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A novel method for asymmetric synthesis of both enantiomers of α-substituted carboxylic acid derivatives from optically active 1-chlorovinyl *p*-tolyl sulfoxides and lithium ester enolates with 1,4-chiral induction from the sulfur chiral center

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Abstract—Treatment of optically active 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from symmetrical ketones and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide in three steps, with lithium enolate of carboxylic acid *tert*-butyl esters gave optically active adducts having a substituent at the α-position with high 1,4-chiral induction from the sulfur chiral center in high yields. The adducts were converted to optically active esters and carboxylic acids having a chiral center at the α-position. When this addition reaction was carried out with the ester enolate generated from excess carboxylic acid *tert*-butyl ester with LDA in the presence of HMPA, the diastereomer of the adduct was obtained. By using the two reaction conditions for the generation of the ester enolates, a new method for asymmetric synthesis of both enantiomers of carboxylic acid derivatives having a substituent at the α-position from the one chiral source, (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide, was realized.

Carboxylic acids, esters, amides, and their derivatives are obviously among the most important and fundamental compounds in organic chemistry,[1] bioorganic chemistry,[2] and synthetic organic chemistry. Innumerable studies on the chemistry and preparation of these compounds have already been reported. On the other hand, synthesis of optically active carboxylic acids and esters is quite an interesting and important aspect of chemistry these days. The optically active compounds are most important in the science of drugs, bioactive compounds, and life.

Control of the stereochemistry of the chiral carbon of carboxylic acids and esters at the α-position is now extensively studied. For example, the chiral aldol-type reactions[3] and chiral substitution of the α-position of esters[4] are well known. However, in view of the importance of the stereoselective formation of the chiral carbon of carboxylic acids and esters at the α-position, new methods for their synthesis are still very much desired.

Recently, we reported a novel method for the synthesis of esters, lactones and amides having a tertiary or a quaternary carbon at the β-position from 1-chlorovinyl *p*-tolyl sulfoxides.[5] The key reaction was the addition of the lithium ester enolate of *tert*-butyl acetate and *N*,*N*-dimethylacetamide to 1-chlorovinyl *p*-tolyl sulfoxides to afford the adducts in almost quantitative yields.

In continuation of our interest in the study of the development of new synthetic methods for optically active carboxylic acid derivatives by using optically active 1-chlorovinyl *p*-tolyl sulfoxides, we recently investigated the reaction described below and interesting results were obtained.

Thus, optically active 1-chlorovinyl *p*-tolyl sulfoxides **3** were synthesized from symmetrical ketones **1** and optically pure (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide **2**.[6] Reaction of the lithium enolate of carboxylic acid *tert*-butyl esters, which were generated from the

