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A new synthesis of β,γ-unsaturated esters and allenic esters with construction of a carbon–carbon bond between α- and β-positions by the reaction of magnesium alkylidene carbenoids with lithium ester enolates

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ABSTRACT

Treatment of lithium ester enolates with magnesium alkylidene carbenoids, generated from 1-chlorovinyl *p*-tolyl sulfoxides with isopropylmagnesium chloride via the sulfoxide–magnesium exchange reaction, gave β,γ-unsaturated esters in moderate to good yields. When this reaction was conducted with the lithium ester enolates of α-chlorocarboxylic acid esters, allenic esters were obtained. This procedure provides an unprecedented way for the synthesis of β,γ-unsaturated esters and allenic esters from ketones with the construction of a carbon–carbon bond between α- and β-positions.

1. Introduction

Carboxylic acids, esters, amides, and their derivatives are undoubtedly among the most important and fundamental compounds in organic, synthetic organic, and bioorganic chemistry.[1] Among the carboxylic acids and their derivatives, the unsaturated ones are also quite important compounds in synthetic organic chemistry. α,β-Unsaturated carboxylic acids and their derivatives are recognized to be easily synthesized from saturated carboxylic acids[2] or from carbonyl compounds by the Horner–Wadsworth–Emmons reaction;[3] however, general synthetic methods for β,γ-unsaturated carboxylic acids or esters are quite limited and the synthesis of β,γ-unsaturated carboxylic acids and their derivatives is still not so easy task.

The procedures so far reported for the synthesis of β,γ-unsaturated carboxylic acids and their derivatives are as follows. One-carbon elongation of α,β-unsaturated esters or aldehydes.[4] Deconjugative protonation[5] or photo deconjugation[6] of α,β-unsaturated esters. Deconjugative alkylation of α,β-unsaturated esters.[7] Reductive deconjugation of α-bromo α,β-unsaturated esters.[8] Modified Knoevenagel condensation,[9] and others.[10]

From the synthetic point of view, carbon–carbon coupling between a vinyl carbon and an α-carbon of carboxylic acids or their derivatives is the straightforward procedure for the synthesis of β,γ-unsaturated carboxylic acids and their derivatives; however, only three reports have appeared about the procedure. The first one is a nickel-catalyzed coupling of vinyl halides with lithium ester enolates.[11] The second one is a carbon–carbon bond formation of iodofluoroacetates with alkenyl iodides in the presence of copper.[12] The third one is a radical alkenylation of α-halo esters or amides with alkenylindiums.[13]

We have also been interested in the synthesis of β,γ-unsaturated carboxylic acids and their derivatives by our own method using the rearrangement of lithium carbenoids[4c] or magnesium carbenoids.[14] In continuation of our investigation with regard to the development of new synthetic methods for β,γ-unsaturated carboxylic acids and their derivatives, we recently found a new procedure for the synthesis of β,γ-unsaturated carboxylic acid esters and allenic esters as follows (Scheme 1). Thus, 1-chlorovinyl *p*-tolyl sulfoxides **2** were synthesized from ketones **1** and chloromethyl *p*-tolyl sulfoxide.[15] Vinyl sulfoxides **2** were treated with isopropylmagnesium chloride at −78 °C to afford magnesium alkylidene carbenoids **3**.[16] Magnesium alkylidene carbenoids **3** were treated with lithium ester enolates, which were generated from esters with LDA at −78 °C, to give β,γ-unsaturated carboxylic acid esters **4** in moderate to good yields. When this reaction was conducted with lithium enolates of α-chlorocarboxylic esters, allenic esters **5** were obtained. It is noteworthy that in both reactions, a carbon–carbon bond between an alkenyl carbon and the α-carbon of the esters was constructed. Details and mechanism of these reactions are reported hereinafter.

