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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.

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(R^2)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 before[6] 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 (^{1}H NMR spectrum; δ 5.38, 1H, br s). Finally,

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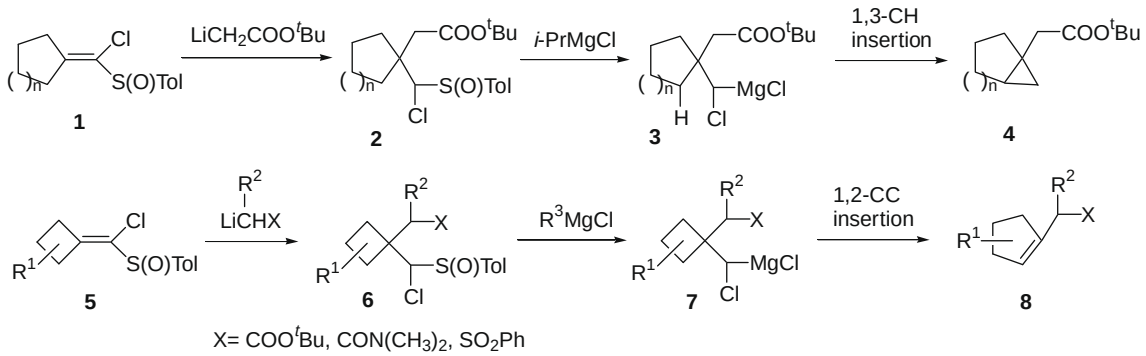
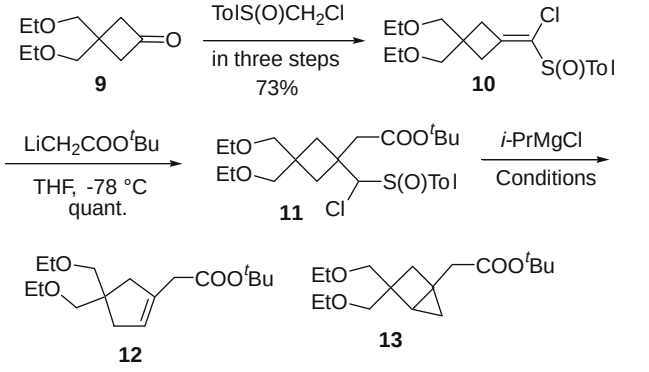


Scheme 1.

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*-PrMgCl (equiv)	Conditions			**12**
		Temp (°C)	Time (h)	Solvent	Yield (%)
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_2Cl_2	45

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

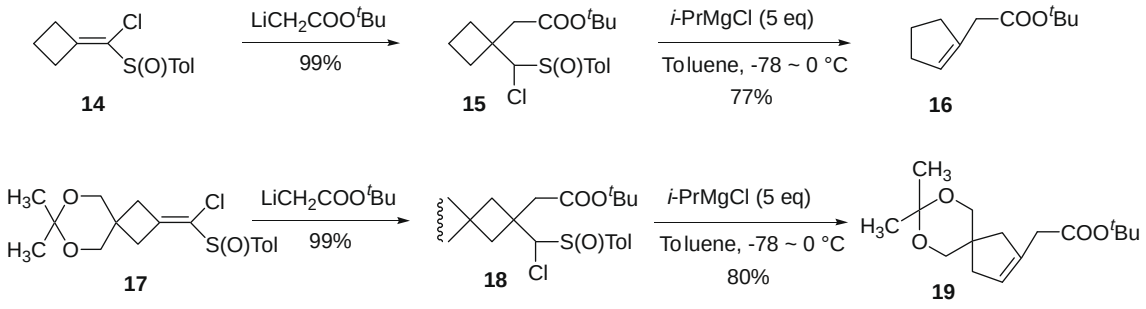
the structure of the product was determined to be *tert*-butyl acetate bearing 1-cyclopentene moiety **12** on the bases of IR, NMR, and MS spectral data. Obviously, the product was produced by magnesium carbenoid 1,2-CC insertion reaction. To the best of our knowledge, this is the first example of one-carbon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

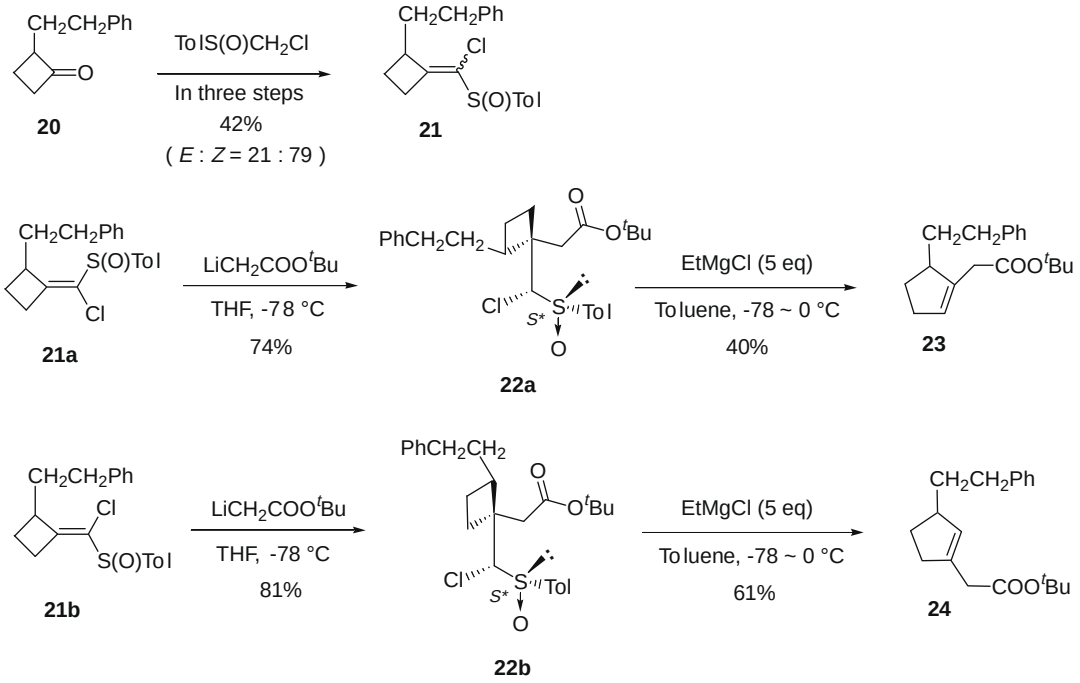
Other two examples of this procedure are shown in Scheme 2. Thus, 1-chlorovinyl *p*-tolyl sulfoxide **14**, derived from cyclobutanone, was treated with lithium enolate of *tert*-butyl acetate to give adduct **15** in a quantitative yield. 1-Chlorovinyl *p*-tolyl sulfoxide **17** having an acetal group 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.

