



A synthesis of esters, amides, and sulfones bearing a 1-cyclopentenyl group at the α -position from cyclobutanones with one-carbon ring-expansion

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ABSTRACT

Treatment of 1-chlorovinyl *p*-tolyl sulfoxides, derived from cyclobutanones and chloromethyl *p*-tolyl sulfoxide, with lithium enolate of carboxylic acid *tert*-butyl esters, lithium enolate of carboxylic acid *N,N*-dimethylamides, or lithium α -carbanion of alkyl phenyl sulfones gave adducts in high yields. The adducts were treated with isopropylmagnesium chloride or ethylmagnesium chloride in dry toluene to give esters, amides, and sulfones bearing a 1-cyclopentenyl group at the α -position in moderate to good yields with one-carbon ring-expansion via magnesium carbenoid 1,2-CC insertion reaction. The magnesium carbenoid 1,2-CC insertion reaction proved to be highly stereospecific. The reaction mechanism and origin of the specificity are described.

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Carbenes and carbenoids are obviously one of the most interesting highly reactive carbon species and are frequently used as versatile intermediates in organic synthesis.¹ Carbenes and carbenoids show a variety of reactions, such as addition into a carbon–carbon double bond to give cyclopropanes, dimerization to give olefins, and ylide formation with sulfides. Rearrangement and insertion are other most striking reactions of carbenes and carbenoids.² Insertion reaction is very interesting and highly useful for construction of molecules, because the reaction enables the formation of a carbon–carbon bond between a carbene (or carbenoid) carbon and a non-activated carbon or enables the formation of olefins.

We recently reported a synthesis of bicyclo[*n*.1.0]alkanes **4** by 1,3-CH insertion reaction of magnesium carbenoid **3** as a key reaction.³ Thus, 1-chlorovinyl *p*-tolyl sulfoxides **1** (*n* is one or over) were synthesized from cyclic ketones with chloromethyl *p*-tolyl sulfoxide. Addition reaction of **1** with lithium enolate of *tert*-butyl acetate gave adducts **2** in high yields. Treatment of **2** with *i*-PrMgCl in toluene resulted in the formation of magnesium carbenoid **3** via the sulfoxide-magnesium exchange reaction. Magnesium carbenoid 1,3-CH insertion reaction of **3** took place smoothly to afford **4** in quantitative yields (Scheme 1).³

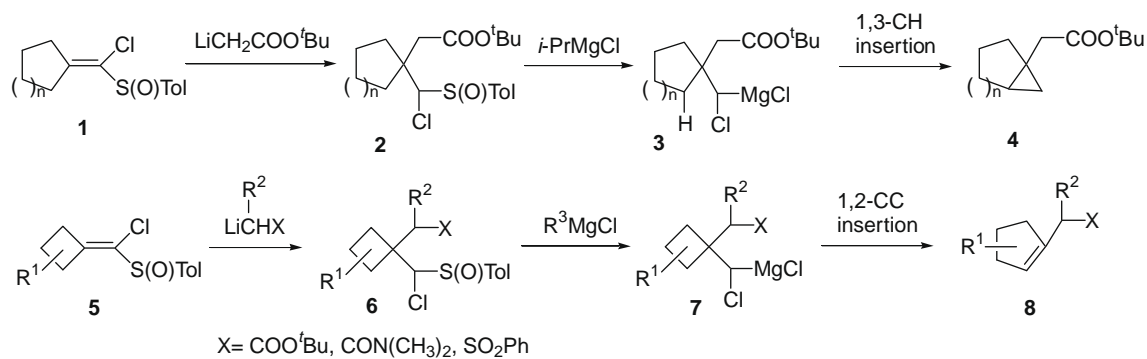
In continuation of our interest in the chemistry of magnesium carbenoid 1,3-CH insertion reaction, we further investigated the reaction mentioned above by using adduct **6** (*X* = COO^{*t*}Bu), derived