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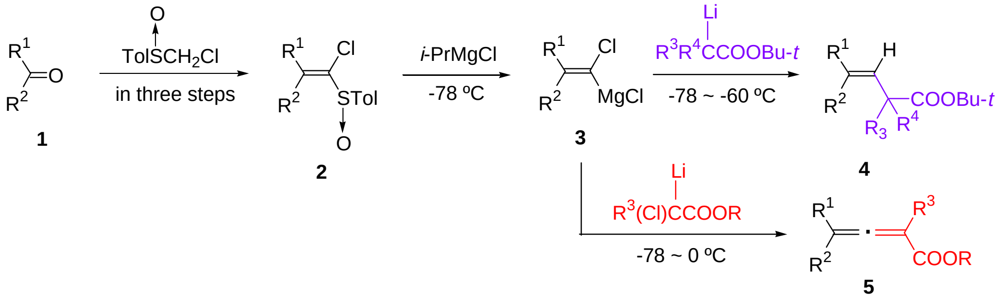


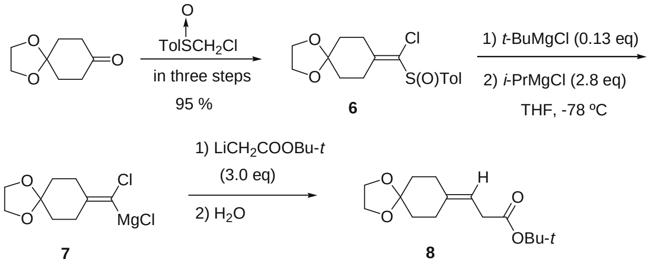
Scheme 1.

2. Results and discussion

At first, to a solution of 1-chlorovinyl *p*-tolyl sulfoxide **6**[17] in THF at −78 °C was added *t*-BuMgCl (0.13 equiv) to remove a trace of moisture in the reaction mixture. To this solution was added *i*-PrMgCl (2.8 equiv) to afford magnesium alkylidene carbenoid **7**. A solution of lithium enolate of *tert*-butyl acetate (3 equiv), which was generated from *tert*-butyl acetate with LDA at −78 °C, was added to the solution of magnesium alkylidene carbenoid **7** through a cannula and the reaction mixture was stirred at −78 °C for 30 min (Table 1, entry 1).

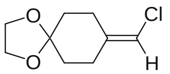
Fortunately, the desired reaction took place to afford the desired β,γ-unsaturated ester **8** in 42% yield. From this reaction, however, about 20% of alkenyl chloride **9**, which is the protonated product of magnesium alkylidene carbenoid **7**, was obtained as a by-product. This result implied that the desired reaction had not been completed. In order to improve the yield of product **8**, the optimal conditions were investigated and the results are summarized in Table 1.

Table 1
Generation of magnesium alkylidene carbenoid **7** from 1-chlorovinyl *p*-tolyl sulfoxide **6** and reaction with lithium enolate of *tert*-butyl acetate to give β,γ-unsaturated ester **8**



Entry	Solvent	Conditions	Yield (%)
1	THF	−78 °C, 30 min	42[a]
2	THF	−78 ~ −60 °C, 30 min	57
3	THF	−78 ~ −60 °C, 30 min, then −60 °C, 2 h	69
4	THF	−78 ~ −40 °C, 1 h	65
5	Toluene	−78 ~ −60 °C, 30 min	58
6	Toluene	−78 ~ −60 °C, 30 min, then −60 °C, 2 h	63

[a] About 20% of vinyl chloride **9** was obtained.



