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The first example of magnesium carbenoid 1,3-CH insertion reaction: a novel method for synthesis of cyclopropanes from 1-chloroalkyl phenyl sulfoxides in high yields

Tsuyoshi Satoh,* Jun Musashi and Atsushi Kondo

Department of Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

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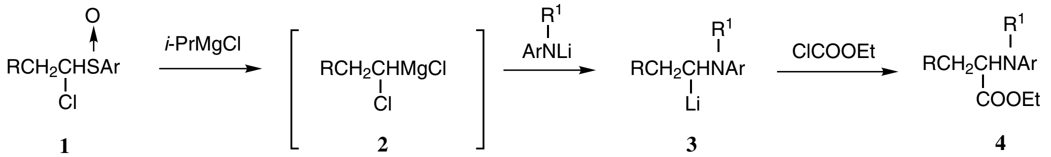
Abstract—Treatment of 1-chloroalkyl phenyl sulfoxides having a geminal methyl group or a geminal benzyl group at the 2-position in THF at −78 °C with isopropylmagnesium chloride gave magnesium carbenoids. Carbenoid 1,3-CH insertion reaction of the magnesium carbenoids took place instantaneously to afford cyclopropanes in high to quantitative yields.

Carbenes and carbenoids have long been recognized to be highly reactive carbon species and are frequently used as useful intermediates in organic synthesis.[1,2] Carbon–hydrogen insertion (CH insertion) is a characteristic reaction of carbenes and carbenoids. This reaction is quite interesting, because formation of a carbon–carbon bond between a carbene (carbenoid) carbon and inactivated carbon is realized. Recently, intramolecular 1,5-CH insertion reaction of alkylidene carbenes and the intramolecular formation of a carbon–carbon bond with carbenes generated from α-diazocarbonyl compounds have been widely investigated for the construction of cyclopentenes and cyclopentanones, respectively.[2] 1,3-CH insertion reactions also have been known and used in the synthesis of cyclopropanes.[1a]

In this decade, we have investigated the generation of several magnesium carbenoids by sulfoxide–magnesium exchange reaction of aryl 1-halovinyl sulfoxides and aryl 1-haloalkyl sulfoxides.[3] Their properties and application to new synthetic methods were also widely studied.[4] Recently, simple magnesium carbenoides **2** were generated from aryl 1-chloroalkyl sulfoxides **1** with *i*-PrMgCl. The magnesium carbenoids **2** were found to be fairly stable at below −60 °C and showed several interesting reactivities to some nucleophiles.[5a] For example, the carbenoids **2** reacted with *N*-lithio arylamines to afford nonstabilized α-amino-substituted carbanions **3**, from which α-amino acids **4** were obtained in good yields (Scheme 1).[5b]

In continuation of our interest in the reactivity of magnesium carbenoids, recently we investigated the reactivity of 1-chloroalkyl phenyl sulfoxides having geminal methyl or benzyl groups at the 2-position **5** with *i*-PrMgCl and found that the generated magnesium carbenoid **6** instantaneously underwent 1,3-CH insertion between the methyl group to afford cyclopropanes **7** in high to quantitative yields (Scheme 2).



Scheme 1.

Keywords: Cyclopropane; Sulfoxide; Sulfoxide–magnesium exchange; Magnesium carbenoid; C–H insertion.

* Corresponding author. Tel.: +81 3 5228 8272; fax: +81 3 3235 2214; e-mail: tsatoh@ch.kagu.tus.ac.jp

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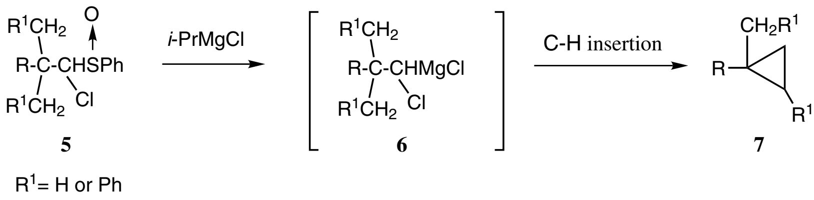


Scheme 2.

