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The first example for the asymmetric synthesis of allenes by the Doering–LaFlamme allene synthesis with enantiopure cyclopropylmagnesium carbenoids

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ABSTRACT

The reaction of lithium α-sulfinyl carbanion of enantiopure dichloromethyl *p*-tolyl sulfoxide with α,β-unsaturated carbonyl compounds gave optically active 1-chlorocyclopropyl *p*-tolyl sulfoxides having a carbonyl group with high asymmetric induction from the sulfur chiral center. Reduction of the carbonyl group followed by treatment with Grignard reagent, the 1-chlorocyclopropyl *p*-tolyl sulfoxides resulted in the formation of enantiopure allenic alcohols via the Doering–LaFlamme-type rearrangement of enantiopure cyclopropylmagnesium carbenoid intermediates. This is the first example for the asymmetric synthesis of allenes by the Doering–LaFlamme allene synthesis.

1. Introduction

Allenes are quite interesting and highly important compounds in organic, synthetic organic, and bioorganic chemistry.[1] Allenyl structure is frequently found in biologically active natural products and pharmaceuticals.[2] Allenes are characterized by a 1,2-diene structure and some allenes have axial chirality. Asymmetric synthesis of optically active allenes has received considerable attention in these days.[3] In the several synthetic methods for allenes, Doering–LaFlamme allene synthesis[4] is characterized by the rearrangement of cyclopropylidenes (cyclopropylcarbenes)[5] usually generated from *gem*-dibromocyclopropanes with alkyllithium or magnesium. Although this name reaction has been known for over 50 years, to the best of our knowledge, the asymmetric synthesis of allenes through the Doering–LaFlamme allene synthesis has never been achieved.

We also have been interested in the synthesis of allenes by using our original chemistry of sulfoxide–metal exchange reaction[6] and some new synthetic methods were reported.[7] In continuation of our studies for the development of new synthetic method of allenes, we describe herein the first example for the asymmetric synthesis of allenes by the Doering–LaFlamme allene synthesis via the selective rearrangement of enantiopure cyclopropylmagnesium carbenoids as a key reaction.

Thus, as shown in Scheme 1, addition reaction of α,β-unsaturated carbonyl compounds **1** with lithium α-sulfinyl carbanion of enantiopure (*R*)-dichloromethyl *p*-tolyl sulfoxide **2** resulted in the formation of optically active 1-chlorocyclopropyl *p*-tolyl sulfoxides **3** with high asymmetric induction from the sulfur chiral center. The carbonyl group of the cyclopropanes **3** was reduced to alcohols **4**, which were treated with *i*-PrMgCl at 0 °C to give cyclopropylmagnesium carbenoid intermediates **5**. Stereoselective Doering–LaFlamme-type rearrangement took place from the magnesium carbenoid intermediates **5** to afford enantiopure allenes **6** in good yields. In this Letter, aforementioned chemistry, determination of the absolute configuration of the products and the stereochemistry of the rearrangement are described.

2. Results and discussion

We previously reported the reaction of α,β-unsaturated carbonyl compounds with α-sulfinyl carbanion of dichloromethyl *p*-tolyl sulfoxide derived from racemic **2** to result in the formation of 1-chlorocyclopropyl *p*-tolyl sulfoxide in good yields with high chiral induction from the sulfur chiral center.[8] We carried out this reaction with enantiopure (*R*)-**2**[9] in order to verify if optically active 1-chlorocyclopropyl *p*-tolyl sulfoxide could be provided by this reaction. The reaction of α,β-unsaturated ketone **7** with (*R*)