9

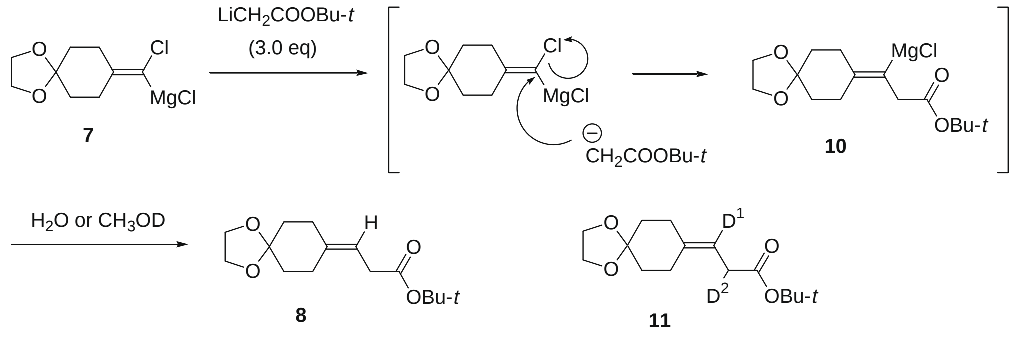
When the reaction mixture was slowly allowed to warm to −60 °C, the yield remarkably improved to 57% (entry 2). The best yield, 69%, was obtained when the temperature of the reaction was −60 °C and the temperature was maintained for 2 h (entry 3).[18] Higher temperature was not effective (entry 4). Toluene was also found to be a useful solvent in this reaction (entries 5 and 6). We used the conditions given in entry 3 throughout this study.

The presumed mechanism of this reaction is shown in Scheme 2. Thus, the lithium ester enolate attacks the carbenoid carbon to give alkenylmagnesium intermediate **10** with inversion of the configuration of the carbenoid carbon.[16] Quenching this intermediate **10** with water gave β,γ-unsaturated ester **8**. The evidence for the presence of alkenylmagnesium intermediate **10** was obtained when the reaction was quenched with deuterated methanol (Table in Scheme 2). Thus, as shown in entry 1, when this reaction was quenched after 10 min at −78 °C with CH_3OD, β,γ-unsaturated ester **11** deuterated at the olefinic carbon (D content 61%) was obtained. A trace of deuterium was incorporated at the α-carbon (4%). The anion was found to be rearranged slowly from the olefinic carbon to the α-carbon and after 2 h the α-carbon was deuterated about 20% (entry 3). Finally, after the reaction mixture was stirred at −60 °C for 2 h, the anion was dispersed between the olefinic carbon and the α-carbon (entry 5).

In order to know the scope and limitation of this reaction, the reaction was carried out with 1-chlorovinyl *p*-tolyl sulfoxides **12a–c**, prepared from cycloheptanone, cyclododecanone, and cyclopentadecanone. The results are summarized in Scheme 3. As shown in Scheme 3, the reaction of magnesium alkylidene carbenoids generated from **12a–c** with lithium enolates generated from *tert*-butyl acetate gave the desired β,γ-unsaturated esters **13a–c** in up to 63% yield and the universality of this reaction was verified.

Next, the reactions of magnesium alkylidene carbenoid **7**, generated from **6**, with the lithium ester enolates other than lithium enolate of *tert*-butyl acetate were investigated and the results are summarized in Table 2. Entries 1 and 2 show the reaction with methyl acetate and phenyl acetate. The results were quite worse compared with those of *tert*-butyl acetate. The results with *tert*-butyl propionate, *tert*-butyl phenylacetate, and *tert*-butyl 4-methylphenylacetate are summarized in entries 3–5. These reactions gave the desired β,γ-unsaturated esters bearing a substituent at the α-position **14** in up to 57% yield. It is worthy to note that in these reactions no double bond migration (giving α,β-unsaturated esters) was observed. Lithium ester enolates generated from α,α-disubstituted acetate also gave the desired product; however, the yields were found to be low (entries 6 and 7). In these cases, methyl esters gave better yields compared with the corresponding *tert*-butyl esters.

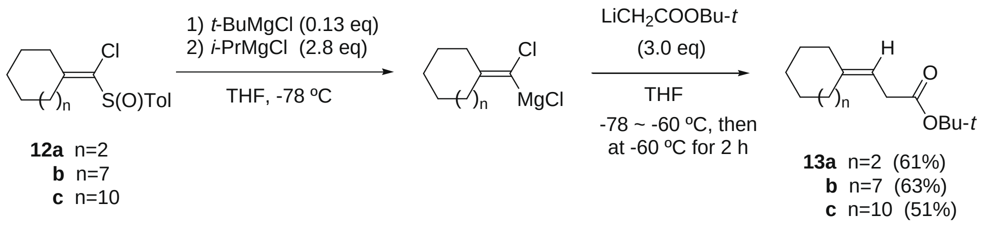
In continuation of the aforementioned reaction, we used lithium ester enolate of *tert*-butyl chloroacetate as the lithium enolate,



