



A new synthesis, including asymmetric synthesis, of alkylidenecyclopropanes by 1,2-CC insertion of cyclobutylmagnesium carbenoides as the key reaction

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ABSTRACT

Treatment of 1-chlorovinyl *p*-tolyl sulfoxides, derived from ketones and chloromethyl *p*-tolyl sulfoxide, with lithium enolate of carboxylic acid *tert*-butyl esters gave adducts in high yields. The adducts were converted to 1-chlorocyclobutyl *p*-tolyl sulfoxides in four steps in high overall yields. Treatment of the 1-chlorocyclobutyl *p*-tolyl sulfoxides with cyclopentylmagnesium chloride in THF at -40°C resulted in the formation of cyclobutylmagnesium carbenoids. The magnesium carbenoid 1,2-CC insertion reaction took place smoothly from the cyclobutylmagnesium carbenoids to afford alkylidenecyclopropanes in good to high yields. An asymmetric synthesis of optically active alkylidenecyclopropane was successfully achieved starting from optically active 1-chlorovinyl *p*-tolyl sulfoxide.

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1. Introduction

Alkylidenecyclopropanes, including methylenecyclopropanes, are quite interesting compounds. They are structurally highly strained; however, usually present as stable compounds at room temperature. Because of their highly strained nature, alkylidenecyclopropanes show various reactivities and have long been used widely in organic synthesis.¹ Moreover, some biologically active compounds comprising an alkylidenecyclopropane moiety as a basic skeleton, such as G1499-2, amphimic acids, and 9-hydroxymethylcyclopropylidene-methylenyladenine,² have been known. Therefore, new methods for the synthesis of alkylidenecyclopropanes are very much desired.

A variety of the methods for synthesis of alkylidenecyclopropanes have been reported;³ however, synthesis of optically active alkylidenecyclopropanes is limited.⁴ We are also interested in the chemistry of alkylidenecyclopropanes and reported their synthesis based on the reaction of cyclopropylmagnesium carbenoids with lithium α -sulfonyl carbanions.⁵ In continuation of our interest in the chemistry of magnesium carbenoids in organic synthesis,⁶ recently, we developed a new method for a synthesis, including asymmetric synthesis, of alkylidenecyclopropanes by our original method as shown in Scheme 1.

Thus, 1-chlorovinyl *p*-tolyl sulfoxides **2**, synthesized from ketones **1**,⁷ are treated with lithium enolate of *tert*-butyl carboxylates to give adducts **3** in high yields. The *tert*-butyl ester moiety is

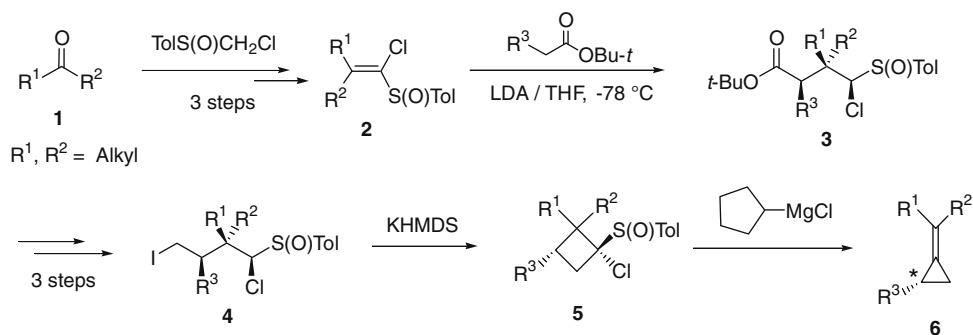
converted to an iodide group under conventional reactions to give iodides **4**, which are treated with a base to afford 1-chlorocyclobutyl *p*-tolyl sulfoxides **5** in high yields. Finally, sulfoxides **5** are treated with cyclopentylmagnesium chloride to give alkylidenecyclopropanes **6** in good yields. When optically active 1-chlorovinyl *p*-tolyl sulfoxide **2** was used in this procedure, an asymmetric synthesis of optically active alkylidenecyclopropane **6** was achieved. In this Letter we report the above-mentioned procedure.

