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A short synthesis of α-allenic alcohols from α,β-unsaturated carbonyl compounds with dichloromethyl *p*-tolyl sulfoxide

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ABSTRACT

The reaction of the α-sulfinyl carbanion of dichloromethyl *p*-tolyl sulfoxide with α,β-unsaturated carbonyl compounds gave 1-chlorocyclopropyl *p*-tolyl sulfoxides having a carbonyl group in good to high yields. The carbonyl groups in the products were reduced or treated with alkylmetals to give alcohols. Finally, the alcohols were treated with Grignard reagent to give α-allenic alcohols via the rearrangement of the cyclopropylmagnesium carbenoid intermediates, which were generated by the sulfoxide-magnesium exchange reaction, in good to high yields. This procedure provides a new method for a short synthesis of various α-allenic alcohols in two or three steps from relatively easily available α,β-unsaturated carbonyl compounds.

1. Introduction

Allenes, characterized by a 1,2-diene structure, are quite interesting and important compounds in organic and synthetic organic chemistry, and a large number of studies have been reported on their chemistry, synthesis, and synthetic uses.[1] Allenes having a hydroxyl group on the carbon adjacent to the allene system are called α-allenic alcohols. α-Allenic alcohol moiety is frequently found in allenic natural products and pharmaceuticals, such as grasshopper ketone, fucoxanthin, and allenic nucleoside analogues.[2] Furthermore, α-allenic alcohols are used as versatile intermediates in the synthesis of a variety of 2,5-dihydrofurans,[3] 1,4-dienes, and cross-conjugated trienes.[4]

General method for the synthesis of α-allenic alcohols is classified into two categories as follows. One is the reaction of carbonyl compounds with propargylic titanium,[5] propargylic bromides,[6] propargylic acetate,[7] or propargylic phosphates.[8] The other is the reactions of propargylic epoxides with several reagents, such as organo copper,[9] Grignard reagents,[10] dialkylzinc,[11] arylboronic acids,[12] summarium diiodide with ketones,[13] and palladium-catalyzed carbonylation.[14] Recently, some enantioselective syntheses of α-allenic alcohols were reported.[15]

We are also interested in the synthesis of allenes by using our original chemistry of sulfoxide-metal exchange reaction and some new synthetic methods were reported.[16] In continuation of our studies for the development of new synthesis of allenes, here, we describe a short synthesis of various α-allenic alcohols from α,β-unsaturated carbonyl compounds with dichloromethyl *p*-tolyl sulfoxide in up to three steps (Scheme 1). Thus, conjugate addition of the α-carbanion of dichloromethyl *p*-tolyl sulfoxide with α,β-unsaturated carbonyl compounds **1** afforded 1-chlorocyclopropyl *p*-tolyl sulfoxides having a carbonyl group **2** in high yields.[17] The carbonyl group was reduced or reacted with alkylmetals to give alcohols, which were treated with Grignard reagent to give cyclopropylmagnesium carbenoids. Doering–LaFlamme-type rearrangement[18] of the generated cyclopropylmagnesium carbenoids afforded α-allenic alcohols **3** in good to high yields.

2. Results and discussion

Representative example of the presented procedure is described as follows (Scheme 2). α,β-Unsaturated ester **4** was treated with the sodium α-carbanion of dichloromethyl *p*-tolyl sulfoxide[17] to give 1-chlorocyclopropyl *p*-tolyl sulfoxide **5** having ethoxycarbonyl group at the 2-position in 84% yield. A solution of cyclopropane **5** in toluene was added to a solution of excess *i*-PrMgCl in toluene at 0 °C and after 10 min, the reaction was quenched with satd aq NH_4Cl. At first, we expected that Doering–LaFlamme-type rearrangement will occur and allene having an ethoxycarbonyl group will be the product. Instead of the expected allene, we obtained desulfinylated product **7** in good yield as the product. Obviously, the intermediate of this reaction was cyclopropylmagnesium carbenoid **6**; however, the expected Doering–LaFlamme-type rearrangement did not take place at all.