Entry	Conditions		**11**, D-content / %	
	Temp. / °C	Time / min.	D^1	D^2
1	-78	10	61	4
2	-78	30	54	8
3	-78	120	49	20
4	-78 ~ -60	30	72	18
5[a)]	-78 ~ -60	120	48	43

a) The reaction was conducted at -78 to -60 °C for 30 min then at -60 °C for 2 h before quenching with CH_3OD.

Scheme 2. The reaction of magnesium alkylidene carbenoid **7** with lithium enolate of *tert*-butyl acetate followed by deuterio methanol.



Scheme 3.

and quite interesting results were obtained (Scheme 4). Thus, treatment of magnesium alkylidene carbenoid **7** with lithium enolate of *tert*-butyl chloroacetate under the above-mentioned conditions gave allenic ester **16**. After the investigation of optimized conditions, LHMDS was used as the base and the reaction mixture was allowed to warm from −78 to 0 °C, the yield was improved to 54%.[19] This reaction is presumed to proceed as follows. The lithium ester enolate attacks the carbenoid carbon of **7** to give alkenylmagnesium intermediate **15** with inversion of the configuration of the carbenoid carbon.[16] β-Elimination of both the magnesium chloride and the chlorine atom of intermediate **15** took place simultaneously to afford allenic ester **16**.

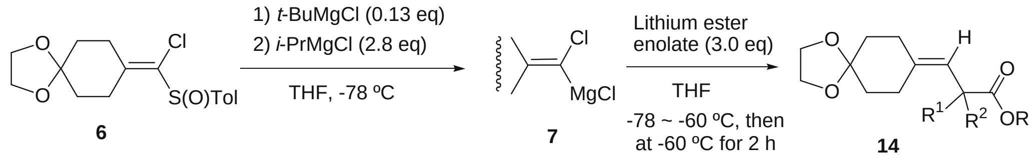
Allenes are very interesting and important compounds in organic and synthetic organic chemistry.[20] We investigated the generality of the synthesis of allenic esters using 1-chlorovinyl *p*-tolyl sulfoxides **12a–d** and the results are summarized in Scheme 5. As shown in the scheme, the reaction starting from **12a–d** gave the desired allenic esters **17a–d**; however, unfortunately, the yields were not satisfactory (22–38%).

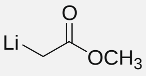
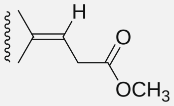
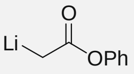
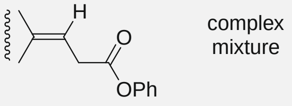
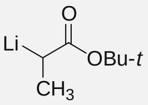
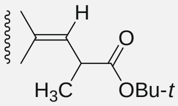
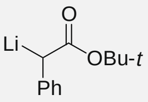
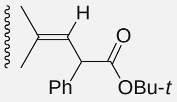
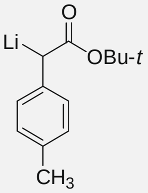
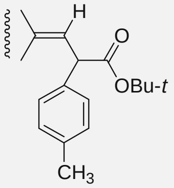
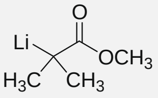
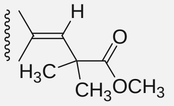
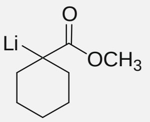
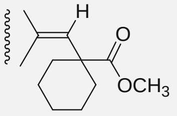
Finally, we studied the synthesis of fully substituted allenic esters based on our method described above and the results are summarized in Table 3. At first, 1-chlorovinyl *p*-tolyl sulfoxide **7** was treated with lithium enolate of *tert*-butyl α-chloropropionate (entry 1). The reaction gave the desired fully substituted allenic ester **18** ($R^3 = CH_3$); however, the yield was miserable. Fortunately, the yield was improved to 47% by using lithium enolate of methyl 2-chloropropionate (entry 2). Entries 3–6 show the results for the reaction of **7** with various esters of 2-chlorophenylacetic acid. The *tert*-butyl, phenyl, and ethyl esters gave up to 40% yield of the desired fully substituted allenic esters bearing a phenyl group. Methyl ester, again, gave much better yield (entry 6).