from 1-chlorovinyl *p*-tolyl sulfoxide **5**, with *i*-PrMgCl and found that the reaction resulted in the formation of an ester bearing a 1-cyclopentenyl group at the α -position **8** (*X* = COO^{*t*}Bu) in good yields (Scheme 1). Obviously, 1,2-CC insertion reaction, instead of the expected 1,3-CH insertion reaction, took place from magnesium carbenoid **7**. As we recognized that this reaction is very useful for synthesis of cyclopentenes bearing various functionalities at the olefinic carbon **8** by assemblage of three components, cyclobutanones, chloromethyl *p*-tolyl sulfoxide, and nucleophiles (LiC(R²)HX), we further investigated this reaction. We report herein a synthesis of esters, amides, and sulfones bearing a 1-cyclopentenyl group at the α -position **8** from cyclobutanones with one-carbon ring-expansion via 1-chlorovinyl *p*-tolyl sulfoxides **5** and magnesium carbenoids **7**.

At first, 1-chlorovinyl *p*-tolyl sulfoxide **10** was synthesized from cyclobutanone **9**⁴ with chloromethyl *p*-tolyl sulfoxide in good overall yield (Table 1).⁵ Addition reaction of **10** with lithium enolate of *tert*-butyl acetate was carried out in the same manner as described before⁶ to give the desired adduct **11** in a quantitative yield. Finally, the adduct **11** was treated with 2 equiv of *i*-PrMgCl in toluene at -78 °C and the temperature of the reaction mixture was slowly allowed to warm to 0 °C for 2 h (Table 1, entry 1). Although significant amount of the starting material remained, the reaction mixture was rather clean and a product was obtained. Initially, we expected that the product was bicyclo[2.1.0]pentane derivative **13** (the product from the 1,3-CH insertion reaction of magnesium carbenoid intermediate);³ however, the product had an olefinic hydrogen (¹H NMR spectrum; δ 5.38, 1H, br s). Finally,

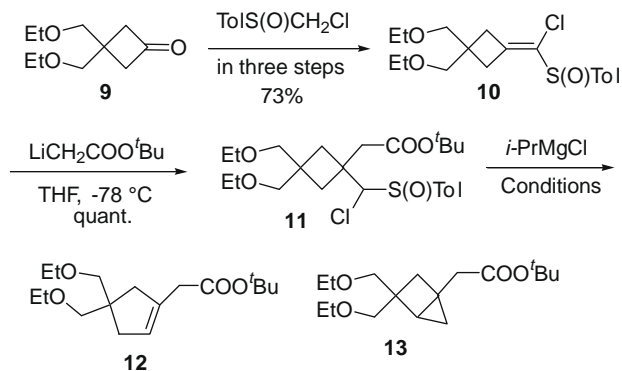
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Scheme 1.

Table 1
A synthesis of *tert*-butyl acetate bearing a 1-cyclopentenyl group at the α -position **12** from cyclobutanone **9** with one-carbon ring-expansion



Entry	<i>i</i> -PrMgCl (equiv)	Conditions			12 Yield (%)
		Temp (°C)	Time (h)	Solvent	
1	2	-78~0	2	Toluene	35 ^a
2	3	-78~0	2	Toluene	54 ^a
3	5	-78~0	2	Toluene	73
4	5	-40~0	1	Toluene	51
5	5	0	0.5	Toluene	54
6	5	-78~0	2	THF	70
7	5	-78~0	2	CH ₂ Cl ₂	45

^a Some amount of the starting material **11** was recovered.

