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# A novel synthesis, including asymmetric synthesis, of α-quaternary α-amino acid methyl esters from ketones via sulfinyloxiranes

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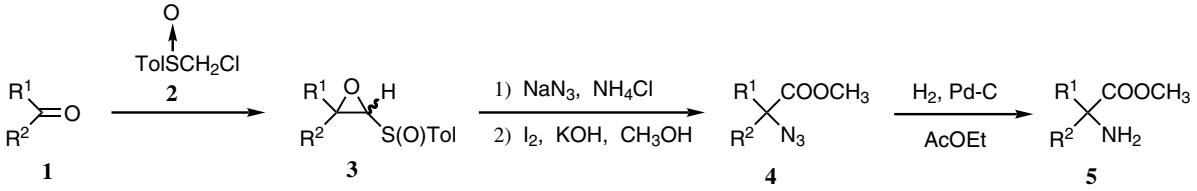
**Abstract**—Sulfinyloxiranes were synthesized from ketones and chloromethyl *p*-tolyl sulfoxide in two steps in almost quantitative yields. The sulfinyloxiranes were treated with $NaN_3$ in the presence of $NH_4Cl$ to afford α-azido aldehydes, which were oxidized with iodine in the presence of KOH in methanol to give α-azido methyl esters in good overall yields. Catalytic hydrogenation of the α-azido esters afforded α-quaternary α-amino acid methyl esters in quantitative yields. Starting from β-tetralone and optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide, an asymmetric synthesis of optically pure (*R*)-(+)-methyl 2-aminotetraline-2-carboxylate was realized in good overall yields.


α-Amino acids are obviously the fundamental building blocks of peptides, proteins and many natural products and play essential roles in living organisms.[1] Because of the physiological importance of α-amino acids, innumerable studies for their chemistry and synthesis have been published.[2] Recently, α,α-disubstituted (α-quaternary) α-amino acids[3] have received considerable attention. Especially, cyclic α-quaternary α-amino acids that are conformationally constrained are used in controlling peptide secondary structures and in medicinal chemistry.[4] The synthesis and chemistries of α-quaternary and cyclic α-quaternary α-amino acids have attracted much attention these days.[5]

As our contribution to the synthesis of α-amino acid derivatives, we recently reported a novel synthesis of cyclic α-amino acid derivatives based on the conjugate addition of *N*-lithio arylamines to 1-chlorovinyl *p*-tolyl sulfoxides.[6] In continuation of our interest in the synthesis of α-quaternary α-amino acids, we recently developed a new and versatile method for synthesis of α-quaternary α-amino acid methyl esters from ketones and chloromethyl *p*-tolyl sulfoxide. The essence of this procedure is shown in Scheme 1.

Thus, ketone **1** was reacted with a lithium α-carbanion of chloromethyl *p*-tolyl sulfoxide **2** to give the adduct, which was treated with *t*-BuOK to afford sulfinyloxirane **3** in almost quantitative yield. Treatment of the sulfinyloxirane **3** with $NaN_3$ in the presence of $NH_4Cl$ resulted in the formation of azido aldehyde. The azido aldehyde was oxidized with $I_2$ and KOH in methanol to give azido methyl ester **4** in good overall yield from **3**. Finally, catalytic hydrogenation of the azido methyl ester **4** afforded the desired α-quaternary α-amino acid methyl ester **5** in quantitative yield.




