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A versatile synthesis, including asymmetric synthesis, of bicyclo[*n*.1.0]alkanes from cyclic ketones via the magnesium carbenoid 1,3-CH insertion as a key reaction

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Abstract—Treatment of 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from various cyclic ketones and chloromethyl *p*-tolyl sulfoxide in three steps, in high yields, with lithium enolate of *tert*-butyl acetate or its homologues gave the adducts in quantitative yields. The adducts were treated with isopropylmagnesium chloride in ether in dry toluene as the reaction solvent to afford bicyclo[*n*.1.0]alkanes in high to quantitative yields via magnesium carbenoid 1,3-CH insertion. When this method was carried out starting from unsymmetrical cyclic ketones and (*R*)-chloromethyl *p*-tolyl sulfoxide, an asymmetric synthesis of bicyclo[*n*.1.0]alkane was realized.

Cyclopropanes are obviously one of the most important compounds in organic and synthetic organic chemistry. Because the cyclopropane ring is highly strained, ring-opening reaction of cyclopropanes occurs under the influence of a variety of chemical reagents under mild conditions with carbon–carbon or carbon–hetero atom bond-formation. These chemical properties are the reason that cyclopropanes are useful as versatile compounds in organic synthesis. The synthetic methods of cyclopropanes[1] and their use in organic synthesis[2] have widely been reported.

Cyclopropanes in which the cyclopropane ring is fused with another ring, such as **1** in Scheme 1, are referred to as bicyclo[*n*.1.0]alkanes and they are also quite interesting compounds. For example, 2-aminobicyclo-[3.1.0]hexane-2,6-dicarboxylic acid (LY354740), an agonist for the group II metabotropic glutamate receptor, bears a bicyclo[3.1.0]hexane (**1**, $m = 1$) core structure.[3] Synthesis of bicyclo[*n*.1.0]alkanes has been carried out mainly by three ways as shown in Scheme 1. The first one is the Simmons–Smith type cyclopropanation of cyclic olefins **2**.[1c,4] The second one is the intramolecular cyclopropanation of diazoalkenes **3**.[1a,c] The third is the intramolecular S_N2-type reaction of **4**.[3b]

We have also been interested in the compounds containing a cyclopropane ring.[5] In continuation of our study for the development of new synthetic methods for cyclopropanes, we recently established a versatile synthesis of bicyclo[*n*.1.0]alkanes **1** from cyclic ketones **5** via 1-chlorovinyl *p*-tolyl sulfoxides **6**. The key reaction of this method is the 1,3-CH insertion[6] of magnesium carbenoid **8** derived from **7** by a sulfoxide–magnesium exchange reaction.[7]

The procedure using 1-chlorovinyl *p*-tolyl sulfoxide **9** is reported as a representative example as shown in Table 1. 1-Chlorovinyl *p*-tolyl sulfoxide **9**, derived from cyclopentadecanone,[8] was treated with lithium enolate of *tert*-butyl acetate to give the adduct **10** in quantitative yield.[9] First, a solution of the adduct **10** in THF was added to a solution of 2.5 equiv of *i*-PrMgCl (in THF solution) in THF at −78 °C with stirring and the temperature of the reaction mixture was slowly allowed to warm to 0 °C. All the starting material **10** disappeared and two products were obtained. From a detailed inspection of the ^{1}H NMR of the products, cyclopropane **11** and chloride **12** were recognized to be the products. Interestingly, no cyclopropane **13** was