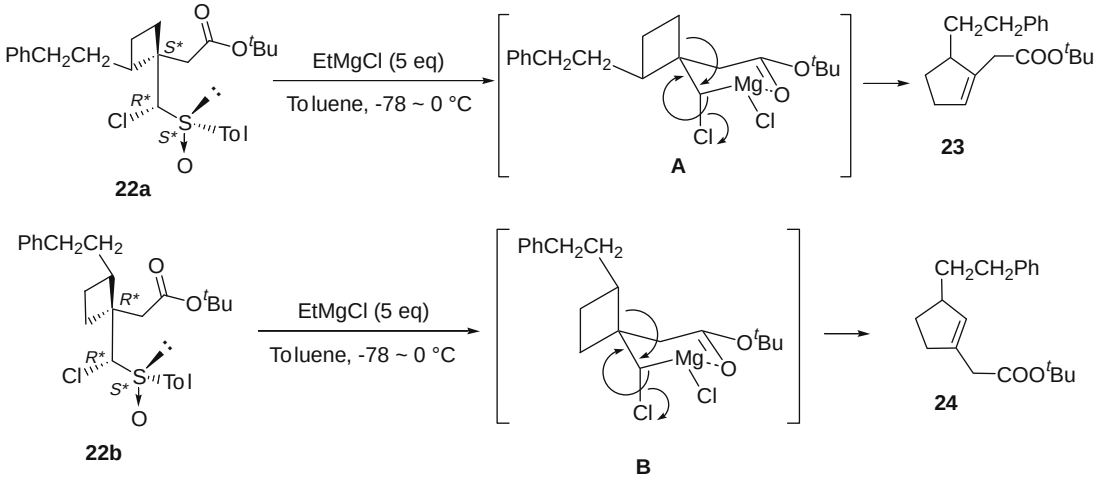


Scheme 3.

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]

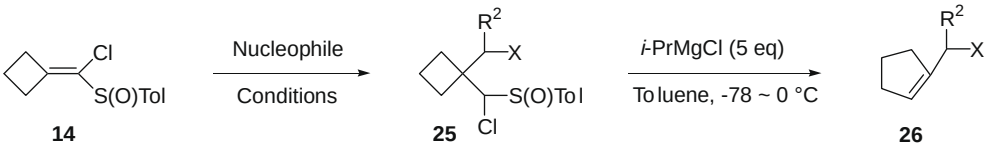
The mechanism of this interesting and highly stereospecific magnesium carbenoid 1,2-CC insertion reaction can be explained as follows (see Scheme 4). As the sulfoxide-magnesium exchange reaction is known to proceed with retention of the configuration of the carbon bearing the sulfinyl group,[12] treatment 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-cyclopentenel 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*-dimethylamides[13] gave adducts **25c** and **25d** both in quantitative yields.

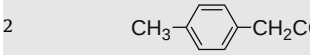


Scheme 4.

Table 2
Synthesis 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



14 **25** **26**

Entry	Nucleophile	Conditions	**25**	**26**		
			Yield (%)	R^2	X	Yield (%)
1	$CH_3CH_2COO^tBu$	LDA, THF, −78 ∼ −30 °C, 1 h[a]	**25a** 99[c]	CH_3	COO^tBu	70
2		LDA, THF,−78 °C, 15 min[b]	**25b** 99		COO^tBu	92
3	$CH_3CON(CH_3)_2$	LDA, THF,−78 °C, 15 min[a]	**25c** 99[d]	H	$CON(CH_3)_2$	77
4	$CH_3CH_2CON(CH_3)_2$	LDA, THF,−78 °C, 15 min[b]	**25d** 99[e]	CH_3	$CON(CH_3)_2$	81
5	CH_3SO_2Ph	LDA, THF,−78 °C, 15 min[a]	**25e** 87	H	SO_2Ph	78
6	$CH_3CH_2SO_2Ph$	LDA, THF,−78 °C, 15 min[b]	**25f** 60[f]	CH_3	SO_2Ph	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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7. *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. NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ 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 $C_{24}H_{37}ClO_5S$: 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. NH_4Cl and the whole was extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ 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 $C_{17}H_{30}O_4$: M, 298.2144. Found: m/z 298.2148.
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