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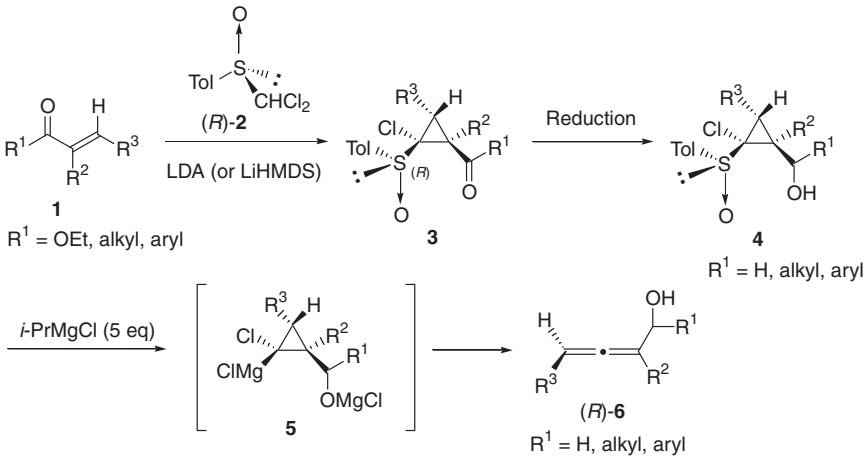
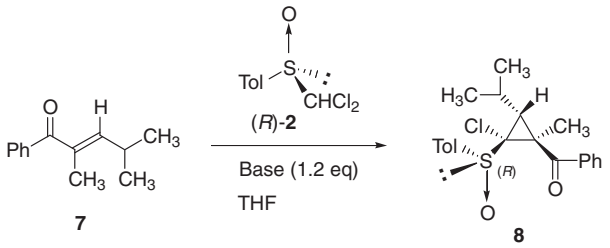


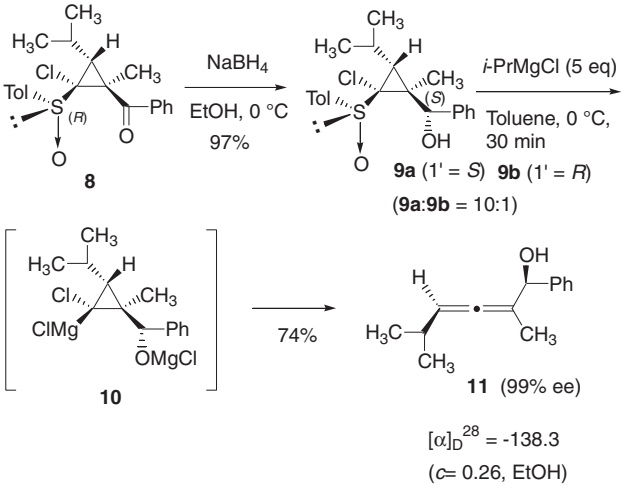
Scheme 1.

Table 1
Reaction of α,β-unsaturated ketone **7** with (*R*)-dichloromethyl *p*-tolyl sulfoxide **2** in the presence of a base at low temperature



Entry	Base	Conditions	8		
			Diastereomeric ratio[a]	Yield (%)	% ee[b]
1	NaHMDS	−78 °C to rt[c]	Single isomer	77	59
2	LDA	−78 °C to rt[d]	8:1	80	94
3	NaHMDS	−85 °C to rt[c]	Single isomer	78	94
4	LDA	−85 °C to rt[d]	Single isomer	93	99
5	LiHMDS	−85 °C to rt[d]	Single isomer	96	99
6	KHMDS	−85 °C to rt[c]	20:1	58	59

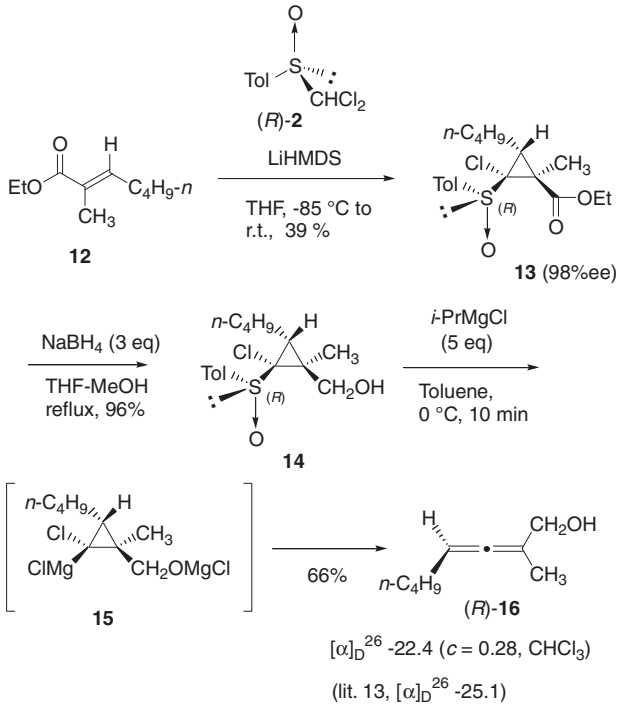
[a] Determined by ^{1}H NMR.
[b] Determined by HPLC with chiral stationary column, CHIRALCEL OD.
[c] A solution of the base was added to a solution of **7** and (*R*)-**2**.
[d] To a solution of the base was added a solution of (*R*)-**2** followed by a solution of **7**.