Keywords: Bicyclo[*n*.1.0]alkane; Cyclopropane; Sulfoxide–magnesium exchange; Magnesium carbenoid; C–H insertion.
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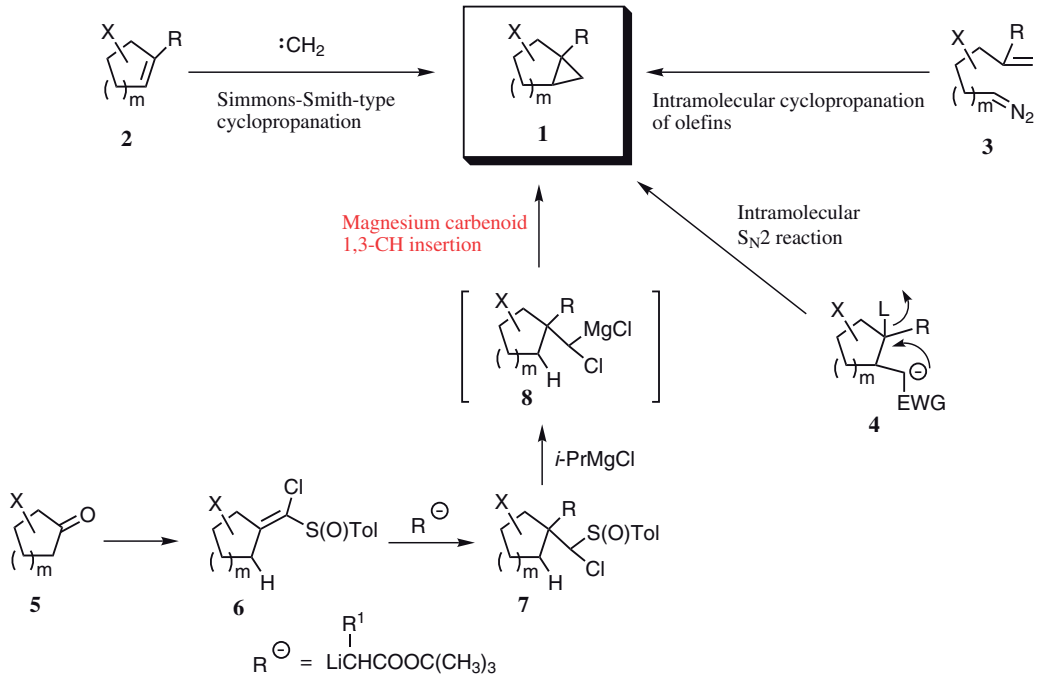
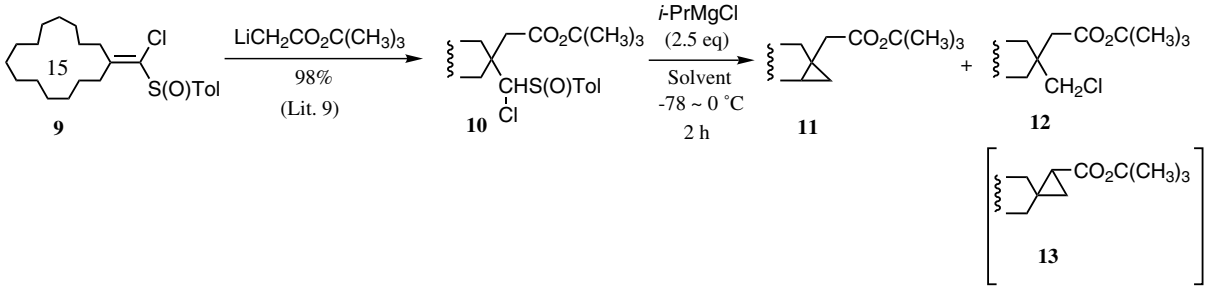


Scheme 1.

Table 1. Examination of the best conditions for the cylopropanation of **10** with *i*-PrMgCl through the magnesium carbenoid 1,3-CH insertion reaction to give bicyclo[13.1.0]hexadecane **11**



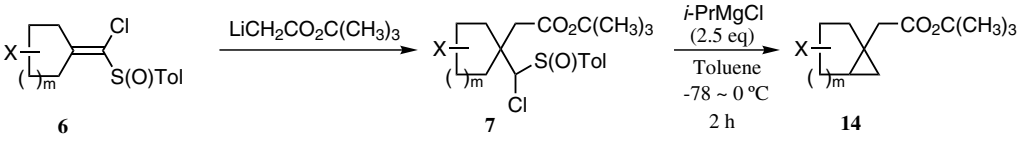
Entry	*i*-PrMg Cl/solvent[a]	Solvent[b]	**11** Yield (%)	**12** Yield[c] (%)
1	THF	THE	62	21
2	THF	Et_2O	69	7
3	THF	Toluene	70	5
4	Et_2O	THE	68	19
5	Et_2O	Et_2O	78	5
6	Et_2O	Toluene	96	0

[a] The solvent dissolving isopropylmagnesium chloride.
[b] The solvent for carrying out the reaction.
[c] The yield of **l2** was calculated from its ^{1}H NMR.

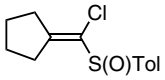
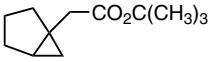
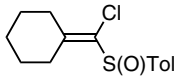
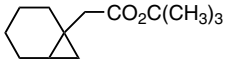
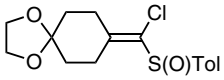
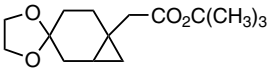
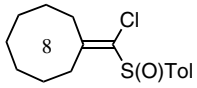
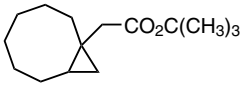
obtained judging from the ^{1}H NMR. Cyclopropane **11** was the desired product; however, it was contaminated with a considerable amount of **12**, which was derived from protonation of the magnesium carbenoid intermediate. Unfortunately, **12** could not be separated from the desired **11**.