**Scheme 1.**

*Keywords*: Sulfoxide; Sulfinyloxirane; α-Amino acid; α-Quaternary α-amino acid; Asymmetric synthesis.
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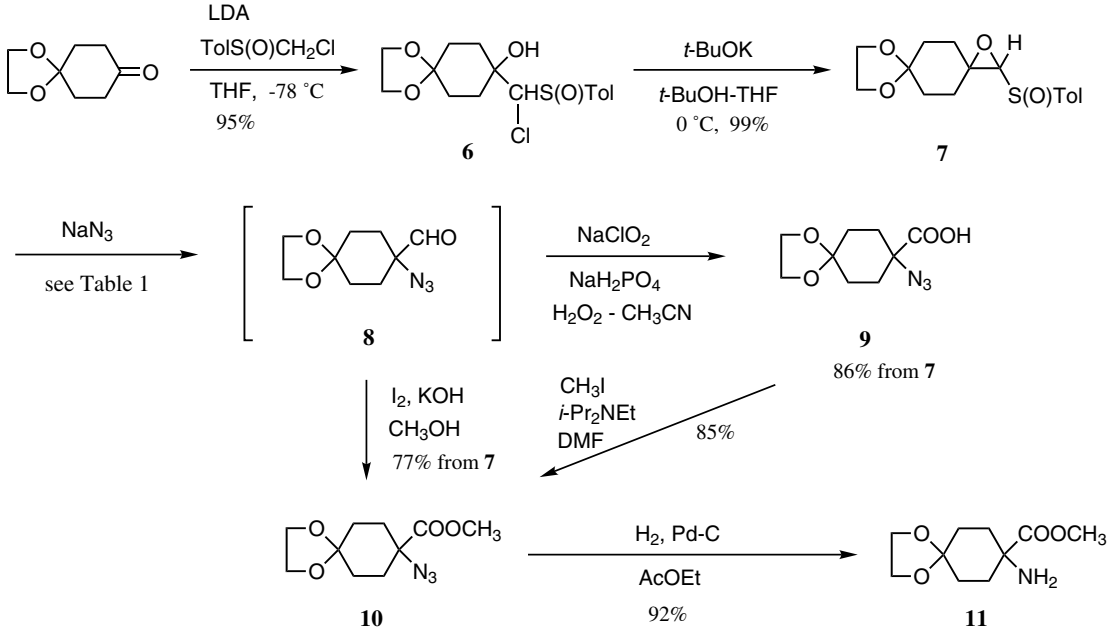
The details of this procedure are reported by using 1,4-cyclohexanedione mono ethylene ketal as a representative example (Scheme 2). Chloromethyl *p*-tolyl sulfoxide was treated with LDA at −78 °C and the resultant carbanion was reacted with 1,4-cyclohexanedione mono ethylene ketal to give the adduct **6** in almost quantitative yield. The adduct was then treated with *t*-BuOK in a mixture of *t*-BuOH and THF at 0 °C to give sulfinyloxirane **7** in quantitative yield.[7]

Next, we attempted to open this sulfinyloxirane with the azido anion expecting the formation of azido aldehyde **8**. Initially, **7** was warmed with 3 equiv of $NaN_3$ in DMSO at 65 °C for 43 h (see Table 1, entry 1). The starting material disappeared and the desired azido aldehyde **8** was obtained with some by-products. Purification of **8** proved to be difficult and also **8** was found to be somewhat unstable. The crude aldehyde **8** was oxidized with $NaClO_2$ in the presence of $H_2O_2$ in acetonitrile[8] to give the azido carboxylic acid **9** in 65% overall yield from **7**.

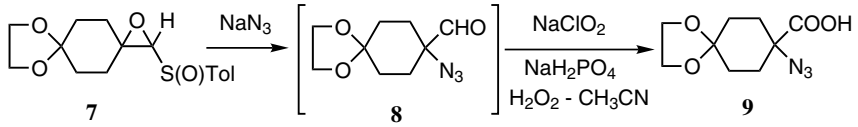
In order to obtain better yield of **9**, we investigated the conditions, additive, concentration of the reaction as shown in Table 1; however, better yield was not observed (entries 2–4). Finally, we changed the conditions of this reaction from an aprotic solvent to protic media as reported by Caron and Sharpless[9] and Crotti and coworkers[10] (entry 5). This condition worked and much higher yield (82% of **9** from **7**) was obtained. The best yield was obtained under the conditions shown in entry 6. The carboxylic acid **9** was converted to methyl ester **10** with iodomethane in the presence of *N*,*N*-diisopropylethylamine in 85% yield (Scheme 2).

The three-step reaction from **7** to **10** seemed to be reasonable as the overall yield was 73%; however, treatment of the carboxylic acid **9** was not convenient. We




**Scheme 2.**

**Table 1.** Reaction of the sulfinyloxirane **7** with $NaN_3$ followed by oxidation of the resultant azido aldehyde **8**




| Entry | $NaN_3$ (equiv) | Solvent | Concentration (mol/L) | Conditions | Yield of **9**[a] (%) |
|---|---|---|---|---|---|
| 1 | 3 | DMSO | 0.1 | 65 °C, 43 h | 65 |
| 2 | 3[b] | DMSO | 0.1 | 60 °C, 34 h | 61 |
| 3 | 3 | DMSO | 0.5 | 65 °C, 36 h | 24 |
| 4 | 3 | DMSO | 0.05 | 65 °C, 43 h | 61 |
| 5 | 3 | MeOH–$H_2O$ (8:1)[c] | 0.1 | Reflux, 16 h | 82 |
| 6 | 5 | MeOH–$H_2O$ (8:1)[c] | 0.1 | Reflux, 12 h | 86 |