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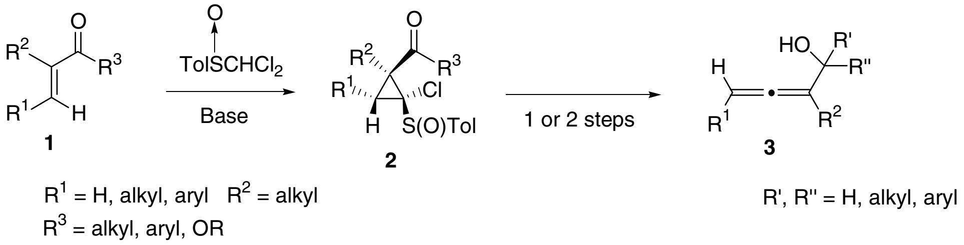
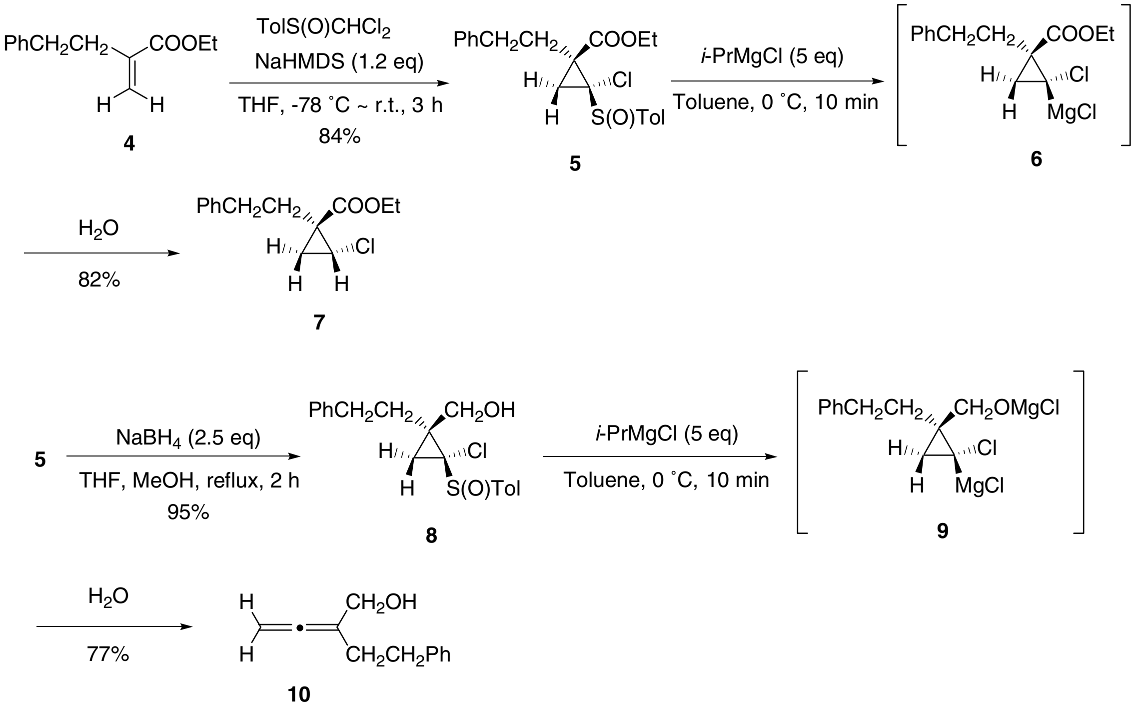


Scheme 1.



Scheme 2.

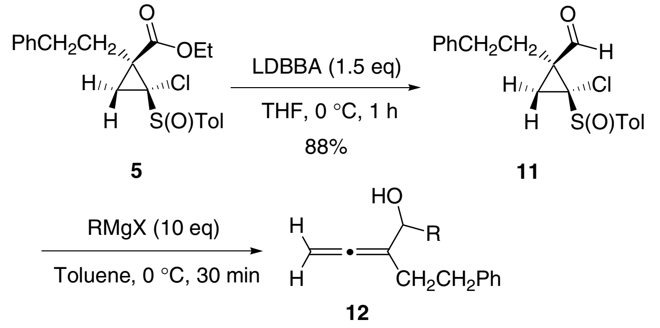
Next, the ester moiety was reduced to a hydroxylmethyl group by treatment with NaBH$_4$[19] to give alcohol **8** in a quantitative yield. Alcohol **8** was treated with *i*-PrMgCl under the same conditions as described above. Quite interestingly, the treatment gave the desired primary α-allenic alcohol **10** in 77% yield.[20] The intermediate of this reaction was obviously cyclopropylmagnesium carbenoid having a magnesium alkoxide moiety **9**. From this magnesium carbenoid the expected Doering–LaFlamme-type rearrangement took place quickly at 0 °C. From these two results described above, though the real reason is obscure at present, it is anticipated that the Doering–LaFlamme-type rearrangement is prevented by the presence of an ethoxycarbonyl group.