First, 1-chloroalkyl phenyl sulfoxide **8** was synthesized from commercially available 2,2-dimethyl-3-phenyl-1-propanol.[6] The sulfoxide **8** was treated in THF at −78 °C with 3 equiv of *i*-PrMgCl. The starting material instantaneously disappeared and after the reaction mixture was allowed to warm to room temperature, we obtained an inseparable mixture of two cyclopropanes, **9** and **10** (the ratio was determined to be 7:1 from ^{1}H NMR). Unfortunately, the products were quite volatile and the accurate yield was obscure (Scheme 3).

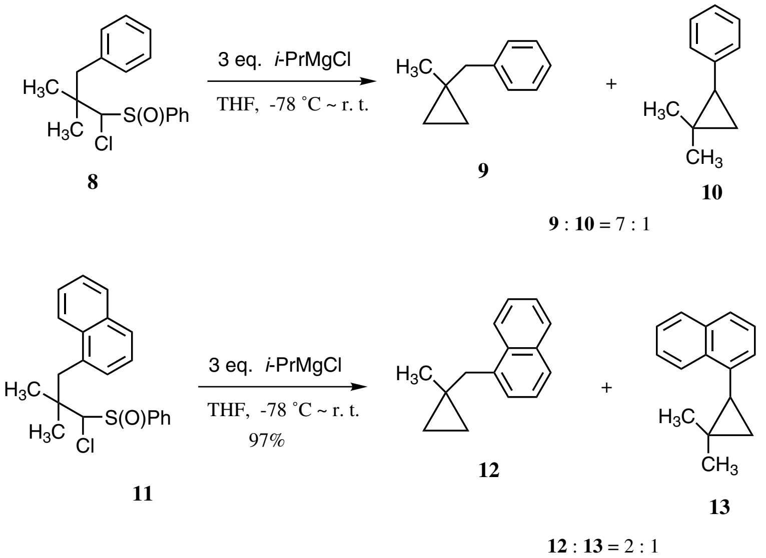
We synthesized 1-chloroalkyl phenyl sulfoxide having a 1-naphthyl group **11** and it was treated with *i*-PrMgCl under the same conditions as described above. This time we obtained an inseparable mixture of two cyclopropanes, **12** and **13**, and the ratio was found to be 2:1 in 97% yield. Although the 1,3-CH insertion to give the cyclopropanes was already known by lithium carbenoid and carbenes,[7] to the best of our knowledge, the results described above is the first example of the 1,3-CH insertion reaction of magnesium carbenoid to give cyclopropanes.

To investigate the generality of this reaction, we synthesized three 1-chloroalkyl phenyl sulfoxides **14**, **16** and **18** from 2,2-dimethyl-1,3-propanediol[8] and they were treated with 3 equiv of *i*-PrMgCl at −78 °C and the results are summarized in Scheme 4.

