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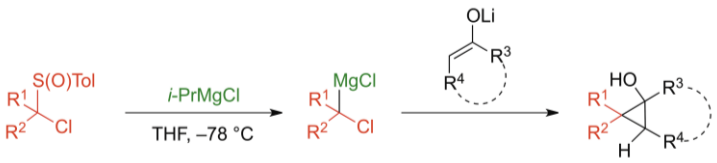

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A novel one-pot synthesis of cyclopropanols based on the reaction of magnesium carbenoids with lithium enolate of ketones

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ABSTRACT

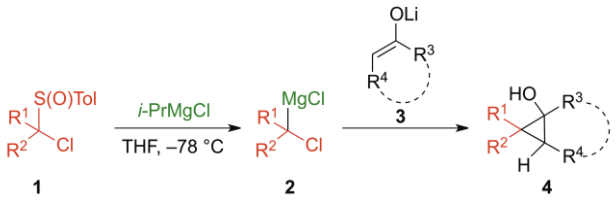
The reaction of magnesium carbenoids with lithium enolate of ketones resulted in the formation of cyclopropanols in moderate to good yields. These reactive species (i.e., magnesium carbenoids and lithium enolate of ketones) were generated from 1-chloroalkyl *p*-tolyl sulfoxides with *i*-PrMgCl and ketones with LDA in the reaction medium at –78 °C in a one-pot reaction.

Cyclopropanes and their derivatives are one of the most important and fundamental compounds in organic and synthetic organic chemistry. The cyclopropane skeletal structure is frequently found in natural products and in unnatural compounds. Cyclopropanes and their derivatives undergo a variety of ring-opening reactions under various conditions with carbon-carbon and carbon-heteroatom bond formation or rearrangement. Based on these properties, cyclopropane derivatives have been recognized to be one of the most useful compounds in organic synthesis.[1] Among the cyclopropanes, cyclopropanol and its derivatives are versatile intermediates in organic synthesis.[2, 3]

Several procedures for the synthesis of cyclopropanols are known. For example, the Kulinkovich reaction[2b,2d,4] is the method using esters. The Simmons-Smith-type cyclopropanation of silyl enol ethers or enol ethers is also available.[2d] However, in view of the importance of cyclopropanols in organic synthesis, new methods for their synthesis are still very much desired.

We have been interested in the synthesis of cyclopropanes based on our original methods, which include the 1,3-CH insertion of magnesium carbenoids[5] and the nucleophilic reaction of cyclopropylmagnesium carbenoids with carbanions.[6] As a continuation of the development of new synthetic methods by the reaction of magnesium carbenoids with carbanions, magnesium carbenoid **2**, which was generated from **1** with *i*-PrMgCl by a sulfoxide-magnesium exchange reaction,[7] was reacted with lithium enolate of ketone **3**. The reaction gave multisubstituted cyclopropanols **4** in moderate to good yields (Scheme 1). In this Letter, a novel method for the synthesis of the cyclopropanols mentioned above in a one-pot procedure is reported.

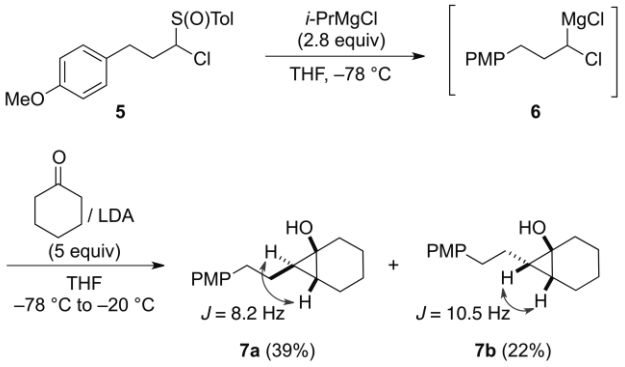
As shown in Scheme 2, 1-chloro-3-(4-methoxyphenyl)propyl *p*-tolyl sulfoxide **5** was reacted with 2.8 equivalents of *i*-PrMgCl in THF at –78 °C to generate magnesium carbenoid **6**.[8] In another flask, lithium enolate of cyclohexanone (5 equiv) was generated in THF at –78 °C in the usual manner. Then, the solution containing lithium enolate was transferred into the solution containing magnesium carbenoid **6** via a cannula, and the reaction mixture was stirred and gradually allowed to warm to –20 °C. From this reaction, two products were obtained that were separable by silica gel column chromatography.