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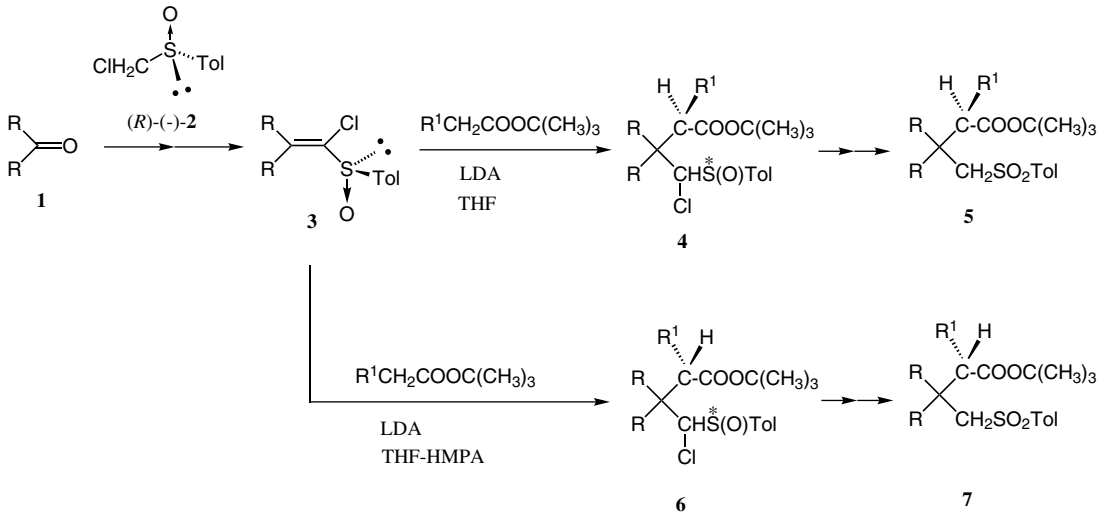
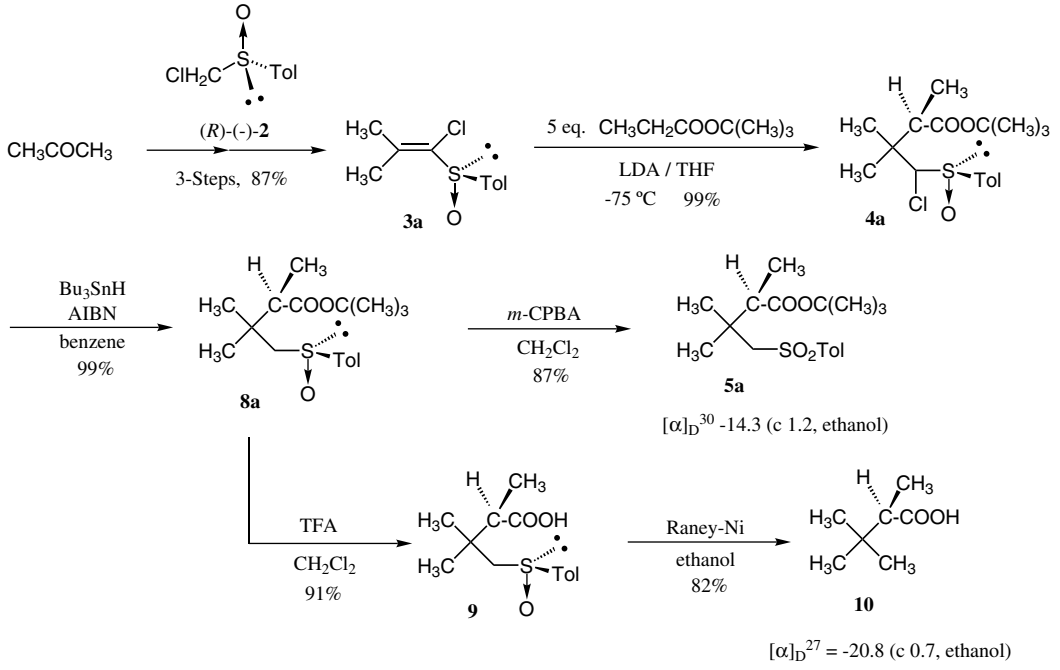


Scheme 1.

corresponding esters with LDA, with the optically active 1-chlorovinyl *p*-tolyl sulfoxides **3** gave optically active adduct **4** in high yield with high 1,4-chiral induction from the sulfur chiral center (Scheme 1). Interestingly, the reaction of the lithium enolate of carboxylic acid *tert*-butyl esters generated from the excess esters with LDA in the presence of HMPA with the optically active **3** gave the diastereomer **6** (corresponding to **4**) in high yield. As the result, both enantiomers of the α-substituted esters **5** and **7** could be obtained from the same chiral source (*R*)-(−)-**2** by choosing the conditions for the generation of the *Z*-enolates or *E*-enolates.