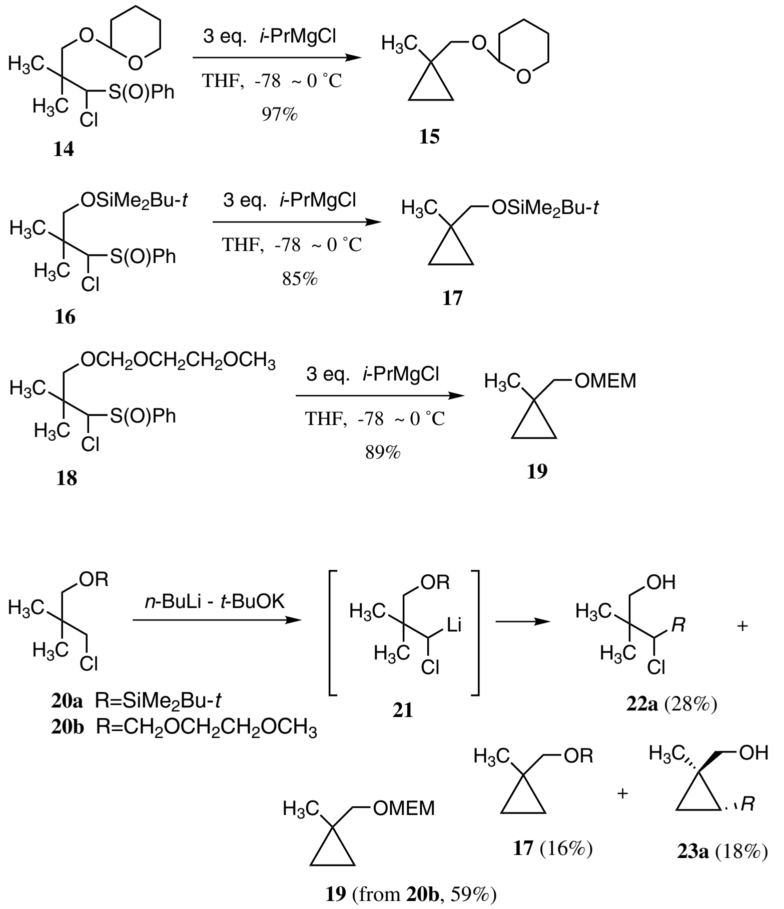
A solution of 1-chloroalkyl phenyl sulfoxide **14** in THF was added dropwise to a solution of *i*-PrMgCl at −78 °C and the reaction mixture was allowed to warm to 0 °C. This reaction gave a quite clean reaction mixture and the desired cyclopropane **15** was obtained in 97% yield. Somewhat surprisingly, the product was only **15** and no isomer was observed.[9]

Encouraged by this result, the sulfoxides **16** and **18** were treated with *i*-PrMgCl under the same conditions as described above. The reaction mixture was again quite clean and cyclopropanes **17** and **19** were obtained in over 85% isolated yield as a single product.

Julia and Clayden recently reported the 1,3-CH insertion reaction of lithium carbenoid derived from primary alky chloride by H–Li exchange reaction.[10] For example, they treated the chloride having a siloxy group at the 3-position **20a** with a mixture of *n*-BuLi and *t*-BuOK at −70 °C and allowed it to warm to −10 °C to give three products, **22a**, **17** and **23a** (Scheme 4). The intermediate of this reaction was proposed to be the lithium carbenoid **21**. It is noteworthy that the corresponding α-chlorosulfoxide **16** gave cyclopropane **17** in 85% yield as a single product. The MEM-protected chloride **20b** was reported to give cyclopropane **19** in 59% yield by treatment with *n*-BuLi and *t*-BuOK. In our case, the corresponding sulfoxide **18** gave the cyclopropane **19** in 89% yield.



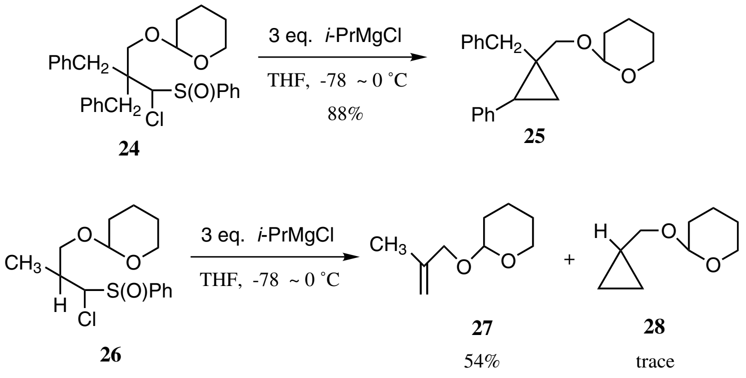
Scheme 3.



Scheme 4.