Scheme 1. Reaction of magnesium carbenoids **2** with lithium enolate of ketones **3** to afford cyclopropanols **4**.

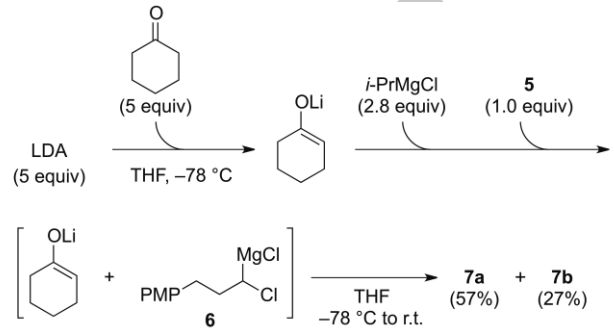
The major product **7a** had a molecular formula of $C_{16}H_{22}O_2$ and an O-H absorption in its IR spectrum. The ^{1}H NMR exhibited two characteristic signals at δ 0.43 and δ 0.66, which suggested the presence of a cyclopropane skeletal structure. In addition, the ^{13}C NMR (DEPT) and ^{1}H NMR spectra suggested that the carbon bearing the hydroxyl group is quaternary. From these data and coupling constant between two cyclopropane protons (J = 8.2 Hz), the major product **7a** was determined to be *cis*-7-[2-(4-methoxyphenyl)ethyl]bicyclo[4.1.0]heptan-1-ol (*cis*: relative configuration of the hydroxyl group and the 2-arylethyl group), as shown in Scheme 2. The structure of the minor

product was determined to be the *trans*-diastereomer **7b** based on its spectral data.



Scheme 2. A two-pot synthesis of cyclopropanols **7a** and **7b** from 1-chloro-3-(4-methoxyphenyl)propyl *p*-tolyl sulfoxide **5** and cyclohexanone.

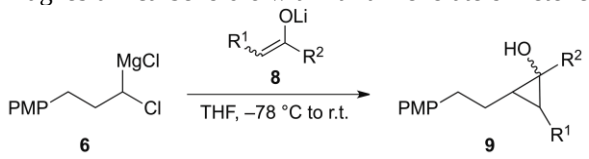
As the transfer of the reactive species via a cannula is not an expedient procedure, we investigated more convenient methods for performing this reaction. Fortunately, the reaction of sulfoxide **5** with lithium enolate of ketones was very slow at –78 °C. Therefore, the one-pot reaction shown in Scheme 3 was successfully designed. To a flame-dried flask, THF and diisopropylamine were added followed by BuLi at –78 °C to generate LDA. Cyclohexanone was subsequently added with stirring. After 20 min, *i*-PrMgCl was added followed by the addition of a solution containing **5** in a small amount of THF. Next, the temperature of the whole reaction mixture was slowly warmed to room temperature. The reaction was quenched with saturated aqueous NH_4Cl to yield cyclopropanols **7a** and **7b** in better yields of 57 and 27%, respectively.[9]

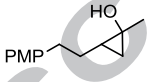
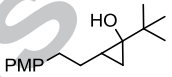
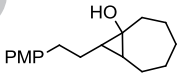
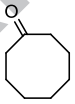
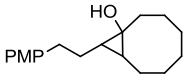
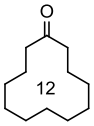
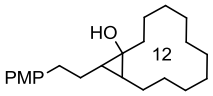
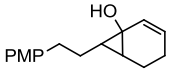


Scheme 3. A one-pot synthesis of cyclopropanols **7a** and **7b** from cyclohexanone and 1-chloro-3-(4-methoxyphenyl)propyl *p*-tolyl sulfoxide **5**.