A representative example is reported as follows (Scheme 2). First, 1-chlorovinyl *p*-tolyl sulfoxide **3a** was synthesized from acetone and (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide **2**[6] in three steps in 87% overall yield.[7] Lithium enolate (5 equiv) of *tert*-butyl propionate was generated from *tert*-butyl propionate with LDA in THF at −75 °C. The addition reaction of **3a** with the enolate was found to be instantaneous and adduct **4a** was obtained within one minute in 99% yield. Quite interestingly, although the adduct **4a** has three stereogenic centers, only a single isomer was observed judging from its ^{1}H NMR spectrum. This result indicated that the stereochemistry of both the carbons bearing the chlorine and the methyl group was induced from the sulfur chiral center.

In order to eliminate two stereogenic centers, **4a** was first treated with Bu_3SnH[8] to give the reduced **8a** in quantitative yield. The sulfinyl group in **8a** was oxidized with *m*-chloroperbenzoic acid (*m*-CPBA) to afford sul-



Scheme 2.

fone **5a**. The enantiomeric excess of sulfone **5a** was determined to be 96% by HPLC using Chiralpak AD as a chiral stationary column.

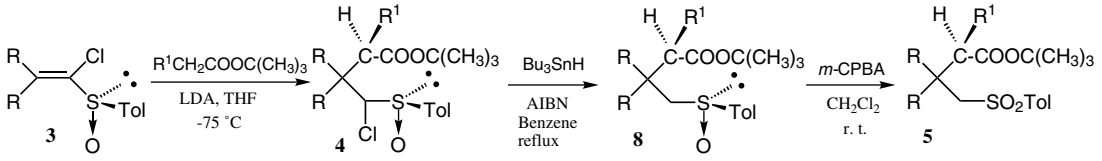
In order to determine the absolute configuration of the carbon bearing the methyl group, **8a** was converted to known carboxylic acid **10**. Thus, **8a** was treated with trifluoroacetic acid in dichloromethane to give the carboxylic acid **9**. Finally, the sulfinyl group in **9** was reduced with Raney-Ni to give 2,3,3-trimethylbutyric acid **10**. As the sign of the specific rotation of (*S*)-**10** was reported to be plus,[9] the absolute configuration of the synthesized **10**, which has a minus sign for the specific rotation, was determined to be *R*.

Next, we examined the generality of this reaction and the results are summarized in Table 1. We selected 1-chlorovinyl *p*-tolyl sulfoxides **3** synthesized from acetone, cyclohexanone, and cyclopentadecanone. *tert*-Butyl propionate, *tert*-butyl butyrate, and *tert*-butyl hexanoate were selected as the esters.

As shown in Table 1, the addition reaction of the lithium enolates (generated from the esters with LDA in THF at −75 °C) to the vinyl sulfoxides **3** proceeded to give the adducts **4** in high yields, except in one case (entry 7). Reduction of the chlorine atom in **4** followed by oxidation of the resulting sulfoxide **8** gave sulfone **5** in high yields. The enantiomeric excess of all the sulfones **5** was determined to be 93–99% by using HPLC with Chiralpak AD. All of the signs of the specific rotation of the sulfones **5** showed minus.

A plausible mechanism of this 1,4-chiral induction from the sulfur chiral center is proposed as shown in Figure 1. Previously, we reported a plausible transition state model for the addition reaction of lithium enolate of *tert*-butyl acetate to optically active 1-chlorovinyl *p*-tolyl sulfoxides **3**.[5d] Thus, the lithium cation forms a five-membered chelate between the oxygen of the sulfoxide and the chlorine atom. In this event, the enolates were introduced to the vinyl sulfoxides from the less hindered *re* face (Fig. 1).