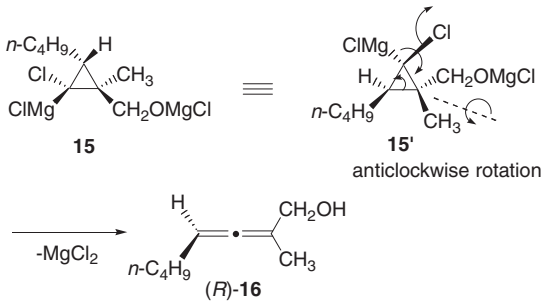
Scheme 2. Synthesis of enantiopure allene **11** from enantiopure 1-chlorocyclopropyl *p*-tolyl sulfoxide **8** by reduction followed by treatment with *i*-PrMgCl via cyclopropylmagnesium carbenoid intermediate **10**.

-2 was selected as the representative example and the results are summarized in Table 1.

To a mixture of enone **7** and (*R*)-**2** in THF at −78 °C was added a solution of sodium hexamethyldisilazide (NaHMDS; 1.2 equiv) and the reaction mixture was slowly allowed to warm to room temperature.[8] This reaction afforded the desired cyclopropane **8** in 77% yield; however, the optical purity was found to be 59% ee (entry 1). This low optical purity was thought to be due to the racemization of the sulfur chiral center of dichloromethyl *p*-tolyl sulfoxide **2** with a base at low temperature.[10] Slight modification of the conditions of this reaction was made next. Thus, to a solution of LDA in THF at −78 °C was added a solution of (*R*)-**2** and enone **7**, in order, and the reaction mixture was slowly allowed to warm to room temperature (entry 2). Significant improvement for the optical purity of the product **8** was observed. The reaction was started from −85 °C with several bases and we found that LDA and LiHMDS were suitable bases to this reaction (entries 3–6). We decided to



Scheme 3. Asymmetric synthesis of optically active allene (*R*)-**16** from α,β-unsaturated ester **12** and (*R*)-**2** by the Doering–LaFlamme allene synthesis.



Scheme 4. A proposed mechanism for the stereochemistry of the rearrangement of cyclopropylmagnesium carbenoid intermediate **15**.

use the conditions mentioned in entries 4 and 5 throughout in this study. The absolute configuration of the product **8** was proved to be as shown in Table 1 based on the results in previous study.[8]

The ketone carbonyl group of **8** was reduced with $NaBH_4$ to give alcohol **9** in quantitative yield as a 10:1 mixture of two diastereomers (Scheme 2). In order to confirm the absolute configuration and the stereochemistry of the newly generated hydroxyl group, the main product **9a** was separated and its X-ray analysis was carried out.[11] Absolute configuration of **9a** was confirmed to be as shown in Scheme 2 and the absolute configuration of the carbon bearing the hydroxyl group was determined to be *S*.

Next, **9a** was treated with excess *i*-PrMgCl in toluene at 0 °C for 30 min to afford the desired allene **11** in 74% yield. Gratifyingly, the optical purity of **11** was proved to be over 99% ee by HPLC with chiral column. It should be noted that at this stage the absolute stereochemistry (axial chirality) of **11** was unclear. Later, the absolute configuration of **11** was proved to be *R* (see below).

