (2)	**3i**(65)	**7b**(12)
3	**2m**	rt(3)	**3i**(48)	**7b**(32)

This paper is dedicated to Prof. Teruaki Mukaiyama on the occasion of his 75th birthday.

References and Notes

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12 The following is a typical experimental procedure. Finely powdered molecular sieves 4 A (150 mg), magnesium turnings (37 mg, 1.5 mmol; purchased from Nacalai Tesque Inc. Kyoto, Japan) and Cp_2TiCl_2 (374 mg, 1.5 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mmHg). After cooling, THF (6.7 ml) and $P(OEt)_3$ (0.51 ml, 3.0 mmol) were added successively with stirring at room temperature under argon, and the reaction mixture was stirred for 3 h. A THF (10 ml) solution of 2,2-dibenzyl-1,3-dichloropropane (**2a**) (147 mg, 0.5 mmol) was added to the reaction mixture dropwise over 15 min. After stirring for 2 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. The solvent was removed at atmospheric pressure, and the residue was purified by PTLC (hexane) to yield 108 mg of 1,1-dibenzylcyclopropane (**3a**) contaminated with a trace amount of 2,2-dimethyl-1,3-diphenylpropane (**4a**). The yields (**3a**; 93%, **4a**; 4%) were determined by NMR analysis.

13 J. K. Kochi, "Organometallic Mechanisms and Catalysis," Academic Press, New York (1978), p 138.

14 A similar mechanism is proposed for the formation of benzylcyclopropane in the zirconium-catalyzed alkylation of silanes with secondary Grignard reagent in the presence of 2-benzyl-1,3-dibromopropane. Y. Ura, R. Hara, and T. Takahashi, *Chem. Commun.*, **2000**, 875.

15 According to the reaction mechanism shown in Scheme 2, one equiv of titanocene(II) reagent **1** is theoretically needed. Since more than two equiv of **1** is necessary to complete the reaction, it is assumed that the reagent **1** is consumed by the reduction of the resulting titanocene dichloride to form a titanocene(III) species.

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