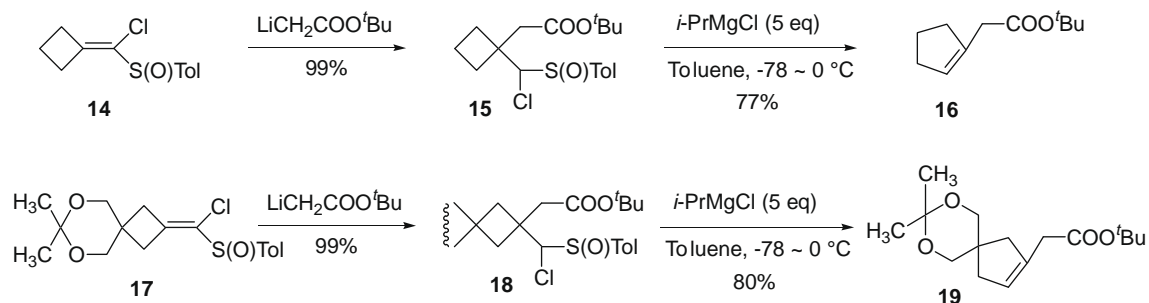
the structure of the product was determined to be *tert*-butyl acetate bearing 1-cyclopentene moiety **12** on the bases of IR, NMR, and MS spectral data. Obviously, the product was produced by magnesium carbenoid 1,2-CC insertion reaction. To the best of our knowledge, this is the first example of one-carbon ring-expansion by the magnesium carbenoid 1,2-CC insertion reaction.

Optimization of the yield of this reaction was investigated and the results are summarized in Table 1. Increasing the amount of *i*-PrMgCl to 3 equiv resulted in 54% yield; however, some amount of the starting material **11** still remained (entry 2). Finally, by the use of 5 equiv of *i*-PrMgCl, all the starting material was consumed and the product **12** was obtained in 73% yield (entry 3).⁷ Use of higher reaction temperature gave worse results (entries 4 and 5). Selection of THF as a solvent gave a similar result (compare the results in entries 3 and 6). Dichloromethane as the solvent gave miserable result (entry 7). We concluded that the conditions in entry 3 are suitable for the reaction.

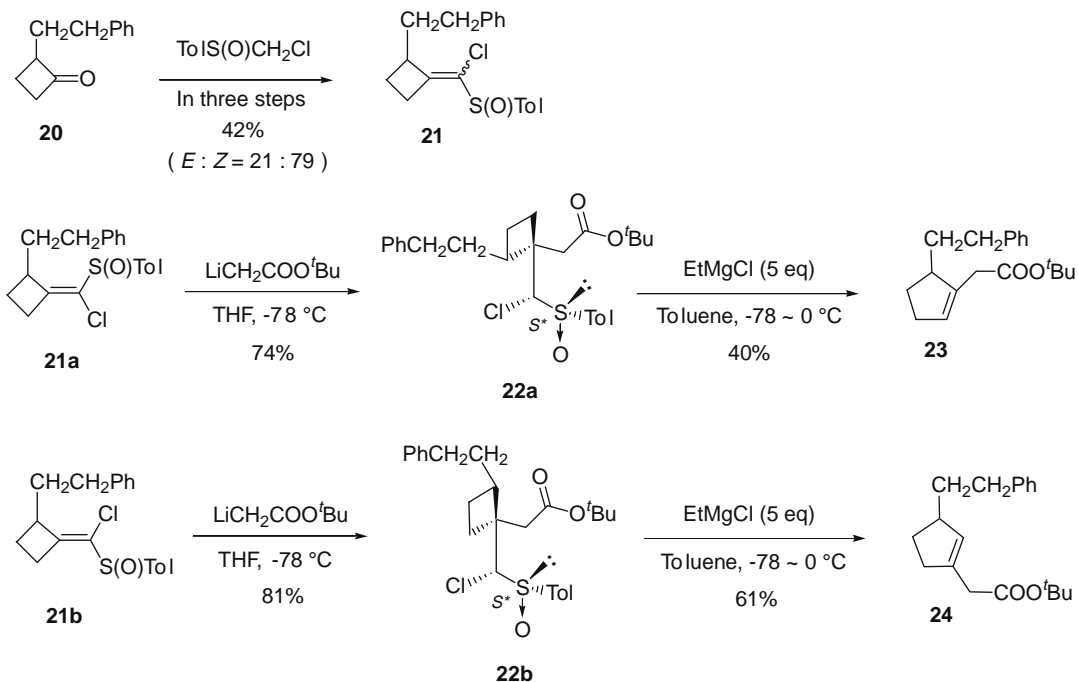
Other two examples of this procedure are shown in Scheme 2. Thus, 1-chlorovinyl *p*-tolyl sulfoxide **14**, derived from cyclobutanone, was treated with lithium enolate of *tert*-butyl acetate to give adduct **15** in a quantitative yield. 1-Chlorovinyl *p*-tolyl sulfoxide **17** having an acetal group gave adduct **18** without any problem. Both adducts **15** and **18** were treated with 5 equiv of *i*-PrMgCl to give the expected *tert*-butyl acetate bearing a 1-cyclopentenyl group at the α -position, **16** and **19**, respectively, in about 80% yield.