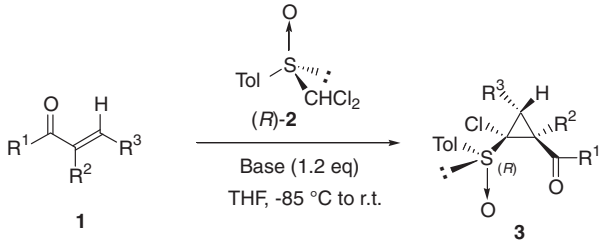
Encouraged by this result, we planned the experiment for determining the absolute configuration of the produced allenes and the stereochemistry of the rearrangement of the cyclopropylmagnesium carbenoid intermediate (Scheme 3). Thus, the reaction of α,β-unsaturated ester **12** with (*R*)-**2** was carried out with LiHMDS to give the desired 1-chlorocyclopropyl *p*-tolyl sulfoxide **13** in high optical purity as a single product;[8] however, the chemical yield of **13** was not satisfactory. The ester group was reduced with $NaBH_4$ in THF–CH_3OH[12] to give alcohol **14** in quantitative yield. After the optical purity was improved to 99% by recrystallization, **14** was treated with *i*-PrMgCl to give optically active allene **16** in 66% yield. Although the optical purity of produced **16** could not be determined, comparing the sign of the specific rotation of **16** with that of the reported (*R*)-2-methylocta-2,3-dien-1-ol[13] the absolute configuration of allene **16** was unambiguously determined to be *R*.

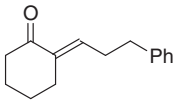
With both the absolute configuration of the starting material, 1-chlorocyclopropyl *p*-tolyl sulfoxide **14**, and the produced allene **16** in hand, we propose the stereochemistry of the ring-opening of the cyclopropylmagnesium carbenoid intermediate **15** as shown in Scheme 4. As the sulfoxide–magnesium exchange reaction was proved to take place with retention of the configuration of the carbon bearing the sulfinyl group,[14] treatment of **14** with *i*-PrMgCl afforded magnesium carbenoid intermediate **15**. Structure of **15** is rewritten as **15′** and the Doering–LaFlamme-type rearrangement (ring-opening of the cyclopropylmagnesium carbenoid) gave (*R*)-**16** as shown in Scheme 4. From the correlation of the structure between **15′** and (*R*)-**16**, the ring-opening is proved to proceed with anticlockwise rotation of the carbon–carbon bond between the carbons bearing the methyl group and the magnesium. This rearrangement is thought to be concerted process; as the optical purity was perfectly retained (see also Table 3).

Next, in order to confirm the generality of the procedure described above, the addition reaction of several α,β-unsaturated carbonyl compounds with (*R*)-**2** was carried out and the results are summarized in Table 2. Lithium diisopropylamide was found to be the suitable base to the reaction of (*R*)-**2** with α,β-unsaturated ketones and both chemical yield and enantiomeric excess of **3** were excellent (entries 1–3). When the reaction was carried out with α,β-unsaturated esters, chemical yield was moderate in one case (entry 5); however, the optical purity of all the products was found to be excellent (entries 4–6).

Finally, the produced 1-chlorocyclopropyl *p*-tolyl sulfoxides **3** derived from α,β-unsaturated carbonyl compounds were

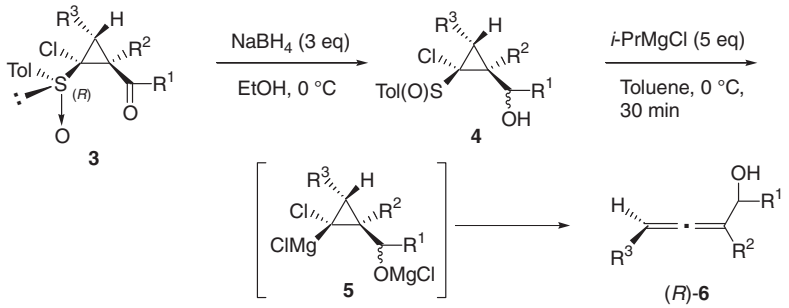
Table 2
Reaction of α,β-unsaturated carbonyl compounds **1** with (*R*)-dichloromethyl *p*-tolyl sulfoxide **2** in the presence of a base at low temperature

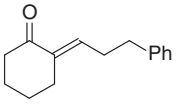


Entry	1			Base	3		
	R^1	R^2	R^3		Diastereomeric ratio[a]	Yield (%)	% ee
1	Ph	CH_3	CH_3CH_2	LDA	10:1	96	96[b]
2	CH_3CH_2	CH_3	$PhCH_3CH_2$	LDA	>99:1	94	98[b]
3				LDA	>99:1	90	—[c]
4	EtO	$PhCH_2CH_2$	*i*-Pr	LDA	>99:1	97	98[b]
5	EtO	$PhCH_2CH_2$	CH_3CH_2	LiHMDS[e]	>99:1	65	99[b]
6	EtO	$PhCH_2CH_2$	$PhCH_2CH_2$	LiHMDS[e]	>99:1	79	95[d]

[a] Determined by ^1H NMR.
[b] Determined by HPLC with chiral stationary column, CHIRALCEL OD.
[c] Could not be obtained by HPLC.
[d] Determined by HPLC with chiral stationary column, CHIRALCEL AD.
[e] 1.4 equiv of base was used.