The magnesium carbenoid 1,3-CH insertion was found to occur not only between the carbenoid carbon and methyl group but also between the carbenoid carbon and methylene group. For example, we synthesized 1-chloroalkyl phenyl sulfoxide having two benzyl groups at 2-position **24** from diethyl malonate and it was treated with *i*-PrMgCl. Interestingly, the C–H insertion reaction between the carbenoid carbon and the benzyl carbon instantaneously took place and gave cyclopropane **25** in 88% yield as a 5:1 mixture of two diastereomers (Scheme 5).

Finally, we synthesized 1-chloroalkyl phenyl sulfoxide having a methyl group and hydrogen at 2-position **26** from 2-methyl-1,3-propanediol. Treatment of **26** with *i*-PrMgCl under the same conditions as above gave an olefin **27** with only trace amount of cyclopropane **28**. This result shows that when the generated magnesium carbenoid has a hydrogen at the 2-position, rearrangement of the hydrogen giving an olefin is faster reaction compared with the 1,3-CH insertion reaction. This result also suggests a limitation of cyclopropanation using the magnesium carbenoids.



Scheme 5.

In conclusion, we have discovered that the magnesium carbenoids generated from 1-chloroalkyl phenyl sulfoxide having a geminal methyl group and a geminal benzyl group with *i*-PrMgCl gave cyclopropanes by 1,3-CH insertion in high to quantitative yields. This is the first example for 1,3-CH insertion of the magnesium carbenoid.[11] Because the α-chlorosulfoxides were easily synthesized from haloalkanes or alcohols and the yields giving cyclopropanes were quite good, the procedure described above will become a good way for synthesis of cyclopropanes. We are continuing to study the scope and limitations of this chemistry.

Acknowledgements

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6. 2,2-Dimethyl-3-phenyl-1-propanol was treated with PhSSPh and Bu_3P in THF to give a sulfide, which was oxidized with *m*-chloroperbenzoic acid to afford a sulfoxide. The sulfoxide was chlorinated with NCS in CCl_4 to give the desired **8** in high overall yield.
7. Lit.,[1a] pp 209–266.
8. 2,2-Dimethyl-1,3-propanediol was treated with PhSSPh and Bu_3P to give mono sulfide, which was oxidized with *m*-chloroperbenzoic acid to give a sulfoxide having a hydroxyl group. The hydroxyl group was protected with dihydropyrane and finally the THP-protected sulfoxide was chlorinated with NCS in THF to give **14** in good yield. The 1-chloroalkyl phenyl sulfoxides **16** and **18** were synthesized from **14**.
9. A solution of *i*-PrMgCl (0.72 mmol) was added to 1.2 mL of THF in a flame-dried flask at −78 °C under Ar atmosphere. After being stirred for 10 min, a solution of **14** (80 mg; 0.24 mmol) in 1.2 mL of dry THF was added to the reaction mixture. The reaction mixture was stirred and slowly allowed to warm to 0 °C and stirred for 1 h at 0 °C. The reaction was quenched by adding satd aq NH_4Cl and the whole was extracted with ether and dried over $MgSO_4$. The product was purified by silica gel column chromatography to give 39.5 mg (97%) of **15** as a colorless oil; IR (neat) 2944, 2871, 1455, 1353, 1202 cm^{-1}. ^1H NMR δ 0.31 (2H, m), 0.42 (2H, m), 1.14 (3H, s), 1.51–1.90 (6H, m), 3.17 (1H, d, $J = 10.4$ Hz), 3.46–3.51 (1H, m), 3.54 (1H, d, $J = 10.4$ Hz), 3.86 (1H, m), 4.62 (1H, t, $J = 3.4$ Hz). MS *m*/*z* (%) 170 (M^+, 0.4), 155 (0.5), 101 (7), 85 (100), 69 (42). Calcd for $C_{10}H_{18}O_2$: M, 170.1307. Found: *m*/*z* 170.1308.
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