As we recognized that this is a quite interesting and novel method for a short synthesis of α-allenic alcohols from α,β-unsaturated carbonyl compounds, scope and limitation of this procedure were investigated. At first, ester **5** was reduced directly to aldehyde **11** with lithium diisobutyl-*tert*-butoxyaluminum hydride (LDBBA)[21] in good yield (Table 1). Aldehyde **11** was treated with excess Grignard reagents (MeMgBr, EtMgBr and PhMgBr) in toluene at 0 °C for 30 min. We obtained the desired secondary α-allenic alcohols **12** in variable yields directly from aldehyde **11**. Reducing the amount of the Grignard reagent resulted in the lowering of the yields of the product.

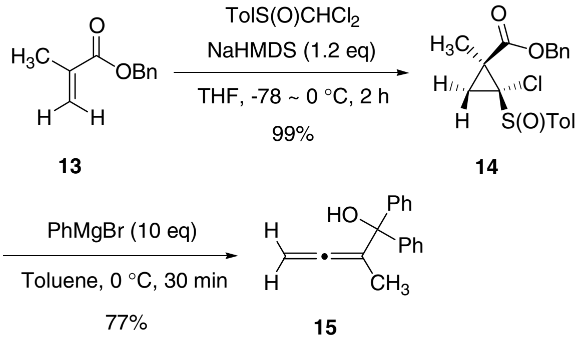
Finally, 1-chlorocyclopropyl *p*-tolyl sulfoxide **14**, having a benzyloxycarbonyl group, was synthesized from α,β-unsaturated ester **13** in a quantitative yield. As the reaction of an ester with excess Grignard reagent is expected to give a tertiary alcohol, **14** was treated with ten equivalents of PhMgBr in toluene at 0 °C for 30 min.

Table 1

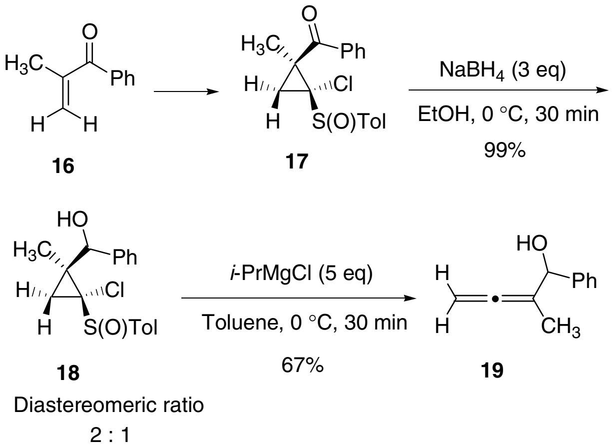
Synthesis of α-allenic alcohols **12** from 1-chlorocyclopropyl *p*-tolyl sulfoxide **5** via aldehyde **11** with Grignard reagents



Entry	RMgX	**12**	
			Yield (%)
1	CH_3MgBr	**12a**	52
2	CH_3CH_2MgBr	**12b**	70
3	PhMgBr	**12c**	35



Scheme 3.



Scheme 4.

Fortunately, both formation of tertiary alcohol and sulfoxide-magnesium exchange reaction took place simultaneously to give the desired tertiary α-allenic alcohol **15** in good yield (Scheme 3).

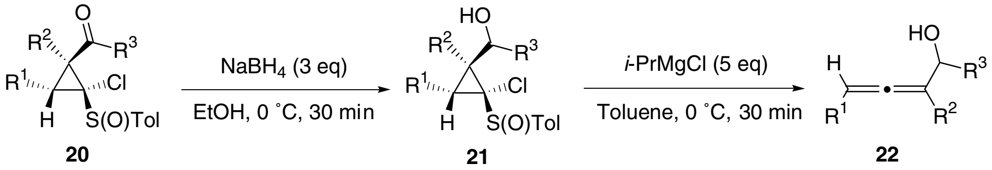
The procedure for the synthesis of α-allenic alcohols presented herein was found to be quite effective even when α,β-unsaturated ketones were used as the starting materials. For example, 1-chlorocyclopropyl *p*-tolyl sulfoxide having a benzoyl group **17** was synthesized from α,β-unsaturated ketone **16** in high yield.[17] The benzoyl group was reduced with $NaBH_4$ to give alcohol **18** in a quantitative yield. Finally, **18** was treated with excess *i*-PrMgCl in toluene at 0 °C to give the desired secondary α-allenic alcohol **19** in 67% yield (Scheme 4).