2. Results and discussion

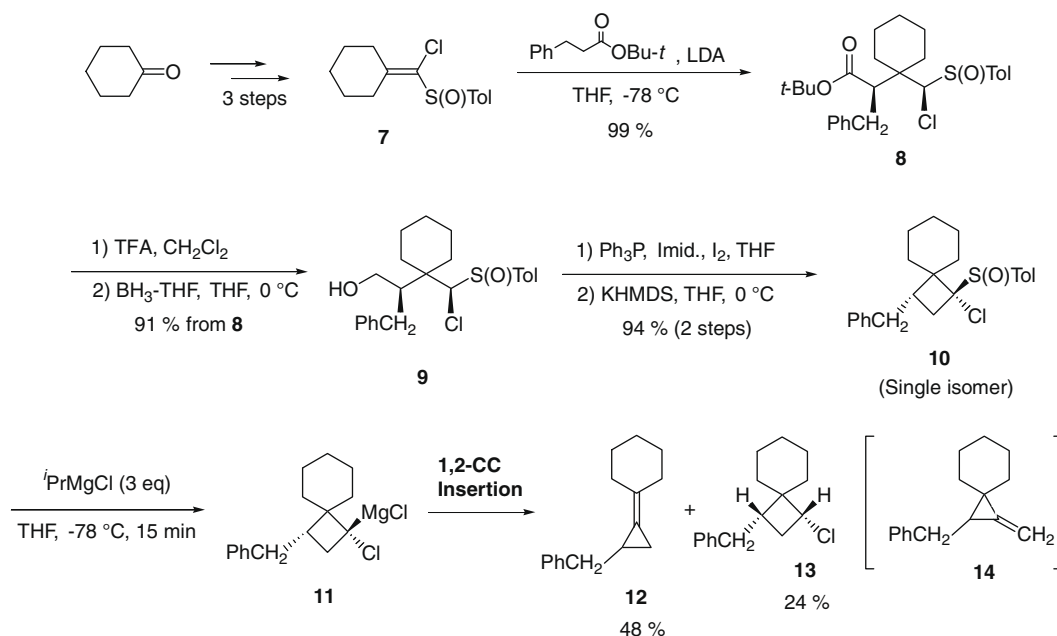
At first, representative example of this procedure is shown using 1-chlorovinyl *p*-tolyl sulfoxide **7**, which was derived from cyclohexanone, as the starting material (Scheme 2). Thus, 1-chlorovinyl *p*-tolyl sulfoxide **7^a** was treated with lithium enolate of *tert*-butyl 3-phenylpropionate to afford adduct **8** in a quantitative yield.⁸ Stereochemistry of adduct **8** (*syn*-relationship between the chlorine atom and the benzyl group) was determined based on our previous study.⁹ The adduct was treated with trifluoroacetic acid in dichloromethane to give a carboxylic acid, which was reduced with BH_3 –THF in THF at 0°C to give alcohol **9** in 91% overall yield from **8**. Attempt to direct reduction of ester **8** with DIBAL to alcohol **9** resulted in low yield (up to 60%). The hydroxyl group in **9** was converted to iodide group under the conventional reaction and the resultant iodide was treated with 2 equiv of KHMDS to give the desired 1-chlorocyclobutyl *p*-tolyl sulfoxide **10** in 94% overall yield from **9** as a single product.¹⁰ Stereochemistry of **10** was determined by NOESY spectrum of the desulfenylated compound **13** (vide infra).

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Scheme 1.



Scheme 2.

The key reaction was carried out as follows. A solution of *i*-PrMgCl in ether (3 equiv) was added to a solution of 1-chlorocyclobutyl *p*-tolyl sulfoxide **10** in THF at $-78\text{ }^{\circ}\text{C}$ under Ar atmosphere. After the reaction mixture was stirred for 15 min, the reaction was quenched with satd aq NH_4Cl . The reaction mixture was rather clean and two products were obtained. The main product was determined to be 2-benzyl(cyclopropylidene)cyclohexane **12** (48%) and the minor product was desulfinylated chlorocyclobutane **13** (24%). Alkyldenecyclopropane **12** is the expected product from 1,2-CC insertion reaction of the cyclobutylmagnesium carbenoid **11**, which was derived from **10** by the sulfoxide–magnesium exchange reaction, and **13** is the protonated product of **11**. Quite interestingly, methylenecyclopropane **14**, which is another expected product from the 1,2-CC insertion reaction of the magnesium carbenoid intermediate **11**, was not observed at all. Configuration of **13** was determined from its ^1H NMR spectrum, especially by NOESY spectrum (NOE was observed between the hydrogens on the carbons bearing the chlorine atom and the benzyl group). Configuration of the starting material **10** was determined to be as shown in Scheme 2 from the stereochemistry of **13**.¹¹

