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Lanthanum metal-assisted cyclopropanation of alkenes with *gem*-dihaloalkanes

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This Letter is dedicated to the heartfelt memory of the late Professor Yoshihiko Ito

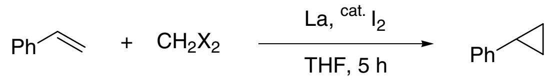
Abstract—It was confirmed that lanthanum metal was an efficient reagent for the reductive dehalogenation of *gem*-dihaloalkanes. When *gem*-dihaloalkanes were allowed to react with lanthanum metal in the presence of alkenes, cyclopropanation of the alkenes occurred under mild conditions giving the corresponding cyclopropanes in moderate to good yields.

The cyclopropane structure unit is found in many important natural products as well as in synthetic compounds used in biological studies.[1] Furthermore, cyclopropanes are useful intermediates for the synthesis of stereodefined cyclic and acyclic molecules.[2] Therefore, a variety of methods have been developed for their preparations.[3] One of the most straightforward synthetic methods is the addition of the carbene (or carbenoid) onto the carbon–carbon double bond; thus, the development of a new method for the generation of carbene (or carbenoid) has attracted considerable attention in organic synthesis.[4]

We have recently reported a new generation method of alkyl radicals by the reductive dehalogenation of alkyl halides with lanthanum metal.[8] Based on our continuous study on the utilization of lanthanum metal in organic synthesis, we have now found a new generation method of carbenes (or lanthanum metal carbenoids) by the reductive dehalogenation of *gem*-dihaloalkanes with lanthanum metal.

When dibromomethane was allowed to react with lanthanum metal in the presence of styrene (**1**) at 25 °C for 5 h, the lanthanum metal gradually dissolved and phenyl cyclopropane (**2**) was obtained in moderate yield (entry 4 in Table 1). For the reaction of diiodomethane, the yield of **2** was low due to the formation of various by-products (entry 6). Contrary to those of dibromo- and diiodomethane, in the case of dichloromethane, the majority of the lanthanum metal did not dissolve and the styrene (76%) was recovered (entry 1). However, when the reaction was carried out at higher reaction temperature (67 °C), the lanthanum metal gradually dissolved and **2** was obtained in 75% yield (entry 2). For the reaction of dibromo- and diiodomethane, the yields of **2** were also improved by the increasing the reaction temperature (entries 5 and 7).[9] The product yield was also affected by the amount of styrene used (entry 3).

Table 1. Lanthanum metal-assisted cyclopropanation of styrene with dihalomethane[a]



Entry	X	Temperature (°C)	Yield[b] (%)
1	Cl	25	15
2	Cl	63	75
3[c]	Cl	63	51
4	Br	25	57
5	Br	63	80
6	I	25	10
7	I	63	48

[a] Reaction conditions: CH_2X_2 (1.0 mmol), styrene (5.0 mmol), lanthanum (2.0 mmol), iodine (0.4 mmol) and THF (1 mL) for 5 h.
[b] GC yields based on CH_2X_2.
[c] Styrene (1.0 mmol) was used.

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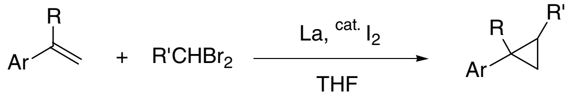
Table 2. Synthesis of various cyclopropanes[a]



Entry	Ar	R	R′	Yield[b] (%) (cis/trans)[c]
1	C_6H_5	H	H	80
2	$4\text{-}CH_3C_6H_4$	H	H	68
3	$4\text{-}CH_3OC_6H_4$	H	H	0
4	$4\text{-}ClC_6H_4$	H	H	50
5	$C_{10}H_7$	H	H	78
6	C_6H_5	CH_3	H	49
7	C_6H_5	H	CH_3	98 (49/51)
8	C_6H_5	H	CH_3	70 (35/65)
9	$4\text{-}CH_3C_6H_4$	H	CH_3	62 (42/58)
10	$4\text{-}ClC_6H_4$	H	CH_3	10 (47/53)

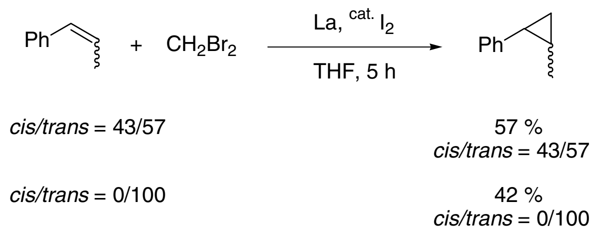
[a] Reaction conditions: R′CHBr$_2$ (1.0 mmol), alkene (5.0 mmol), lanthanum (2.0 mmol), I$_2$ (0.4 mmol) and THF (1 mL) at 67 °C for 5 h.

[b] GC yield based on R′CHBr$_2$.