Quite interesting results were obtained from the reaction starting from unsymmetrical cyclobutanone (Scheme 3). Unsymmetrical cyclobutanone, 2-(2-phenylethyl)cyclobutanone, **20** was synthesized from cyclopropyl phenyl sulfide according to Piras' method.⁸ 1-Chlorovinyl *p*-tolyl sulfoxide **21** was synthesized from **20** with chloromethyl *p*-tolyl sulfoxide in three steps in 42% overall yield as a mixture of two geometrical isomers, which were separated by silica gel column chromatography to give *E*-isomer **21a** and *Z*-isomer **21b** in a ratio of 21:79.⁹

Treatment of both vinyl sulfoxides **21a** and **21b** with lithium enolate of *tert*-butyl acetate afforded adducts **22a** and **22b**, respectively, as a single isomer in good yields. Relative stereochemistry of the adducts was determined to be as shown in Scheme 3 based on the previous study.¹⁰ The sulfoxide-magnesium exchange reaction of **22a** was, at first, carried out with *i*-PrMgCl; however, no reaction was observed. Steric hindrance by the 2-phenylethyl group on the



Scheme 2.



cyclobutane ring was thought to be the reason for this difficulty. Fortunately, **22a** reacted smoothly with EtMgCl to afford the desired ester bearing a 1-cyclopentene moiety **23** in 40% yield as a single product. The same treatment of the diastereomer **22b** with EtMgCl gave the structural isomer **24** in 61% yield again as a single product. Quite interestingly, these reactions are highly stereospecific. The structure of two products, **23** and **24**, was determined by COSY, HSQC, HMBC, and NOESY spectra.¹¹

The mechanism of this interesting and highly stereospecific magnesium carbenoid 1,2-CC insertion reaction can be explained as follows (see Scheme 4). As the sulfoxide-magnesium exchange reaction is known to proceed with retention of the configuration of the carbon bearing the sulfinyl group,¹² treatment of **22a** with EtMgCl gives magnesium carbenoid having *R*^{*}-configuration at the carbon bearing the magnesium atom. The magnesium and carbonyl oxygen atom of the *tert*-butyl ester group must make six-membered intermediate **A**, in which the bulkiest *tert*-butoxy group

would occupy the equatorial position. From this intermediate, the 1,2-CC insertion takes place from behind of the carbon–chlorine bond to give the product **23**. The situation of the reaction of **22b** with EtMgCl is thought to be the same. The magnesium carbenoid intermediate derived from **22b** must make the six-membered intermediate **B** and again the 1,2-CC insertion reaction proceeds from behind of the carbon–chlorine bond to afford **24**.

Additional examples for the synthesis of *tert*-butyl esters bearing 1-cyclopentene moiety at the α -position and further extension of this procedure to a synthesis of amides and sulfones are summarized in Table 2. The addition reaction of **14** with *tert*-butyl propionate and *tert*-butyl (4-methylphenyl)acetate gave adducts **25a** and **25b**, respectively, in quantitative yields. Treatment of the adducts with 5 equiv of *i*-PrMgCl gave the expected products **26a** and **26b**, in good to excellent yields (entries 1 and 2). The addition reaction of **14** with lithium enolate of carboxylic acid *N,N*-dimethylamides¹³ gave adducts **25c** and **25d** both in quantitative yields.