Table 1. Asymmetric synthesis of carboxylic acid *tert*-butyl esters having an alkyl group at the α-position **5** from optically active 1-chlorovinyl *p*-tolyl sulfoxides **3**



Entry	Vinyl sulfoxide **3**		Adduct **4**[a]		Sulfoxide **8**	Sulfone **5**			
	R	R	R^1	Yield/%	Yield/%		Yield/%	ee[b] (%)	$[\alpha]_D$[c]
1	**3b**	–$(CH_2)_5$–	CH_3	99	91	**5b**	96	97	$[\alpha]_D^{30}$ −5.34 (*c* 1.8)
2	**3c**	–$(CH_2)_{14}$–	CH_3	95	92	**5c**	89	97	$[\alpha]_D^{28}$ −4.34 (*c* 0.9)
3	**3a**	CH_3	CH_3	CH_3CH_2	96	99	**5d**	92	93	$[\alpha]_D^{26}$ −3.00 (*c* 1.7)
4		–$(CH_2)_5$–	CH_3CH_2	96	97	**5e**	94	99	$[\alpha]_D^{26}$ −4.93 (*c* 1.8)
5		–$(CH_2)_{14}$–	CH_3CH_2	82	97	**5f**	83	97	$[\alpha]_D^{26}$ −1.74 (*c* 0.9)
6	CH_3	CH_3	*n*-C_4H_9	99	93	**5g**	94	96	$[\alpha]_D^{28}$ −0.47 (*c* 2.8)
7		–$(CH_2)_{14}$–	*n*-C_4H_9	71	82	**5h**	97	97	$[\alpha]_D^{27}$ −1.86 (*c* 0.9)

[a] All the adducts were observed as a single isomer determined from their ^{1}H NMR spectra.
[b] The enantiomeric excess was determined by HPLC using Chiralpak AD.
[c] The specific rotation was determined in ethanol.

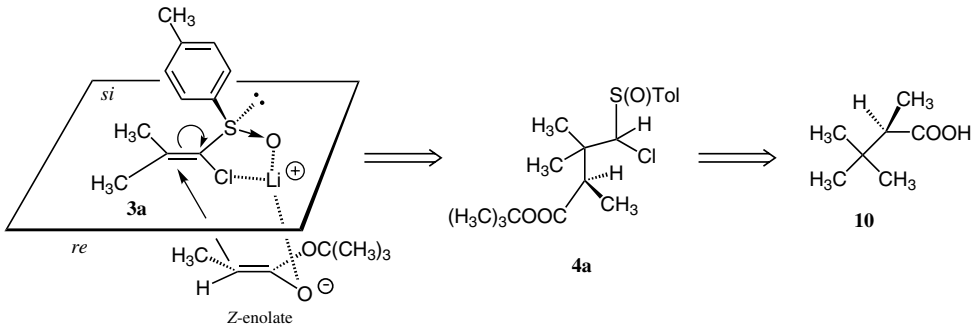
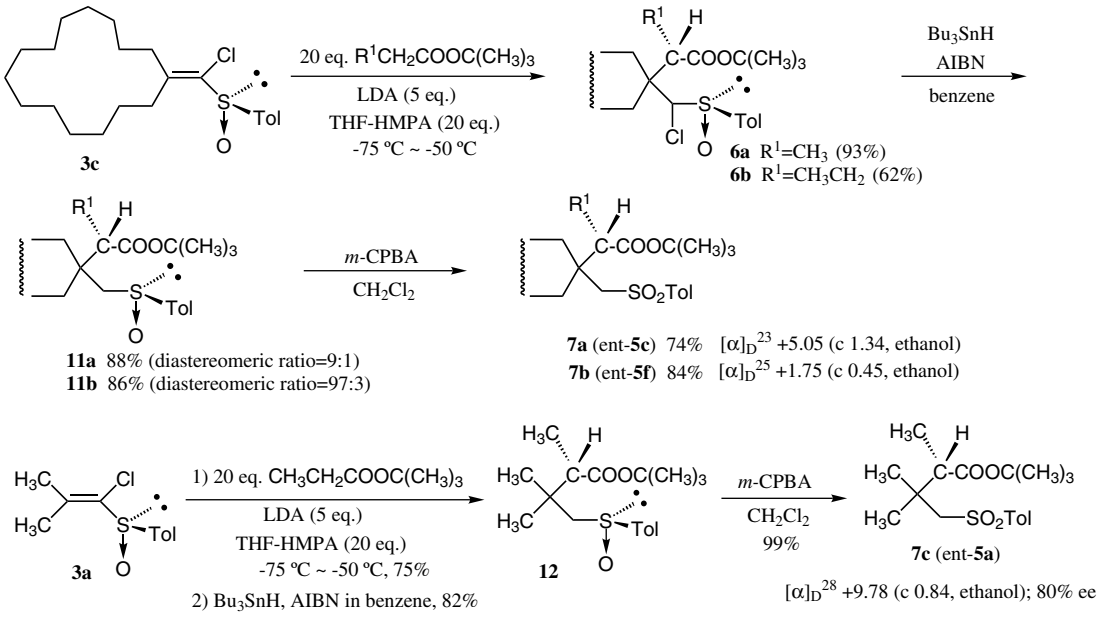