Table 3
Synthesis of enantiopure allenes (*R*)-**6** from optically active 1-chlorocyclopropyl *p*-tolyl sulfoxides **3** via cyclopropylmagnesium carbenoid intermediates **5**



Entry	3			4		(*R*)-6		
	R^1	R^2	R^3	Yield (%)	Diastereomeric ratio	Yield (%)	% ee	$[\alpha]_D$[a]
1	Ph	CH_3	CH_3CH_2	96	10:1	72	99[b]	−144.5
2	CH_3CH_2	CH_3	$PhCH_2CH_2$	99	>99:1	79	99[c]	−74.3
3				90	>99:1	76	99[c]	−33.3
4	OEt	$PhCH_2CH_2$	$(CH_3)_2CH$	99	—[d]	86[d]	99[b]	+34.0
5	OEt	$PhCH_2CH_2$	$PhCH_2CH_2$	84	—[d]	57[d]	99[b]	+28.5

[a] All specific rotations were measured in ethanol at room temperature.
[b] Determined by HPLC with chiral stationary column, CHIRALCEL IA.
[c] Determined by HPLC with chiral stationary column, CHIRALCEL OD-H.
[d] R^1 = H.

recrystallized to give enantiopure **3**. The enantiopure **3** were reduced with $NaBH_4$ and the resultant alcohols **4** were treated with *i*-PrMgCl to give optically pure (*R*)-allenes **6** in up to 86% yield (Table 3).

In conclusion, asymmetric synthesis of allenes from α,β-unsaturated carbonyl compounds with optically pure dichloromethyl *p*-tolyl sulfoxide **2** in up to three steps via the rearrangement of enantiopure cyclopropylmagnesium carbenoids was established. This is the first example for the asymmetric synthesis of allenes by the Doering–LaFlamme allene synthesis. The results presented herein will contribute greatly to the asymmetric synthesis of allenes and to the chemistry of magnesium carbenoids.

Acknowledgments

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11. *Crystal data for Ent-***9a** *(the X-ray crystallographic analysis was carried out with enantiomer of* **9a** *derived from (S)-***2***)*: $C_{21}H_{25}ClO_2S$, M = 376.92, Orthorhombic, $P2_12_12_1$ (#19), a = 7.4258(4) Å, b = 12.5418(7) Å, c = 21.7666(12) Å, V = 2027.19(19) Å^3, Z = 4, $F(0\,0\,0)$ = 800, D_{calcd} = 1.235 g cm^{-3}, μ (MoKα) = 3.02 cm^{-1}, T = 293 K, Radiation = 0.71073 Å, R_1 = 0.0405 for $I > 2.0\,\sigma(I)$, wR_2 = 0.1059 for all data (4621 reflections), GOF = 1.077 (231 parameters), crystal dimensions 0.20 × 0.20 × 0.10 mm^3, absolute structure parameter 0.02(6). The single crystals were mounted on glass fibers. Diffraction data were measured on a Bruker APEX CCD-detector X-ray diffractometer with monochromated MoKα radiation from a rotating anode source apparatus. The absolute structure of *Ent-***9a** is determined by the comparison with the parameter (1.03(10)) of the inversion symmetry structure because the crystal is constructed from all light atoms. The data reduction, structure solution and refinement, and all the necessary computational data processes were performed using APEX, SAINT, SHELXTL programs. Crystallographic data excluding structures have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 813610 for *Ent-***9a**. A copy of the data can be obtained free of charge from CCDC, 12 Union road, Cambridge CB2 1EZ. UK [DIRECT LINE: +44 1223 762910, fax: +44 (0) 1223-336033 or e-mail: deposit@ccdc.cam.ac.uk.
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