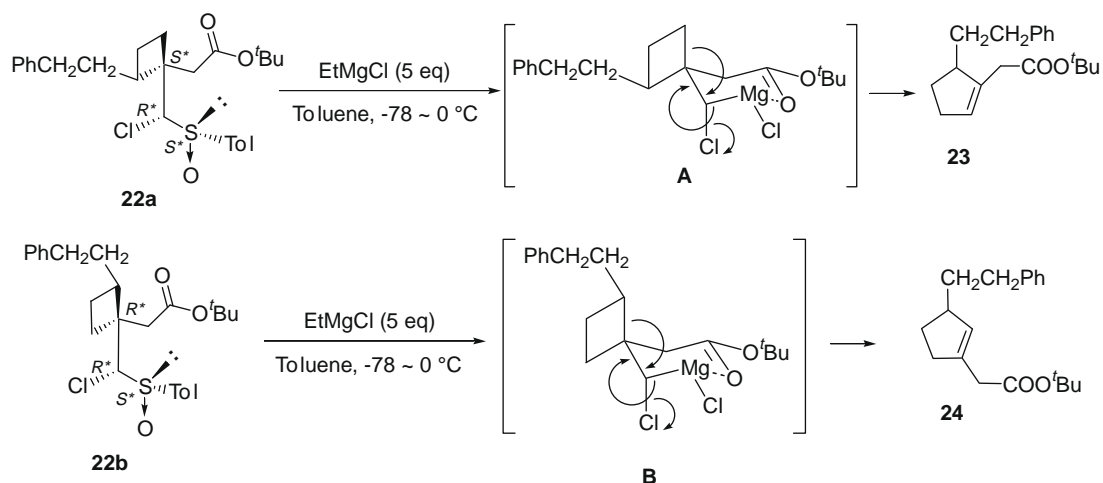
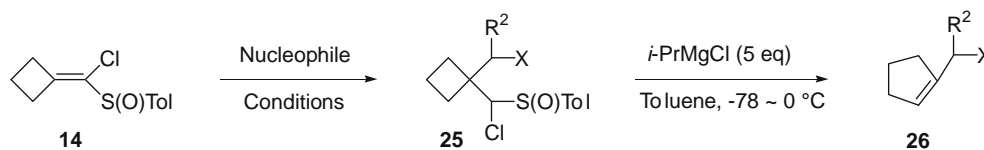


Table 2Synthesis of esters, amides, and sulfones bearing a 1-cyclopentenyl group at the α -position **26** from 1-chlorovinyl *p*-tolyl sulfoxide **14** derived from cyclobutanone

Entry	Nucleophile	Conditions	25		26	
			Yield (%)	R ²	X	Yield (%)
1	CH ₃ CH ₂ COO ^t Bu	LDA, THF, -78 ~ -30 °C, 1 h ^a	25a 99 ^c	CH ₃	COO ^t Bu	70
2	CH ₃ --CH ₂ COO ^t Bu	LDA, THF, -78 °C, 15 min ^b	25b 99	CH ₃ --	COO ^t Bu	92
3	CH ₃ CON(CH ₃) ₂	LDA, THF, -78 °C, 15 min ^a	25c 99 ^d	H	CON(CH ₃) ₂	77
4	CH ₃ CH ₂ CON(CH ₃) ₂	LDA, THF, -78 °C, 15 min ^b	25d 99 ^e	CH ₃	CON(CH ₃) ₂	81
5	CH ₃ SO ₂ Ph	LDA, THF, -78 °C, 15 min ^a	25e 87	H	SO ₂ Ph	78
6	CH ₃ CH ₂ SO ₂ Ph	LDA, THF, -78 °C, 15 min ^b	25f 60 ^f	CH ₃	SO ₂ Ph	96

^a Five equivalents of the nucleophile was used.^b Ten equivalents of the nucleophile was used.^c A 8:1 mixture of two diastereomers.^d A 15:1 mixture of two diastereomers.^e A 2:1 mixture of two diastereomers.^f A 15:1 mixture of two diastereomers.

Treatment of **25c** and **25d** with *i*-PrMgCl resulted in the formation of amides bearing a 1-cyclopentenyl group at the α -position around 80% yields (entries 3 and 4).

The addition reaction of **14** with lithium α -sulfonyl carbanions afforded the expected adducts **25e** and **25f** in somewhat lower yields (entries 5 and 6). 1,2-CC insertion reaction of the magnesium carbenoid generated from the adducts with *i*-PrMgCl proceeded smoothly to give the desired sulfones bearing 1-cyclopentenyl group at the α -position **26e** and **26f** in good to quantitative yields.