Figure 1.



Scheme 3.

Treatment of carboxylic esters including *tert*-butyl propionate with LDA in THF at low temperature was reported to give *Z*-enolate.[10a] While the real reason is obscure at present, the *Z*-enolate of *tert*-butyl propionate would be placed as shown in Figure 1 by chelation with lithium and introduced from *re* face to afford the adduct **4a** with high 1,4-chiral induction from the sulfur chiral center.

Ireland et al.,[10b] Tanaka and Fuji,[10c] and Otera et al.[10d] reported that treatment of carboxylic acid esters with LDA in THF in the presence of HMPA gave *E*-enolates predominantly. Moreover, Otera et al.[10d] reported that increasing the ester/LDA ratio, more *E*-enolates were produced. We thought that if the reaction described above was conducted with the lithium ester enolates generated with LDA in the presence of HMPA and excess of esters, the enantiomer of the α-substituted esters could be synthesized (Scheme 3).

First, optically active 1-chlorovinyl *p*-tolyl sulfoxide **3c** was reacted with the lithium enolates generated from *tert*-butyl propionate (20 equiv) or *tert*-butyl butanoate (20 equiv) with 5 equiv of LDA in the presence of 20 equiv of HMPA at −75 °C to −50 °C. These reactions gave **6a** and **6b** as an inseparable mixture of two diastereomers. The adducts **6a** and **6b** were reduced with Bu_3SnH to give **11a** and **11b**, respectively, in good yields. At this stage two diastereomers could be separated by silica gel column chromatography, and the diastereomeric ratio is shown in Scheme 3. Finally, the main products were oxidized with *m*-CPBA to afford **7a** and **7b**, respectively, in good yield.

The sign of the specific rotation of **7a** showed plus and all the other data indicated that **7a** is the enantiomer of **5c**. The enantiomeric excess was calculated to be over 99% using Chiralpak AD. In the same manner, **7b** was proved to be the enantiomer of **5f** and the enantiomeric excess was found to be over 99%. The minor diastereomer (corresponding to **11a**) was oxidized to sulfone and it was proved to be **5c**.

In order to confirm the generality of this reaction, **3a** was reacted with the *E*-enolate generated from *tert*-butyl propionate under the conditions as above and the adduct was reduced with Bu_3SnH to afford **12** in good yield. Unfortunately, **12** was found to be an inseparable mixture of two diastereomers. The sulfoxide **12** was oxidized with *m*-CPBA to give the sulfone **7c** in quantitative yield. As anticipated, the product **7c** was the enantiomer of **5a** and the enantiomeric excess was measured to be 80% by using HPLC with Chiralpak AD.

In conclusion, a new method for asymmetric synthesis of carboxylic acid derivatives having a substituent at the α-position from (*R*)-(−)-chloromethyl *p*-tolyl sulfoxide was realized. Both enantiomers of the α-substituted carboxylic acid derivatives can be synthesized from one chiral source by choosing the conditions for the generation of the lithium ester enolates, which is the most interesting characteristic of this procedure.

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