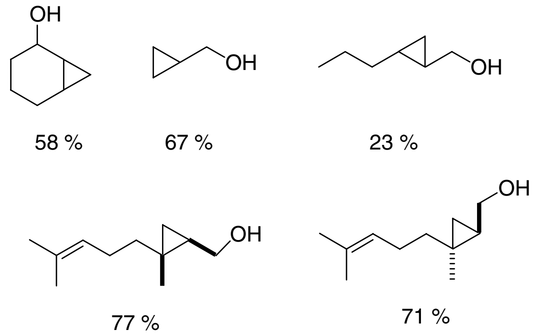
[c] The numbers in parentheses indicate the ratios of cis and trans isomers.

In order to determine the applicability of the formation of cyclopropanes using the dibromomethane/lanthanum metal system, dibromomethane was allowed to react with lanthanum metal in the presence of various alkenes, and the results are shown in Table 2.[10] 1-Cyclopropyl-4-methyl- and 1-cyclopropyl-4-chlorobenzene were prepared by the treatment of dibromomethane with lanthanum metal in the presence of 4-methyl- and 4-chlorostyrene in 68% and 50% yields, respectively (entries 2 and 4). Contrary to those of 4-methyl- and 4-chlorostyrene, for the reaction of 4-methoxystyrene, cyclopropane was not obtained (entry 3). When dibromomethane was treated with lanthanum metal in the presence of 1-napthylethylene, 1-napthylcyclo-propane was formed in 78% yield (entry 5). Similarly, the cyclopropanation of 2-phenylpropene efficiently proceeded; however, the yield decreased due to the preparation of various by-products (entry 6). It is interesting to note that the methyl-substituted carbene was generated by the reaction of *gem*-dibromoethane with lanthanum metal. When 1,1-dibromoethane was treated with lanthanum metal in the presence of aryl-substituted alkenes, 1-aryl-2-methylcyclopropanes were formed in moderate yields with a mixture of stereoisomers (entries 7–10).

When dibromomethane was allowed to react with lanthanum metal in the presence of 1-phenyl-1-propene, which is a mixture of cis and trans isomers (cis/trans = 43:57), 1-methyl-2-phenyl cyclopropane was formed along with a mixture of cis and trans isomers (cis/trans = 43:57) in 57% yield. It is interesting to note that the ratio of two isomers was almost the same as that of the geometry ratio of the alkenes (Scheme 1). In the presence of *trans*-1-phenyl-1-propene, *trans*-1-methyl-2-phenyl cyclopropane was formed as the sole product. From these results, it was suggested that the cyclopropanation of the carbon–carbon double bond using the dibromomethane/lanthanum metal system proceeded stereospecifically with respect to the olefin geometry.



Scheme 1.



Scheme 2.

Similarly, the cyclopropanation of allylic alcohol was proceeded, when diiodomethane was allowed to react with lanthanum metal in the presence of 2-cyclohexen-1-ol, allyl alcohol, and 2-hexene-1-ol. In addition, chemselective cyclopropanation at the C(2)–C(3) double bond of geraniol and nerol was successfully achieved by using La/CH$_2$I$_2$ system (Scheme 2).

In summary, we developed a new method for the generation of carbenes (or carbenoids) by the reductive dehalogenation of *gem*-dihaloalkanes. Furthermore, the reaction of *gem*-dihaloalkanes with lanthanum metal in the presence of alkenes provides a useful method for the synthesis of cyclopropanes, from the viewpoint of simple operations, neutral conditions, moderate to good yields and being stereospecific. Application of the reaction and elucidation of the reaction pathway are now in progress.

Acknowledgement

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9. Lanthanum powder (278 mg, 2.0 mmol) and iodine (102 mg, 0.4 mmol) were placed in a two-necked flask. THF (1 mL), then the alkenes (5.0 mmol) and *gem*-dihaloalkanes (1.0 mmol) were added to the flask, and the mixture was stirred at 67 °C for 5 h under a nitrogen atmosphere. After the reaction, aq HCl (5%) was added to the reaction mixture, and the mixture was extracted with diisopropyl ether (10 mL × 3). The organic layer was washed with saturated aq sodium thiosulfate (30 mL × 1), dried over $MgSO_4$ and filtered. The organic solvent was removed under reduced pressure. Purification of the residue by HPLC afforded the corresponding cyclopropanation products. The products were characterized by a comparison of their spectra data with those of authentic samples.
10. In the case of cyclohexene and 2,3-dimethyl-2-butene, the yields of the cyclopropane derivatives were very low (5% and 10% yields). It was reported that the relative rate constants of cyclopropanation of styrene, cyclohexene and 2,3-di methyl-2-butene with CH_2BrCl/C_4H_9Li are 3.7, 1.0 and 0.29. See: (a) Burger, U.; Huisgen, R. *Tetrahedron Lett.* **1970**, 3049; (b) Huisgen, R.; Burger, U. *Tetrahedron Lett.* **1970**, 3053; (c) Burger, U.; Huisgen, R. *Tetrahedron Lett.* **1970**, 3057.