The scope of this reaction was investigated with a range of ketones **8** with sulfoxide **5** using the one-pot procedure described above, and the results are summarized in Table 1. As shown in entry 1, this procedure was successful with the simplest ketone (i.e., acetone) to afford the desired cyclopropanol **9** in 74% yield. *tert*-Butyl methyl ketone, which is a highly sterically hindered ketone, afforded the desired cyclopropanol in moderate yield (entry 2). Entries 3 to 5 show that cyclic ketones other than cyclohexanone afforded the desired cyclopropanols with up to an 83% yield. Even 2-cyclohexenone, which is an α,β-unsaturated ketone, yielded the desired cyclopropanol with a 67% yield (entry 6). Therefore, this reaction is applicable to a variety of ketones.

Table 1. One-pot synthesis of cyclopropanols by the reaction of magnesium carbenoid **6** with lithium enolate of ketones **8.**



Entry	ketone	**9**	**9**	
			Yield (%)	*trans*:*cis*
1			74	53:22 [a]
2			61	41:20 [b]
3			79	57:22
4			83	70:13
5			73	– [c]
6			67	30:37

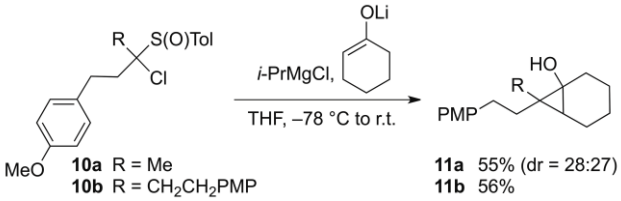
[a] The relative configurations were assigned on the basis of NOESY spectra.
[b] The relative configurations were tentatively assigned on the basis of spectroscopic comparison with the products in entry 1.
[c] A mixture of three diastereomers in a ratio of 49:13:11 was obtained.

Next, the investigation was expanded to the synthesis of more substituted cyclopropanols using 1-chloro-1,1-dialkyl *p*-tolyl sulfoxides **10** as the magnesium carbenoid source (Scheme 4). Sulfoxides **10a** and **10b** were synthesized from **5** and the corresponding iodoalkanes with LDA as a base in high yields. The reaction was conducted in one pot as described above and multisubstituted cyclopropanols **11a** and **11b** were successfully obtained in 55 and 56% yield, respectively.

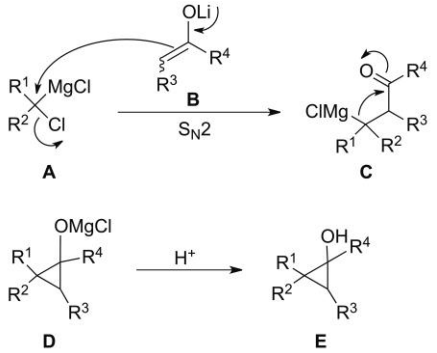
Finally, a plausible reaction mechanism for this reaction is shown in Scheme 5. The nucleophilic substitution of magnesium carbenoid **A** with lithium enolate of ketone **B** affords intermediate **C**.[6e,10] Then, the intramolecular addition reaction of the magnesium carbanion in **C** proceeds to the ketone carbonyl group to yield magnesium cyclopropanolate **D**, which is hydrolyzed in the workup to afford cyclopropanol **E**.

In conclusion, we found that the reaction of magnesium carbenoids with lithium enolate of ketones yielded multisubstituted cyclopropanols with the consecutive formation

of two carbon-carbon bonds. Although the current yields are not always high, the one-pot synthesis described is an unprecedented method and we believe it will substantially contribute to the synthesis of cyclopropanols.



Scheme 4. Synthesis of highly substituted cyclopropanols **11** from 1-chloro-1,1-dialkylmethyl *p*-tolyl sulfoxides **10** and lithium enolate of cyclohexanone.