In conclusion, we have developed a new method for a synthesis of *tert*-butyl carboxylates, carboxylic acid *N,N*-dimethyl amides, and sulfones bearing a 1-cyclopentenyl group at the α -position by assemblage of three components, cyclobutanones, chloromethyl *p*-tolyl sulfoxide, and carboxylic acid derivatives and sulfones with magnesium carbenoid 1,2-CC insertion reaction as the key reaction. We believe that the magnesium carbenoid 1,2-CC insertion reaction presented herein will be used widely in the one-carbon ring-expansion of cyclobutane derivatives to cyclopentenes.

Acknowledgments

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- tert*-Butyl [4,4-bis(ethoxymethyl)cyclopent-1-enyl]acetate **12**. To a solution of LDA (1.3 mmol) in 0.6 mL of dry THF in a flame-dried flask under argon atmosphere was added *tert*-butyl acetate (0.18 mL; 1.3 mmol) at -78 °C with stirring. After the solution was stirred for 10 min, a solution of vinyl sulfoxide **10** (100 mg; 0.26 mmol) in THF (0.7 mL) was added. The reaction mixture was stirred for 15 min and the reaction was quenched by adding saturated aq. NH₄Cl and the whole was extracted with CHCl₃. The organic layer was dried over MgSO₄ and concentrated in vacuo. The product was purified by silica gel column chromatography to afford **11** (123 mg; 99%) as a colorless oil; IR (neat) 2976, 2932, 2870, 1723 (CO), 1368, 1256, 1154, 1107 (COC), 1055 (SO), 811, 755 cm⁻¹; ¹H NMR δ 1.12 (3H, t, *J* = 7.1 Hz), 1.19 (3H, t, *J* = 7.0 Hz), 1.49 (9H, s), 2.20–2.29 (3H, m), 2.42 (3H, s), 2.66 (1H, d, *J* = 13.8 Hz), 2.96 (1H, d, *J* = 15.0 Hz), 3.05 (1H, d, *J* = 15.0 Hz), 3.36–3.41 (4H, m), 3.46–3.50 (4H, m), 5.42 (1H, s), 7.31 (2H, d, *J* = 8.3 Hz), 7.71 (2H, d, *J* = 8.3 Hz). MS *m/z* (%) 472 (M⁺, 0.7), 399 (34), 277 (59), 241 (15), 195 (47), 185 (27), 149 (32), 137 (100), 91 (28). Calcd for C₂₄H₃₇ClO₂S: M, 472.2050. Found: *m/z* 472.2050.
- To a flame-dried flask under argon atmosphere was added dry toluene (0.2 mL) followed by *i*-PrMgCl (in ether; 0.39 mmol; 5 equiv) at -78 °C. A solution of **11** (37 mg; 0.078 mmol) in toluene (0.2 mL) was added dropwise to the solution of the Grignard reagent with stirring, and the reaction mixture was slowly allowed to warm to 0 °C for 2 h. The reaction was quenched by adding saturated aq. NH₄Cl and the whole was extracted with CHCl₃. The organic layer was dried over MgSO₄ and concentrated in vacuo. The product was purified by silica gel column chromatography to afford 17 mg (73%) of ester **12** as colorless oil. IR (neat) 2977, 2853, 1731 (CO), 1369, 1256, 1146, 1111 (COC) cm⁻¹; ¹H NMR δ 1.17 (6H, t, *J* = 7.0 Hz), 1.44 (9H, s), 2.20 (4H, s), 2.97 (2H, s), 3.33 (4H, s), 3.49 (4H, q, *J* = 7.0 Hz), 5.38 (1H, br s). MS *m/z* (%) 298 (M⁺, 9), 242 (15), 196 (16), 183 (12), 152 (10), 150 (55), 137 (48), 105 (43), 91 (55), 57 (100). Calcd for C₁₇H₃₀O₄: M, 298.2144. Found: *m/z* 298.2148.
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