As we recognized that the above-mentioned procedure would become quite interesting and new way for a synthesis of alkyldenecyclopropanes, the proper conditions to the key reaction were

investigated and the results are summarized in Table 1. Entries 1–4 show the effects of four Grignard reagents other than *i*-PrMgCl at $-78\text{ }^{\circ}\text{C}$ for 15 min. The sulfoxide–magnesium exchange reaction did not take place with MeMgCl and PhMgCl. EtMgCl and cyclopentylmagnesium chloride gave **12** in better yields compared to that of *i*-PrMgCl (48%; see Scheme 2). We concluded that cyclopentylmagnesium chloride is the Grignard reagent of choice in this reaction.

Entries 5–9 show the effect of the temperature of the reaction with cyclopentylmagnesium chloride in THF for 15 min. As shown, when the reaction was carried out at $-40\text{ }^{\circ}\text{C}$, the best yield (87%) was obtained (entry 6). Entries 10–13 show the results for the reaction time in THF at $-40\text{ }^{\circ}\text{C}$. Both shortening and prolonging of the reaction time did not give better results. Finally, we investigated the effect of the solvent (entries 14 and 15) and found that both ether and toluene were not effective to this reaction. We concluded that the conditions in entry 6 are the conditions of choice in this reaction.

Next, generality of this procedure was examined and the results are summarized in Table 2. As the starting material for the synthesis of 1-chlorocyclobutyl *p*-tolyl sulfoxides **15a–15g**, cyclopentanone, cycloheptanone, cyclopentadecanone, and cyclohexanone were used as cyclic ketones (entries 1–4). Acetone and 4-phenyl-2-butanone were used as acyclic ketones (entries 5–7). *tert*-Butyl

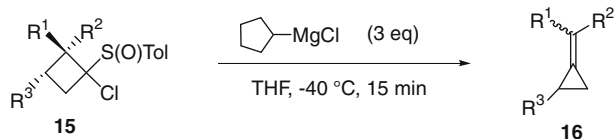
Table 1Examination of the optimum conditions for the synthesis of alkylidenecyclopropane **12** through the magnesium carbenoid 1,2-CC insertion reaction

Entry	Grignard reagent	Conditions			Yield (%)	
		Temp (°C)	Time (min)	Solvent	12	13
1	MeMgCl	−78	15	THF	— ^a	—
2	PhMgCl	−78	15	THF	— ^a	—
3	EtMgCl	−78	15	THF	54	19
4	 MgCl	−78	15	THF	56	29
5	 MgCl	−60	15	THF	76	15
6	 MgCl	−40	15	THF	87	1
7	 MgCl	−20	15	THF	73	2
8	 MgCl	0	15	THF	71	2
9	 MgCl	rt	15	THF	73	1
10	 MgCl	−40	5	THF	74	6
11	 MgCl	−40	10	THF	85	3
12	 MgCl	−40	30	THF	80	1
13	 MgCl	−40	60	THF	75	2
14	 MgCl	−40	15	Et ₂ O	39 ^b	Trace
15	 MgCl	−40	15	Toluene	27 ^c	Trace

^a No reaction was observed and the starting material was quantitatively recovered.^b The starting material was recovered in 58%.^c The starting material was recovered in 69%.

3-phenylpropionate, *tert*-butyl 4-phenylbutyrate, and *tert*-butyl propionate were used as esters.

