Efficient Synthesis of Cyclopropanecarboxylic Acid Esters Starting from the Conjugate Addition of Lithium Ester Enolates to 1-Chlorovinyl *p*-Tolyl Sulfoxides

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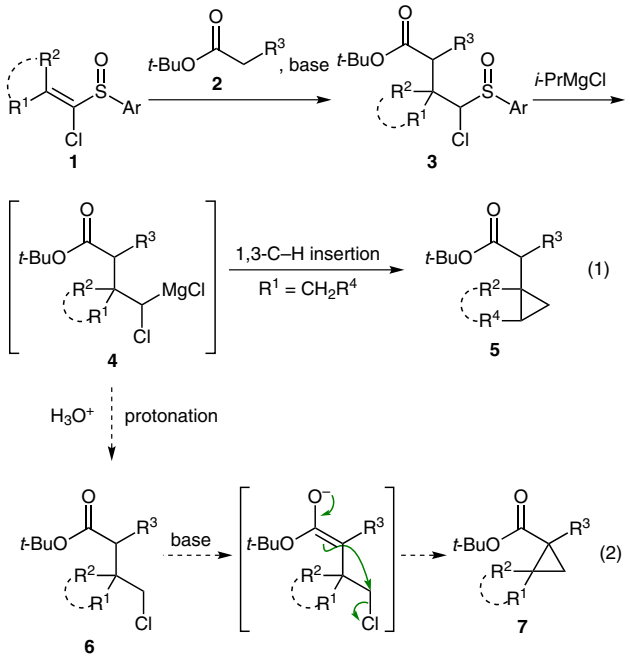
Abstract: An efficient synthesis of *tert*-butyl cyclopropanecarboxylates was achieved in three steps using 1-chlorovinyl *p*-tolyl sulfoxides as key materials. The conjugate addition of lithium ester enolates to the sulfoxides gave *tert*-butyl 4-chloro-4-(*p*-tolylsulfinyl)butanoates in high yield. The *p*-tolylsulfinyl group in the resultant adducts was then removed by the sulfoxide–magnesium exchange reaction with *i*-PrMgCl at –60 °C. Cyclization of the desulfinylated products, *tert*-butyl 4-chlorobutanoates, took place in the presence of NaHMDS in a THF–DMPU mixture to afford *tert*-butyl cyclopropanecarboxylates in good yield. The asymmetric synthesis of both enantiomers of *tert*-butyl cyclopropanecarboxylate was successfully achieved using optically active (*E*)- and (*Z*)-sulfoxides with high enantiomeric excesses.

Key words: conjugate addition, cyclization, chiral auxiliaries, 1-chlorovinyl *p*-tolyl sulfoxides, cyclopropanecarboxylates

Cyclopropane derivatives are versatile compounds in organic synthesis and are often employed in the key steps of natural product synthesis.[1,2] Cyclopropane units are also found in a wide variety of naturally occurring compounds as optically active forms.[3] Much effort has been devoted to developing an efficient method for the construction of cyclopropane rings, and a number of synthetic methods, including the transition-metal-catalyzed decomposition of diazoalkanes in the presence of alkenes, [2+1] cycloadditions of alkenes with metal carbenoids such as zinc carbenoids and lithium carbenoids, and Michael-initiated ring closure, have been established.[4] Recently, we reported various types of cyclopropane syntheses utilizing 1-chlorovinyl *p*-tolyl sulfoxides and magnesium carbenoids as key compounds.[5,6] Among these syntheses, the 1,3-C–H insertion of magnesium carbenoids **4** leading to the formation of 2-cyclopropyl-substituted carboxylic acid esters **5** is representative for our synthetic methods (Scheme 1).[6c,d] Specifically, the conjugate addition of lithium enolates generated from carboxylic acid esters **2** to 1-chlorovinyl *p*-tolyl sulfoxides **1** gave adducts **3** in a highly diastereoselective manner.[7] The adducts **3** were good precursors for the generation of magnesium carbenoids **4**, and magnesium carbenoid induced 1,3-C–H insertion afforded 2-cyclopropyl-substituted esters **5** (Scheme 1, eq. 1). If magnesium carbenoids **4** can be protonated before the 1,3-C–H insertion takes place, 4-chloro-substituted esters **6** can be obtained (Scheme 1, eq. 2). The treatment of esters **6** with a base is expected to result in the formation of cyclopropanecarboxylic acid esters **7**, which are structurally isomeric with esters **5**, through an intramolecular substitution of the resultant enolates. Herein, we report an efficient synthesis of *tert*-butyl cyclopropanecarboxylates **7** via the conjugate addition of lithium enolates generated from *tert*-butyl carboxylates **2** to sulfoxides **1**, the removal of the *p*-tolylsulfinyl group from adducts **3**, and the cyclization of 4-chloro-substituted esters **6**.