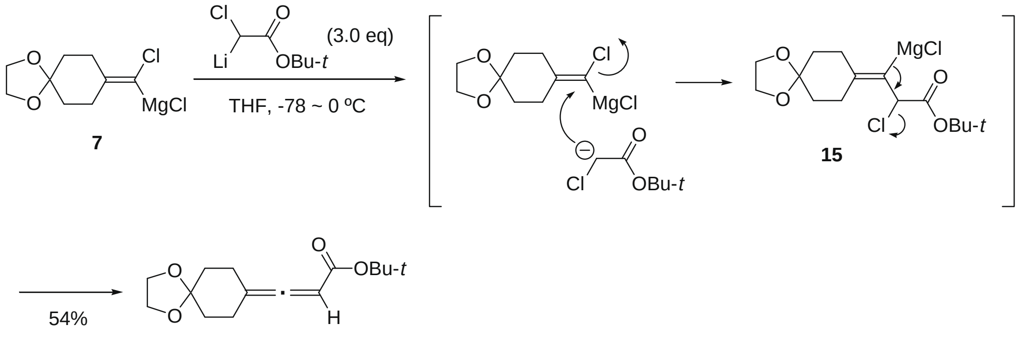
In conclusion, we found that the reaction of magnesium alkylidene carbenoids with lithium ester enolates gave β,γ-unsaturated esters and allenic esters with direct construction of a carbon–carbon bond between α- and β-positions. Although the yields are not always good at the present, the method mentioned above is an unprecedented way and contributes to the synthesis of various β,γ-unsaturated esters and allenic esters, including fully substituted ones.

Table 2

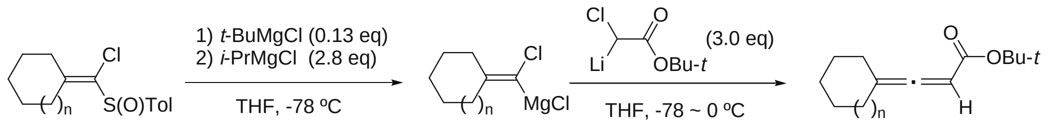
Reaction of magnesium alkylidene carbenoid **7** with various lithium ester enolates to give α,β-unsaturated esters **14**



Entry	Lithium ester enolate	14	
			Yield (%)
1			36
2			Complex mixture
3			51
4			54
5			57
6			35
7			27



Scheme 4.

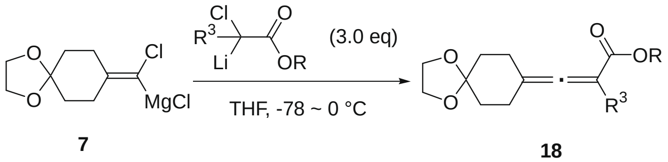


12a n=2
b n=7
c n=10
d n=1

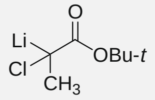
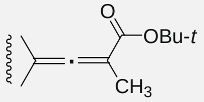
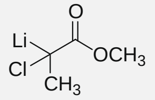
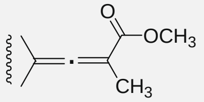
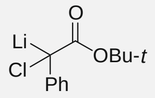
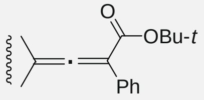
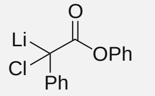
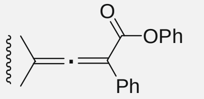
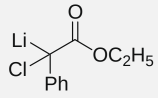
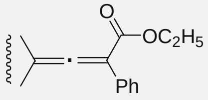
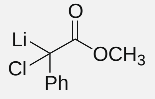
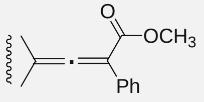
17a n=2 (37%)
b n=7 (22%)
c n=10 (38%)
d n=1 (36%)

Scheme 5.