We studied the reaction conditions for suppressing the by-product **12** and the results are summarized in Table 1. First, ether and toluene were used as the solvent and the toluene was found to show some effect (entries 2 and 3); however, protonated product **12** was not completely suppressed. We thought that the proton source of the reaction would be THF as the solvent for the Grignard reagent. We tried this reaction with *i*-PrMgCl (ether solution) in THF, ether, or toluene as the reaction solvent (entries 4–6) and, fortunately, when this reaction was carried out in toluene, the desired **11**

Table 2. Synthesis of bicyclo[*n*.1.0]alkanes **14** from the adducts **7** derived from 1-chlorovinyl *p*-tolyl sulfoxides **6** with lithium enolate of *tert*-butyl acetate



6 **7** **14**

Entry	**6**	Yield (%)		
		7	**14**	
1		98	**14a** 	74
2		97	**14b** 	68
3		99[a]	**14c** 	95 (93)[b]
4		97	**14d** 	90

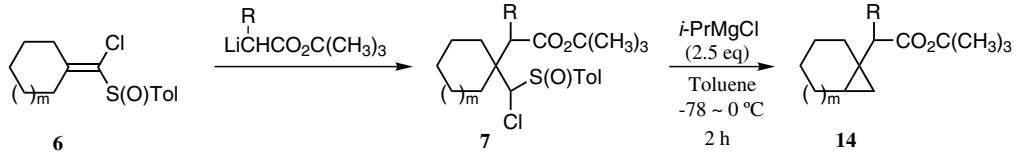
[a] Two isolable diastereomers of the adducts were obtained. The ratio of the main isomer and the minor isomer was 86:14.
[b] The yield in parentheses was obtained from the minor isomer.

was obtained in almost quantitative yield without generation of the protonated chloride **12** (entry 6).[10]

This reaction is, obviously, an unprecedented and outstanding way for the synthesis of bicyclo[*n*.1.0]alkanes from cyclic ketones. We next investigated the generality of this procedure and the results are summarized in Table 2. The addition reaction of 1-chlorovinyl *p*-tolyl sulfoxides **6**, derived from cyclopentanone, cyclohexanone, 1,4-cyclohexanedione mono ethylene ketal, and cyclooctanone gave the adduct **7** in almost quantitative yields (entries 1–4). The key reaction, magnesium carbenoid 1,3-CH insertion, took place smoothly in toluene with *i*-PrMgCl (ether solution) without the protonated chlorides to give bicyclo[*n*.1.0]alkanes having a *tert*-butoxycarbonylmethyl group on the bridgehead carbon **14** in up to 95% yield. From these results, this procedure was confirmed to be effective from small (five-membered) to large-ringed (15-membered) cyclic ketones.

In further development of this procedure, we tried it with *tert*-butyl propionate and *tert*-butyl hexanoate (Table 3). 1-Chlorovinyl *p*-tolyl sulfoxides **6** derived from cyclohexanone, cyclooctanone, and cyclopentadecanone were used and the results are summarized in Table 3. The addition reaction of *tert*-butyl propionate to **6** gave quite high yields of the adducts (entries 1–3); however, the reaction with *tert*-butyl hexanoate gave

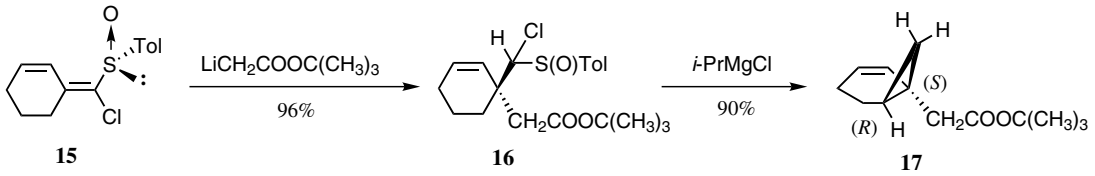
Table 3. Synthesis of bicyclo[*n*.1.0] alkanes **14** from the adducts **7** derived from 1-chlorovinyl *p*-tolyl sulfoxides **6** with lithium enolate of *tert*-butyl propionate and *tert*-butyl hexanoate