Initially, the synthesis of *tert*-butyl 1-methylspiro[2.5]octane-1-carboxylate (**7a**) from 1-chlorovinyl *p*-tolyl sulfoxide (**1a**) and *tert*-butyl propionate (**2a**) was investigated



Scheme 1 Synthesis of 2-cyclopropyl-substituted carboxylic acid esters **5** and cyclopropanecarboxylic acid esters **7** from 1-chlorovinyl *p*-tolyl sulfoxides **1** and *tert*-butyl carboxylates **2**.

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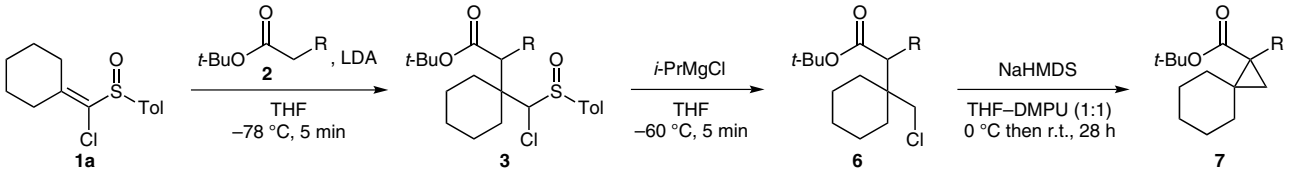
(Table 1, entry 1). As previously reported, the conjugate addition of the lithium enolate, generated from ester **2a** and lithium diisopropylamide (LDA), to sulfoxide **1a** occurred smoothly in THF at –78 °C for five minutes to give adduct **3a** in a quantitative yield.[7,8] The removal of the *p*-tolylsulfinyl group from adduct **3a** was then examined by the sulfoxide–magnesium exchange reaction and the subsequent protonation of the resultant magnesium carbenoid. In our previous study, we found that the 1,3-C–H insertion of magnesium carbenoids **4** proceeded at approximately –30 °C (Scheme 1, eq. 1).[6g,k] Therefore, the sulfoxide–magnesium exchange reaction had to be performed at a lower temperature. After some experimentation, we found that sulfoxide **3a** was completely consumed at –60 °C within five minutes when treated with 3.5 equivalents of isopropylmagnesium chloride. The protonation of the resultant magnesium carbenoid with aqueous NH_4Cl gave a desulfinylated product **6a** in 93% yield.[9] The cyclization of ester **6a** was attempted in the presence of sodium hexamethyldisilazide (NaHMDS) in THF.[10] However, the reaction did not proceed at all. After scrutiny of the reaction conditions, *N*,*N*′-dimethylpropyleneurea (DMPU) proved to be an effective cosolvent.[11] The cyclization of ester **6a** in a THF–DMPU mixture (1:1, v/v) proceeded at room temperature for 28 hours to furnish the desired spirocyclic compound **7a** in a 96% yield.[12]

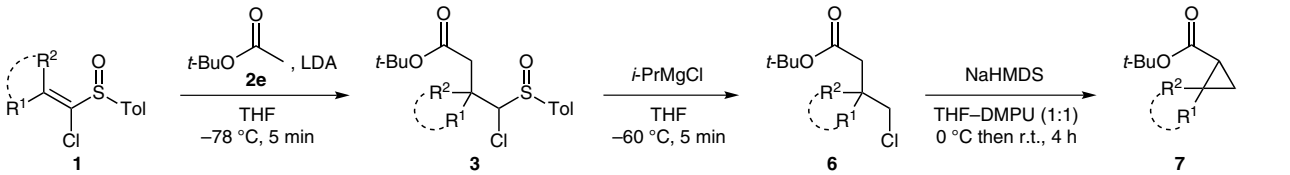
Table 1 Synthesis of *tert*-Butyl Spiro[2.5]octane-1-carboxylates **7** from Sulfoxide **1a** and *tert*-Butyl Carboxylates **2a**–**e**

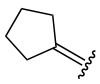
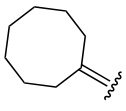
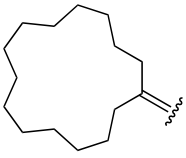