Table 3
A synthesis of allenic esters **18** by the reaction of magnesium alkylidene carbenoid **7** with lithium ester enolates of α-chlorocarboxylic acid esters



7 **18**

Entry	Lithium ester enolate	**18**	
			Yield (%)
1			17
2			47
3			39
4			31
5			40
6			51

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18. *3-(1,4-Dioxaspiro[4.5]dec-8-ylidene)propionic acid tert-butyl ester* (**8**): *t*-BuMgCl (0.025 mmol) was added dropwise to a solution of vinyl sulfoxide **6** (65 mg; 0.2 mmol) in 3 mL of dry THF in a flame-dried flask at −78 °C under argon atmosphere to remove a trace of moisture in the reaction medium. After 10 min, *i*-PrMgCl (0.56 mmol) was added dropwise to the reaction mixture to give magnesium alkylidene carbenoid **7**. In another flame-dried flask at −78 °C under argon atmosphere, THF solution of LDA (0.6 mmol) was prepared and *tert*-butyl acetate (0.6 mmol) was added slowly to this solution. This solution of the lithium ester enolate was transferred into the solution of the carbenoid **7** through a cannula. The reaction mixture was slowly allowed to warm up to −60 °C, and then kept for 2 h at the same temperature. The reaction was quenched by adding satd aq NH_4Cl. The whole mixture was extracted three times with $CHCl_3$ and the organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (hexane/AcOEt) to give **8** (37 mg; 69%) as colorless oil. IR (neat); 2949, 1733 (CO), 1368, 1152, 1095, 1035, 905 cm^{-1}; ^1H NMR δ 1.44 (9H, s), 1.66–1.71 (4H, m), 2.27 (4H, t, *J* = 6.4 Hz), 2.96 (2H, d, *J* = 7.2 Hz), 3.97 (4H, s), 5.32 (1H, t, *J* = 7.2 Hz). MS *m/z* (%) 268 (M^+, 13), 212 (81), 167 (19), 86 (57), 57 (100), Calcd for $C_{15}H_{24}O_4$: M, 268.1673. Found; *m/z* 268.1677.

19. *3-(1,4-Dioxaspiro[4,5]dec-8-ylidene)acrylic acid tert-butyl ester* (**16**): To a solution of **6** (65.4 mg, 0.2 mmol) in 2 mL of dry THF in a flame-dried flask at −78 °C under argon atmosphere was added *t*-BuMgCl (0.025 mmol) dropwise with stirring. After 10 min, *i*-PrMgCl (0.56 mmol) was added dropwise to the reaction mixture at −78 °C to give magnesium alkylidene carbenoid **7**. In another flame-dried flask, *tert*-butyl chloroacetate (0.6 mmol) was added dropwise to a solution of LHMDS (0.6 mmol) in 3 mL of dry THF at −78 °C under argon atmosphere to give light yellow solution of the lithium enolate. This solution was added to the solution of carbenoid **7** through a cannula. The reaction mixture was gradually allowed to warm up to 0 °C for 2 h. The reaction was quenched with satd aq NH$_4$Cl and the whole was extracted with CHCl$_3$ and the organic layer was dried over MgSO$_4$. After removal of the solvent, the product was purified by silica gel column chromatography to give **16** (28.8 mg, 54%) as colorless crystals; mp 99–99.5 °C (AcOEt–hexane). IR (KBr) 3004, 2972, 2932, 2874, 1963 (allene), 1714, 1288, 1230, 1143, 1068, 1027 cm^{-1}; ^{1}H NMR δ 1.47 (9H, s), 1.75–1.83 (4H, m), 2.33–2.46 (4H, m), 3.97 (4H, s), 5.38–5.40 (1H, m). Calcd for C$_{15}$H$_{22}$O$_4$: C, 67.65; H, 8.33. Found: C, 67.57; H, 8.25.

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