6 **7** **14**

Entry	**6**	**7**		**14**[a]	
	m	R	Yield (%)		Yield (%)
1	1	CH_3	99	**14e**	76
2	3	CH_3	88	**14f**	96
3	10	CH_3	93	**14g**	95[b]
4	1	$CH_2CH_2CH_2CH_3$	99	**14h**	95
5	3	$CH_2CH_2CH_2CH_3$	78	**14i**	89
6	10	$CH_2CH_2CH_2CH_3$	89	**14j**	99[c]

[a] All the products **14**, except **14g** and **14j**, were a single isomer.
[b] The product **14g** was obtained as a mixture of two diastereomers (ratio about 3:1).
[c] 5 equiv of *i*-PrMgCl was used in this reaction. The product **14j** was obtained as a mixture of two diastereomers (ratio about 13:10).



15 16 17

(1*S*,6*R*)-bicyclo[4.1.0]hept-2-ene

Scheme 2.

somewhat lower yields of the adducts **7** (entries 4–6). The magnesium carbenoid 1,3-CH insertion took place smoothly to give up to 99% yield of the bicyclo-[*n*.1.0]alkanes having a carboxylic ester at the bridgehead position **14e**–**14j**.

Finally, this procedure was applied to an asymmetric synthesis of bicyclo[*n*.1.0]alkanes. A synthesis of optically active bicyclo[4.1.0]hept-2-ene derivative **17** was investigated as a representative example (Scheme 2). First, 1-chlorovinyl *p*-tolyl sulfoxide **15** was synthesized from 2-cyclohexenone and optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide,[11] and it was treated with lithium enolate of *tert*-butyl acetate to afford the adduct **16** in 96% yield. The enantiomeric excess (over 99%) and the absolute configuration of **16** were reported previously.[12]

The optically pure adduct **16** was treated with *i*-PrMgCl under the conditions described above to afford a quite clean reaction and only one product, (1*S*,6*R*)-bicyclo[4.1.0]hept-2-ene **17** ($[\alpha]_D^{28}$ +137.2 (*c* 0.1, EtOH)), was obtained in 90% yield. Interestingly, as expected, the magnesium carbenoid 1,3-CH insertion reaction occurred only at the methylene carbon on the cyclohexene ring.

In conclusion, we have developed a new method for a synthesis of bicyclo[*n*.1.0]alkanes in good overall yields from cyclic ketones with magnesium carbenoid 1,3-CH insertion as the key reaction. The interesting characteristics of this procedure are as follows. (1) Almost unprecedented and high yielding magnesium carbenoid 1,3-CH insertion was successfully used. As a result, a carbon–carbon bond can be formed at a nonactivated carbon on the ring to give cyclopropanes. (2) Although five steps are requited from cyclic ketones to bicyclo[*n*.1.0]alkanes **1**, the yields of all steps are quite high. (3) Three carbon–carbon bonds are formed in this procedure. (4) All the reactions in this procedure are mild enough and some functional groups such as ester, acetal, olefine, are compatible. (5) Asymmetric synthesis with high optical purity can be realized starting from unsymmetrical ketones and (*R*)-chloromethyl *p*-tolyl sulfoxide.

Acknowledgement

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10. To a flame-dried flask was added dry toluene (4 mL) followed by *i*-PrMgCl (0.5 mmol; 2.5 equiv) in ether at −78 °C. A solution of the adduct **10** (102 mg; 0.2 mmol) in toluene (2.5 mL) was added to the solution of Grignard reagent dropwise with stirring and the reaction mixture was slowly allowed to warm to 0 °C for 2 h. The reaction was quenched with satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The product was purified over silica gel column to afford 64.5 mg (96%) of cyclopropane **11** as a colorless oil. IR (neat) 2929, 2857, 1735 (CO), 1459, 1366, 1309, 1250, 1147, 959, 758 cm^{-1}; ^1H NMR δ 0.25 (1H, dd, $J = 5.8$, 4.8 Hz), 0.47–0.53 (2H, m), 0.59–0.68 (1H, m), 1.08–1.17 (1H, m), 1.21–1.49 (22H, m), 1.46 (9H,

s), 1.54–1.59 (1H, m), 1.76 (1H, d, $J = 15.6$ Hz), 1.99–2.15 (1H, m), 2.57 (1H, d, $J = 15.6$ Hz). MS m/z (%) 336 (M^+, 2), 321 (3), 280 (29), 262 (10), 220 (100), 135 (3), 109 (5). Calcd for $C_{22}H_{40}O_2$: M, 336.3028. Found: m/z 336.3023.

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