The sulfoxide–magnesium exchange reaction was carried out under the best conditions as mentioned above (Table 1, entry 6). As shown in Table 2, all 1-chlorocyclobutyl *p*-tolyl sulfoxides **15**,

Table 2Synthesis of alkylidenecyclopropanes **16** from 1-chlorocyclobutyl *p*-tolyl sulfoxides **15** through the magnesium carbenoid 1,2-CC insertion reaction

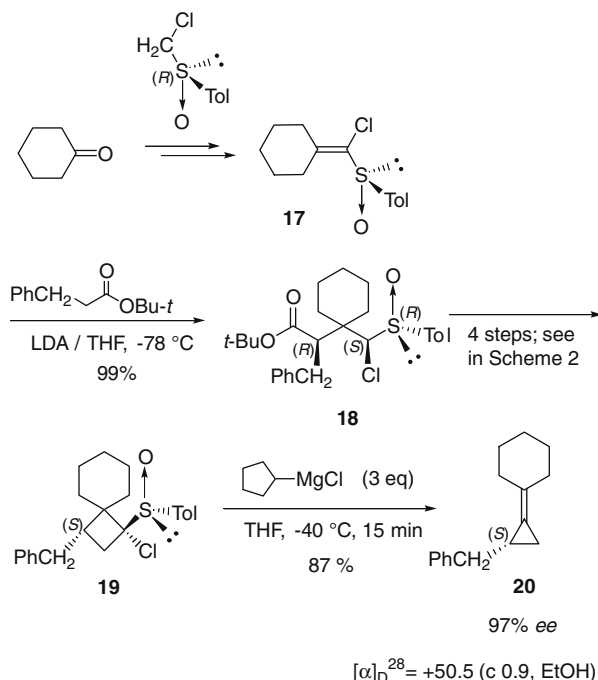
Entry	15			16
	R ¹	R ²	R ³	Yield (%)
1	15a	−(CH ₂) ₄ −	PhCH ₂	62
2	15b	−(CH ₂) ₆ −	PhCH ₂	39 ^a
3	15c	−(CH ₂) ₁₄ −	PhCH ₂	73
4	15d	−(CH ₂) ₅ −	PhCH ₂ CH ₂	86
5	15e	CH ₃	CH ₃	77
6	15f	PhCH ₂ CH ₂	CH ₃	82 ^b
7	15g	CH ₃	PhCH ₂ CH ₂	75 ^c

^a The structure of the other products could not be determined.^b A 2:1 mixture of two geometrical isomers was obtained.^c A 1:1 mixture of two geometrical isomers was obtained.

except one case (entry 2), gave the desired alkylidenecyclopropanes **16** in 62–86% yields. From these results, the procedure presented herein proved to be quite useful for obtaining various alkylidenecyclopropanes. When diastereomers **15f** and **15g** were treated with cyclopentylmagnesium chloride, a mixture of two geometrical isomers was obtained (entries 6 and 7). These results suggested that this 1,2-CC insertion would not be a concerted reaction but a stepwise reaction.

As an application of this procedure, an asymmetric synthesis of optically active alkylidenecyclopropanes was investigated (Scheme 3). Thus, optically active 1-chlorovinyl *p*-tolyl sulfoxide **17** was synthesized from cyclohexanone with (*R*)-chloromethyl *p*-tolyl sulfoxide.¹² Addition reaction of **17** with lithium enolate of *tert*-butyl 3-phenylpropionate gave adduct **18** and all the absolute stereochemistry were unambiguously determined as shown in Scheme 3 based on our previous work.^{9,13} Optically active **18** was converted to optically active (1*R*,3*S*,*R*_s)-1-chloro-3-benzyl-1-(*p*-tolylsulfinyl)spiro[3.5]nonane **19** in the same reaction described above.

Finally, optically active **19** was treated with cyclopentylmagnesium chloride in THF at −40 °C to give optically active (*S*)-2-benzylcyclopropylidenecyclohexane **20** in 87% yield.¹⁴ The optical purity of **20** was easily determined to be over 97% by using a chiral stationary column (CHIRALCEL OD (Daicel); hexane as a developing solvent). As the optical purity of the starting material, (*R*)-chloromethyl *p*-tolyl sulfoxide, was 97–99%,¹² the procedure shown in Scheme 3 is thought to proceed without racemization.



Scheme 3.

In conclusion, we have developed a new method for a synthesis of alkylidenecyclopropanes from 1-chlorovinyl *p*-tolyl sulfoxides asymmetric synthesis of them can be realized. Synthesis of alkylidenecyclopropanes from 1,1-dibromocyclobutanes with methyllithium has been known.¹⁵ The presented procedure is the first example for the synthesis of alkylidenecyclopropanes through the 1,2-CC insertion of cyclobutylmagnesium carbenoids with one-carbon contraction.