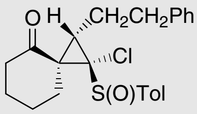
Other examples of the synthesis of secondary α-allenic alcohols, starting from the corresponding 1-chlorocyclopropyl *p*-tolyl sulfoxides **20** via alcohols **21**, are summarized in Table 2. 1,1-Disubstituted α-allenic alcohols (**22a** and **22b**) and 1,1,3-trisubstituted α-allenic alcohols (**22c**, **22d**, and **22e**) were synthesized from corresponding **20** in good to high overall yields in two steps. Cyclic α-allenic alcohol **22f** was also synthesized from **20f**, which was synthesized from 2-(3-phenylpropylidene)cyclohexanone in 90% yield,[17] in good overall yield (entry 6).

Finally, synthesis of tertiary α-allenic alcohols was investigated by combination of ketone **20b** with some carbon nucleophiles and the results are summarized in Table 3. Thus, lithium carbanion of phenylacetylene was treated with **20b** in THF at −78 °C for 1 h. The lithium acetylide was found to be reactive only with the carbonyl carbon at −78 °C and the sulfinyl group was found to be intact with the lithium acetylide to afford the adduct, tertiary alcohol **23a**, in 75% yield. Finally, alcohol **23a** was treated with excess of *i*-PrMgCl to give the desired tertiary α-allenic alcohol **24a** in 81% yield. Reducing the amount of the Grignard reagent resulted in incomplete reaction. The procedure with 2-furyllithium and 2-thienyllithium resulted in the formation of the desired tertiary α-allenic alcohols **24b** and **24c** in good overall yields (entries 2 and 3).

Table 2

Synthesis of various α-allenic alcohols **22** starting from 1-chlorocyclopropyl *p*-tolyl sulfoxides **20**, synthesized from α, β-unsaturated ketones, through alcohols **21**

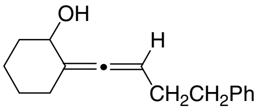


Entry	20				21			22	
		R^1	R^2	R^3	Yield (%)		Diastereomeric ratio	Yield (%)	
1	**20a**	H	$CH_2CH_2CH_3$	Ph	**21a**[a]	93	1:1	**22a**	79
2	**20b**	H	CH_3	$CH_2CH_2CH_2Ph$	**21b**[a]	80	4:1	**22b**	88
3	**20c**	CH_3	CH_3	Ph	**21c**[a]	88	5:1	**22c**[b]	68
4	**20d**	Ph	CH_3	CH_2CH_3	**21d**[a]	99	10:1	**22d**[b]	72
5	**20e**	CH_2CH_2Ph	CH_3	CH_2CH_3	**21e**	99	Single isomer	**22e**[b]	79
6	**20f**				**21f**	96	Single isomer	**22f**[b,c]	76

[a] A mixture of two diastereomers was used in the next reaction.

[b] A single isomer was obtained.

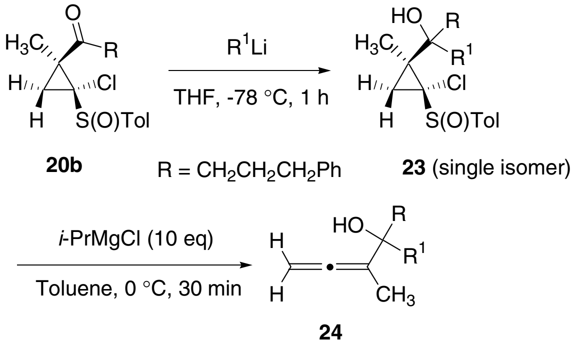
[c] The structure of **22f** is shown in the below.



22f

Table 3

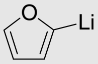
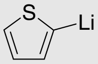
Synthesis of tertiay α-allenic alcohols **24** from 1-chlorocyclopropyl *p*-tolyl sulfoxide **20b** through the adduct with alkynyllithium, furyllithium, and thienyllithium (**23**)



20b

23 (single isomer)

24

Entry	R^1Li		**23** Yield (%)		**24** Yield (%)
1	Ph—≡—Li (2 eq)	**23a**	75	**24a**	81
2	 (3 eq)	**23b**	67[a]	**24b**	73
3	 (3 eq)	**23c**	82	**24c**	65[b]

[a] Starting material **20b** was recovered in 12%.