Scheme 5. A plausible mechanism for the reaction of magnesium carbenoids with lithium enolate of ketones.

Acknowledgments

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9. A 1.64 M solution of *n*-BuLi in hexane (0.61 mL, 1.0 mmol) was added dropwise to a solution of diisopropylamine (0.15 mL, 1.1 mmol) in THF (1.6 mL) at 0 °C. The mixture was stirred for 10 min at 0 °C and cooled to –78 °C. Cyclohexanone (0.10 mL, 0.97 mmol) was added dropwise to the resulting solution at -78°C. After further stirring for 20 min, a 2.0 M solution of *i*-PrMgCl in THF (0.28 mL; 0.56 mmol) and a solution of sulfoxide (65 mg; 0.2 mmol) in THF (0.4 mL) were added in turn to the resulting solution at –78 °C. The reaction mixture was warmed to room temperature over a period of 2 h. The reaction was quenched with sat. aq. NH_4Cl (1.5 mL), and the mixture was extracted with $CHCl_3$ (3 × 7 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to yield *cis*-7-[2-(4-methoxyphenyl)ethyl]bicyclo[4.1.0]heptan-1-ol **7a** (28.0 mg, 57%) and **7b** (13.5 mg, 27%) as light yellow oils. **7a**: IR (neat) 3407 (OH), 2931, 2854, 1612, 1512, 1464, 1448, 1246, 1177, 1037, 828 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.43 (td, *J* = 5.8, 8.2 Hz, 1H), 0.66 (ddd, *J* = 1.6, 6.1, 8.2 Hz, 1H), 1.03-1.07 (m, 1H), 1.15-1.24 (m, 2H), 1.31-1.47 (m, 2H), 1.60-1.79 (m, 3H), 1.83-1.97 (m, 3H), 2.55 (ddd, *J* = 6.8, 8.7, 13.5 Hz, 1H), 2.72 (td, *J* = 6.3, 13.5 Hz, 1H), 3.79 (s, 3H), 6.82-6.86 (m, 2H), 7.09-7.13 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 21.4 (CH_2), 21.7 (CH_2), 24.3 (CH_2), 24.7 (CH), 28.9 (CH), 30.1 (CH_2), 32.8 (CH_2), 35.3 (CH_2), 55.2 (CH_3), 57.7 (C), 113.7 (CH), 129.5 (CH), 134.7 (C), 157.7 (C); MS (EI) *m*/*z* (%) = 246 (M^+, 28), 148 (27), 134 (49), 121 (100); HRMS (EI) calcd for $C_{16}H_{22}O_2$: 246.1620, found: 246.1621. **7b**: IR (neat) 3346 (OH), 2931, 2855, 1612, 1512, 1465, 1447, 1246, 1177, 1038, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (td, *J* = 7.0, 10.5 Hz, 1H), 1.14 (ddd, *J* = 2.2, 9.0, 10.5 Hz, 1H), 1.17-1.31 (m, 4H), 1.45-1.68 (m, 3H), 1.78 (br s, 1H), 1.83-1.94 (m, 3H), 2.61 (ddd, *J* = 7.1, 8.9, 13.6 Hz, 1H), 2.68 (ddd, *J* = 6.6, 8.5, 13.6 Hz, 1H), 3.79 (s, 3H), 6.82-6.85 (m, 2H), 7.11-7.14 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 18.8 (CH_2), 21.4 (CH), 22.0 (CH_2), 22.3 (CH_2), 26.2 (CH_2), 28.3 (CH), 28.8 (CH_2), 35.2 (CH_2), 55.2 (CH_3), 55.7 (C), 113.7 (CH), 129.3 (CH), 134.5 (C), 157.7 (C); MS (EI) *m*/*z* (%) = 246 (M^+, 33), 148 (30), 134 (50), 121 (100); HRMS (EI) calcd for $C_{16}H_{22}O_2$: 246.1620, found: 246.1617.
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