Acknowledgments

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 - TFA (0.92 mL; 12.4 mmol) was added to a solution of **8** (1.18 g; 2.5 mmol) in 25 mL of CH_2Cl_2 with stirring. The solution was stirred for 1 day and the reaction was quenched with satd aq NaHCO_3 . The whole was extracted with CH_2Cl_2 , and the organic layer was dried over MgSO_4 . The solvent was evaporated to afford crude carboxylic acid. A solution of $\text{BH}_3\text{-THF}$ complex (12.4 mmol) in 11.7 mL of THF was added dropwise to a solution of the crude carboxylic acid in 25 mL of THF under argon atmosphere with stirring. The solution was stirred for 1 day and the reaction was quenched with satd aq NH_4Cl . The whole was extracted with CHCl_3 , and the organic layer was dried over MgSO_4 . The solvent was evaporated and the residue was purified by silica gel column chromatography to afford alcohol **9** (918 mg; 91% from **8**) as colorless crystals. Mp $108\text{--}109^{\circ}\text{C}$ (AcOEt–hexane); IR (KBr) 3445 (OH), 3060, 3026, 2927, 1738, 1597, 1495, 1455, 1399, 1304, 1244, 1082, 1050 (SO) cm^{-1} ; ^1H NMR δ 1.37–1.56 (3H, m), 1.63–1.87 (4H, m), 1.91–2.05 (1H, m), 2.12–2.25 (1H, m), 2.34–2.48 (2H, m), 2.45 (3H, s), 2.86 (1H, dd, $J = 13.4, 11.5$ Hz), 3.19 (1H, dd, $J = 13.4, 2.8$ Hz), 3.68–3.81 (1H, m), 3.88–4.00 (1H, m), 4.95 (1H, s), 7.17–7.27 (1H, m), 7.28–7.39 (6H, m), 7.72–7.79 (2H, m). MS m/z (%) 405 ($[\text{M}+\text{H}]^+$, trace), 387(5), 230 (12), 229 (72), 211 (16), 199 (6), 155 (5), 140 (66), 141 (28), 117 (34), 90 (29), 91 (100). Calcd for $\text{C}_{23}\text{H}_{30}\text{ClO}_2\text{S}$: M^+ , 405.1646. Found; m/z 405.1650.
 - Ph_3P (2.97 g; 11.3 mmol) and I_2 (1.44 g; 11.3 mmol) were added to a solution of **9** (918 mg; 2.3 mmol) in 23 mL of THF with stirring. After the solution was stirred for 10 min, imidazole (771 mg; 11.3 mmol) was added to the reaction mixture. After 15 min of stirring, the reaction was quenched with satd aq Na_2SO_3 . The whole was extracted with CHCl_3 , and the organic layer was dried over MgSO_4 . The solvent was evaporated and the residue was purified by silica gel column chromatography to give the desired iodide. A solution of KHMDS (4.5 mmol) in 9.1 mL of toluene was added dropwise to a solution of the iodide in 91 mL of THF at 0°C under argon atmosphere with stirring. The reaction mixture was stirred for 15 min and the reaction was quenched with satd aq NH_4Cl . The whole was extracted with CHCl_3 , and the organic layer was dried over MgSO_4 . The solvent was evaporated and the residue was purified by silica gel column chromatography to afford **10** (822 mg; 94% in two steps) as colorless oil; IR (neat) 3026, 2928, 2856, 1598, 1495, 1454, 1086, 1059 (SO) cm^{-1} ; ^1H NMR δ 1.34–1.60 (4H, m), 1.66–1.95 (4H, m), 1.96–2.15 (2H, m), 2.18–2.31 (1H, m), 2.34–2.49 (2H, m), 2.39 (3H, s), 2.72–2.86 (1H, m), 3.05 (1H, dd, $J = 13.6, 4.1$ Hz), 7.08–7.15 (2H, m), 7.15–7.31 (5H, m), 7.46–7.54 (2H, m). MS m/z (%) 386 (M^+ , trace), 247 (10), 212 (12), 211 (61), 201 (5), 169 (5), 155 (6), 143 (15), 140 (54), 129 (17), 107 (32), 91 (100). Calcd for $\text{C}_{23}\text{H}_{27}\text{ClOS}$: M , 386.1471. Found; m/z 386.1478.
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