[b] The reaction mixture was stirred at 0 °C for overnight. Starting material **23c** was recovered in 7%.

In conclusion, a procedure for the short synthesis of α-allenic alcohols from α,β-unsaturated carbonyl compounds with dichloromethyl *p*-tolyl sulfoxide in up to three steps via the rearrangement of cyclopropylmagnesium carbenoids as the key reaction was established. Various kinds of primary, secondary, and tertiary α-allenic alcohols can be synthesized from α,β-unsaturated carbonyl compounds with reducing agents and carbon nucleophiles. The results presented herein will contribute greatly to the synthesis of α-allenic alcohols.

Acknowledgment

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20. The experimental procedure for the synthesis of α-allenic alcohol **10** is as follows. To a solution of 2-(2-phenylethyl)acrylic acid ethyl ester **4** (245 mg; 1.2 mmol) and dichloromethyl *p*-tolyl sulfoxide (223 mg; 1.0 mmol) in 10 mL of dry THF at −78 °C was added a solution of sodium hexamethyldisilazide (1.9 M solution in THF, 0.63 mL; 1.2 mmol) dropwise with stirring. Temperature of the reaction mixture was slowly allowed to rise to room temperature for 3 h. The reaction was quenched by satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to give **5** (328 mg; 84%) as a colorless oil. IR (neat) 2998, 1727(CO), 1495, 1454, 1266, 1136, 1091, 1062, 811 cm^{-1}, ^1H NMR δ 1.30 (1H, d, J = 7.4 Hz), 1.36 (3H, s), 1.99 (1H, dt, J = 14.0, 8.5 Hz), 2.32–2.42 (1H, m), 2.41 (3H, s), 2.58 (1H, d, J = 7.5 Hz), 2.73 (2H, d, J = 8.0 Hz), 4.28 (2H, q, J = 7.1 Hz), 7.14–7.21 (3H, m), 7.32 (2H, d, J = 8.1 Hz), 7.59 (2H, d, J = 8.1 Hz).
    To a solution of ester **5** (78 mg; 0.2 mmol) in 2 mL of THF was added $NaBH_4$ (19 mg; 0.5 mmol) at room temperature. The suspension was stirred and heated under reflux for 5 min. To the suspension was added MeOH (0.2 mL) dropwise with stirring and the reaction mixture was refluxed for 2 h. The reaction was quenched by adding satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to give **8** (66 mg; 95%) as colorless crystals. IR (KBr) 3325 (OH), 2901, 1499, 1438, 1074, 1030, 812 cm^{-1}; ^1H NMR δ 1.21 (1H, d, J = 7.7 Hz), 1.48 (3H, s), 1.95 (1H, d, J = 7.2 Hz), 2.42 (3H, s), 3.13 (1H, br s), 3.82 (1H, dd, J = 12.0, 5.8 Hz), 4.06 (1H, dd, J = 12.0, 3.8 Hz), 7.32 (2H, q, J = 7.7 Hz), 7.68 (2H, d, J = 8.8 Hz).
    To a solution of **8** (34.9 mg; 0.1 mmol) in 2 mL of dry toluene at 0 °C was added *i*-PrMgCl (2.0 M solution in Et_2O, 0.25 mL; 0.5 mmol) dropwise with stirring. After 10 min, the reaction was quenched by satd aq NH_4Cl and the whole was extracted with $CHCl_3$. The product was purified by silica gel column chromatography to give 2-(2-phenylethyl)buta-2,3-dien-1-ol **10** (13.4 mg; 77%) as a colorless oil. IR (neat) 3364 (OH), 2923, 1957 (allene), 1496, 1454, 1015, 850, 741, 698 cm^{-1}; ^1H NMR δ 1.50 (1H, s), 2.27–2.35 (2H, m), 2.75–2.80 (2H, m), 4.06 (2H, s), 4.89 (2H, quintet, J = 3.2 Hz), 7.15–7.21 (3H, m), 7.25–7.31 (2H, m). MS (FAB) *m/z* (%) 197 ($[M+Na]^+$, 35), 157 (51), 129 (38), 115 (100), 91 (89), 23 (82). Calcd for $C_{12}H_{14}ONa$: *M*, 197.0942. Found: *m/z* 197.0946.
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