[a] Two-step overall yield from **7**.
[b] 3.6 equiv of 15-crown-5 was added.
[c] In the presence of $NH_4Cl$.

further investigated direct oxidation of the aldehyde **8** to methyl ester **10**. For the purpose of this oxidation, we tried oxidation using iodine in the presence of KOH in methanol reported by Inch et al.[11] and fortunately the desired ester **10** was obtained in 77% yield from **7**. Finally, catalytic hydrogenation of the azido group in **10** was carried out with Pd–C in ethyl acetate under $H_2$ atmosphere to give α-amino acid methyl ester **11** in 92% yield. By the result of the successful direct oxidation of the aldehyde **8** to the methyl ester **10**, this procedure gave the desired α-amino acid methyl ester **11** from 1,4-cyclohexanedione mono ethylene ketal in five operations in 67% overall yield.

In order to study the generality of this procedure, we investigated this procedure starting from three cycloalkanones (cyclobutanone, cyclodecanone and cyclopentadecanone), and two unsymmetrical acyclic ketones (4-phenyl-2-butanone and 1-phenyl-2-butanone) and the results are summarized in Table 2.

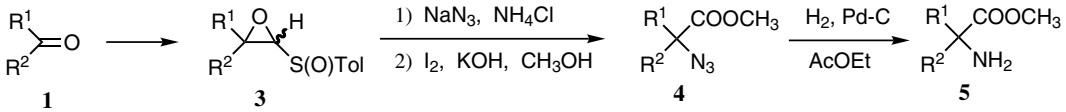
As shown in Table 2, synthesis of the sulfinyloxiranes **3** gave almost quantitative yields except in one case (entry 2). Opening of the epoxides **3** to azido aldehydes followed by oxidation to methyl esters **4** took place smoothly; however, the sulfinyloxirane derived from cyclobutanone gave a somewhat lower yield (entry 1). The catalytic hydrogenation of the azido group did not present any problem and the desired amines were obtained in almost quantitative yields. From these results we concluded that the procedure mentioned above is quite generally used for a variety of ketones and many α-quaternary α-amino acid methyl esters could be synthesized.

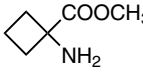
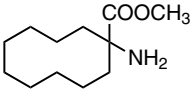
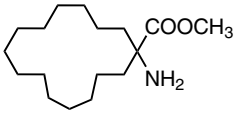
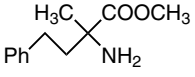
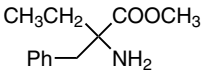
Finally, we applied this procedure to the asymmetric synthesis of optically pure (*R*)-(+)-methyl 2-aminotetraline-2-carboxylate (*R*)-(+)-**16** starting from β-tetralone and optically pure (*R*)-chloromethyl *p*-tolyl sulfoxide (Scheme 3).

The reaction of β-tetralone with the lithium α-sulfinyl carbanion, which was generated from (*R*)-chloromethyl *p*-tolyl sulfoxide[12] and lithium diisopropylamide in THF at −78 °C, gave 82% yield (99% yield from consumed sulfoxide)[13] of the adduct **12** as a mixture of two diastereomers. Without separation, the mixture was treated with *t*-BuOK to afford 3:1 mixture of sulfinyloxiranes **13** and **14** in 93% yield. The products were easily separated by silica gel column chromatography. The enantiomeric excess of these sulfinyloxirans **13** and **14** was determined to be over 99% by HPLC using CHIRALPAK AD as a chiral stationary column.