Entry	2	R	Yield of 3 (%)	Yield of 6 (%)	Yield of 7 (%)
1	**2a**	Me	**3a** 99	**6a** 93	**7a** 96
2	**2b**	$BnCH_2$	**3b** 99	**6b** 92	**7b** 94
3[a,b]	**2c**	BnO	**3c** 94	**6c** 88	**7c** 92
4[a,b]	**2d**	Bn_2N	**3d** 96	**6d** 90	**7d** 96
5[c]	**2e**	H	**3e** 97	**6e** 95	**7e** 99

[a] The reaction of sulfoxide **1a** with ester **2** was performed at –45 °C for 1 h.
[b] The cyclization of **6** was carried out under reflux for 28 h.
[c] The cyclization of **6** was performed at r.t. for 4 h.

Table 2 Synthesis of *tert*-Butyl Cyclopropanecarboxylates **7** from Sulfoxides **1b**–**f** and *tert*-Butyl Acetate (**2e**)



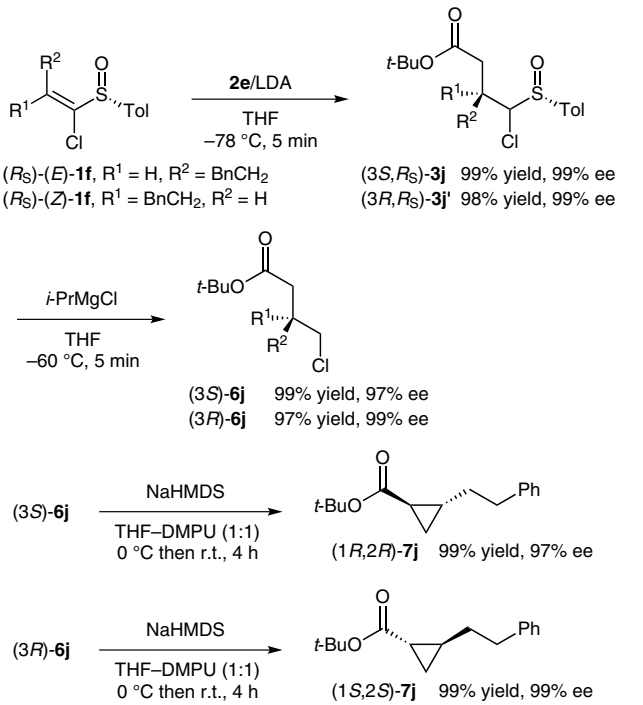
Entry	1	R^1	R^2	Yield of 3 (%)	Yield of 6 (%)	Yield of 7 (%)
1	**1b**			**3f** 98	**6f** 88	**7f** 96
2	**1c**			**3g** 97	**6g** 86	**7g** 95
3	**1d**			**3h** 98	**6h** 90	**7h** 99
4	**1e**	$BnCH_2$	$BnCH_2$	**3i** 96	**6i** 93	**7i** 93

The scope of this three-step procedure for the synthesis of *tert*-butyl cyclopropanecarboxylates was explored with a series of *tert*-butyl carboxylates **2b**–**e** (Table 1, entries 2–5). Ester **2b**, which bears a 2-phenylethyl group at the α position, could be converted into spirocyclic ester **7b** in an 86% yield over three steps (Table 1, entry 2). The cyclization of desulfinylated esters **6c** and **6d**, which were derived from α-heteroatom-substituted esters **2c** and **2d**, was sluggish at room temperature, and the cyclization of esters **6c** and **6d** under reflux afforded α-benzyloxy-substituted ester **7c** and cyclopropane amino acid derivative **7d** in 92 and 96% yields, respectively (Table 1, entries 3 and 4).[13] By contrast, the cyclization of ester **6e**, which was prepared from *tert*-butyl acetate (**2e**), proceeded smoothly at room temperature within four hours to give the desired product **7e** (Table 1, entry 5).

This three-step synthetic method was also applicable to a range of 1-chlorovinyl *p*-tolyl sulfoxides **1b**–**e** (Table 2). *tert*-Butyl spiro[2.n]alkane-1-carboxylates **7f**–**h** (n = 4, 7, 14) were obtained from ester **2e** and sulfoxides **1b**–**d** bearing a 5-, 8-, or 15-membered ring at the β position in good overall yields. Acyclic sulfoxide **1e** could also be used as a substrate (Table 2, entry 4).

The asymmetric syntheses of *tert*-butyl cyclopropanecarboxylates (1*R*,2*R*)-**7j** and (1*S*,2*S*)-**7j** were examined utilizing an optically active *S*-chiral *p*-tolylsulfinyl group as a chiral auxiliary (Scheme 2). The reaction of lithium ester enolate, generated from ester **2e** and LDA, with optically active *S*-chiral sulfoxide (R_S)-(*E*)-**1f**, which has two different substituents at the β position, gave adducts (3*S*,R_S)-**3j** as a single diastereomer, and the reaction with the *Z* isomer (R_S)-(*Z*)-**1f** afforded another diastereomer (3*R*,R_S)-**3j′**.[7b] The *p*-tolylsulfinyl group was removed from adducts (3*S*,R_S)-**3j** and (3*R*,R_S)-**3j′** without significant loss of enantiomeric excess to give both enantiomers of *tert*-butyl 3-(chloromethyl)-5-phenylpentanoate, (3*S*)-**6j** and (3*R*)-**6j**. The cyclization of 4-chloro-substituted esters (3*S*)-**6j** and (3*R*)-**6j** in the presence of NaHMDS provided optically active *tert*-butyl cyclopropanecarboxylates (1*R*,2*R*)-**7j** and (1*S*,2*S*)-**7j** as a 1:20 mixture of the *cis* and *trans* isomers with high enantiomeric excesses.[14]

In summary, we established a highly efficient method for the synthesis of *tert*-butyl cyclopropanecarboxylates utilizing 1-chlorovinyl *p*-tolyl sulfoxides as key materials. The conjugate addition of lithium ester enolates to sulfoxides led to the formation of adducts having chloro and *p*-tolylsulfinyl groups on the same carbon atom. The removal of the *p*-tolylsulfinyl group from the adducts resulted in umpolung of the carbon atom, allowing the second nucleophilic attack of the enolates. Further applications of the present method to the synthesis of optically active cyclopropane amino acid derivatives are currently being investigated and will be reported in due course.



Scheme 2 Asymmetric synthesis of *tert*-butyl cyclopropanecarboxylates (1*R*,2*R*)-**7j** and (1*S*,2*S*)-**7j**.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) **Synthesis of *tert*-Butyl 4-Chloro-4-(*p*-tolylsulfinyl)butanoates 3 – Typical Procedure**
A 1.65 M solution of BuLi in hexane (9.09 mL, 15.0 mmol) was added to a solution of *i*-Pr_2NH (1.52 g, 15.0 mmol) in THF (55 mL) at 0 °C, and the mixture was stirred at that temperature for 10 min. *tert*-Butyl propionate (**2a**, 1.95 g, 15.0 mmol) was added dropwise to the solution at –78 °C, and the mixture was stirred at that temperature for 10 min. A solution of sulfoxide **1a** (806 mg, 3.00 mmol) in THF (5 mL) was added to the resulting solution at –78 °C, and the reaction mixture was stirred at that temperature for 5 min. The reaction was quenched with sat. aq NH_4Cl (5 mL), and the mixture was extracted with $CHCl_3$ (3 × 80 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [R_f = 0.51 (hexane–EtOAc = 2:1)] to give **3a** as a colorless oil; yield 1.18 g (2.97 mmol, 99%).

(9) **Synthesis of *tert*-Butyl 4-Chlorobutanoates 6 – Typical Procedure**
A solution of **3a** (978 mg, 2.45 mmol) in THF (10 mL) was added dropwise to a 75.9 mM solution of *i*-PrMgCl in THF (113 mL, 8.58 mmol) at –60 °C, and the reaction mixture was stirred at that temperature for 5 min. The reaction was quenched with sat. aq NH_4Cl (5 mL), and the mixture was extracted with $CHCl_3$ (3 × 80 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [R_f = 0.54 (hexane–EtOAc = 10:1] to give **6a** as a colorless oil; yield 594 mg (2.28 mmol, 93%).

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(12) **Synthesis of *tert*-Butyl Cyclopropanecarboxylates 7 – Typical Procedure**
A 1.9 M solution of NaHMDS in THF (0.082 mL, 0.16 mmol) was added dropwise to a solution of **6a** (27.2 mg, 0.104 mmol) in a THF–DMPU mixture (0.52 mL/0.52 mL) at 0 °C, and the reaction mixture was stirred at r.t. for 28 h. The reaction was quenched with sat. aq NH_4Cl (0.5 mL), and the mixture was extracted with toluene (3 × 8 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [R_f = 0.51 (hexane–EtOAc = 10:1] to give **7a** as a colorless oil; yield 22.5 mg (0.100 mmol, 96%).

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