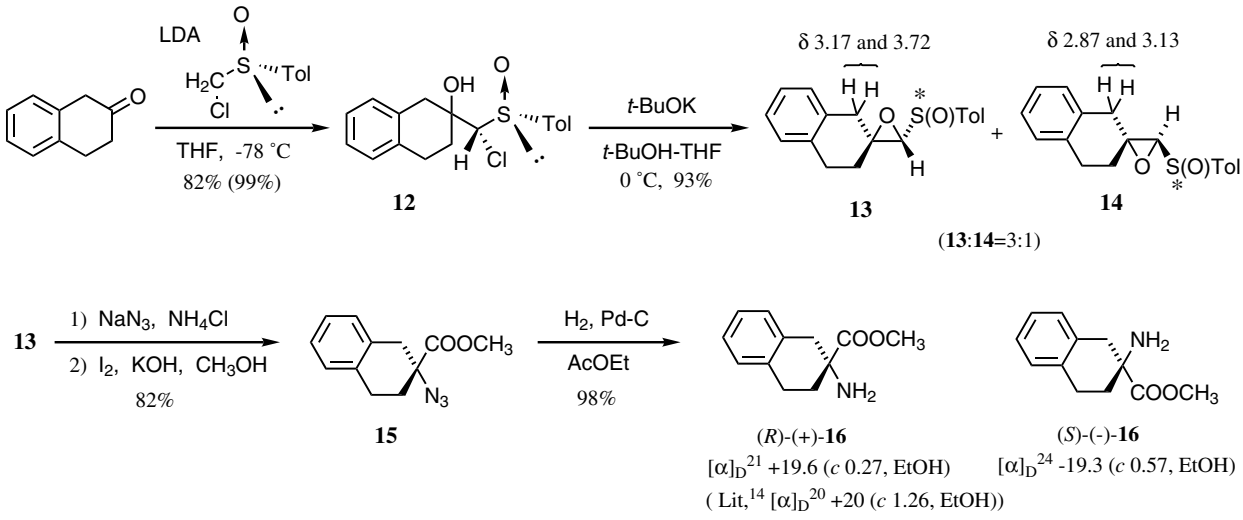
As the addition reaction of the lithium α-sulfinyl carbanion of (*R*)-chloromethyl *p*-tolyl sulfoxide to carbonyl carbon was proved to induce *R* configuration at the carbon bearing the chlorine atom,[12] the whole stereochemistry of the sulfinyl oxiranes **13** and **14** was easily determined from the $^1$H NMR spectrum. As shown in Scheme 3, the chemical shift of the benzylic hydrogens of the main product **13** was markedly lowered compared with those of **14**, which indicates that the benzylic carbon and the sulfinyl group of **13** must be *cis*.

**Table 2.** Synthesis of α-quaternary α-amino acid methyl esters **5** from ketones **1** via sulfinyloxiranes **3**




| Entry | 1 | | 3 | 4 | 5 | |
|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | Yield[a] (%) | Yield[b](%) | | Yield (%) |
| 1 | –(CH$_2$)$_3$– | | 92 | 55 |  | 98 |
| 2 | –(CH$_2$)$_9$– | | 80 | 72 |  | 95 |
| 3 | –(CH$_2$)$_{14}$– | | 94 | 75 |  | 95 |
| 4 | $CH_3$ | $PhCH_2CH_2$ | 90[c] | 67 |  | 99 |
| 5 | $CH_3CH_2$ | $PhCH_2$ | 98[d] | 90 |  | 97 |

[a] Two-step overall yield from **1**.
[b] Two-step overall yield from **3**.
[c] A mixture of two diastereomers (59:41).
[d] A mixture of two diastereomers (65:35).




**Scheme 3.** Asymmetric synthesis of (*R*)-(+)-methyl 2-aminotetraline-2-carboxylate **16** from β-tetralone.

The main product **13** was treated with $NaN_3$ and the resulting azido aldehyde was oxidized with $I_2$ in methanol to give the desired azido methyl ester **15** in 82% overall yield from **13**. The enantiomeric excess of **15** was determined to be over 99% by HPLC using CHIRALCEL OD as a chiral stationary column. Finally, the catalytic hydrogenation of **15** with Pd–C/$H_2$ gave the expected (*R*)-(+)-methyl 2-aminotetraline-2-carboxylate (*R*)-(+)-**16** in a quantitative yield. All the spectral data and the specific rotation were highly consistent with the reported value.[14] From the minor sulfinyloxirane **14**, the same treatment gave the enantiomer (*S*)-(−)-**16** in a similar yield.

In conclusion, we have developed a new and versatile method for the synthesis of α-quaternary α-amino acid methyl esters from ketones in good overall yields. This procedure was extended to an asymmetric synthesis and we believe that the method presented here is one of the most useful procedures for the asymmetric synthesis of optically pure α-quaternary α-amino acid methyl esters. We are continuing to study the scope and limitation of this procedure.

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