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# The Asymmetric Favorskii Rearrangement: A Synthesis of Optically Active α-Alkyl Amides from Aldehydes and (-)-1-Chloroalkyl *p*-Tolyl Sulfoxide

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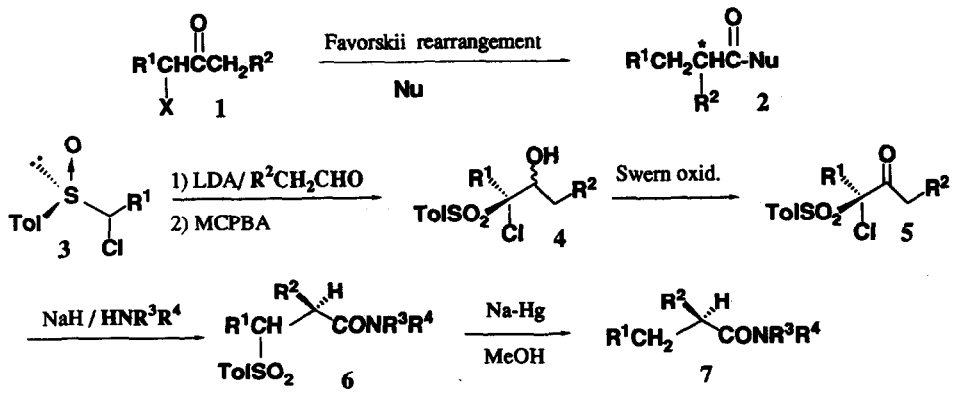
*Abstract: The first asymmetric Favorskii rearrangement is described. Optically active α-alkyl amides of enantiomeric excess up to 94% were realized from aldehydes and optically active (-)-1-chloroalkyl p-tolyl sulfoxides via the Favorskii rearrangement of optically active α-chloro α-sulfonyl ketones.*

The Favorskii rearrangement is a well-known reaction of α-halo ketones with bases in the presence of nucleophiles to give the carboxylic acids and their derivatives, with a skeletal rearrangement.[1] When α-halo ketone **1** ($R^2 \neq H$) is subjected to the rearrangement, a new chiral center α to the carbonyl carbon is generated in the product **2**. This means that if the appropriate substrate and conditions are used, the asymmetric Favorskii rearrangement must be possible. However, to the best of our knowledge, no report relating to the asymmetric




**Scheme 1**

Favorskii rearrangement has been made. One reason for this is the difficulty of a synthesis of chiral α-halo ketones, and the other is the easy racemization of the products under the strong basic conditions.

We recently reported several novel synthetic methods, including asymmetric synthesis, using 1-haloalkyl aryl sulfoxides.[2] Moreover, we reported a new synthesis of amides from carbonyl compounds via the Favorskii rearrangement of α-chloro α-sulfonyl ketones.[3] In continuation of our study for development of a new synthetic method using 1-haloalkyl aryl sulfur compounds, here we report an asymmetric synthesis of α-alkyl amides **7** from aldehydes and optically active (-)-1-chloroalkyl *p*-tolyl sulfoxide **3** via the asymmetric Favorskii rearrangement of optically active α-chloro α-sulfonyl ketone **5** (Scheme 1).

Optically active α-chloro α-sulfonyl ketones **5** were easily synthesized in a three-step conversion from (-)-**3** (over 98% ee)[4] and aldehydes in high overall yields as shown in Scheme 1. The yields of **4** and **5**, and specific rotations of **5** are summarized in Table 1. The absolute configuration of **5** is *R* and ee about 98%.[4]

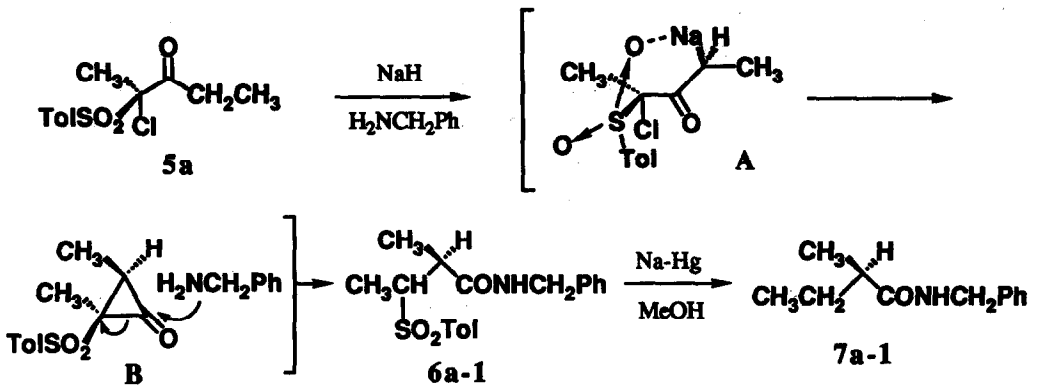
Table 1. Synthesis of Optically Active α-Chloro α-Sulfonyl Ketone **5**

| Entry | **3** | Aldehyde | **4** | | **5** | | |
|---|---|---|---|---|---|---|---|
| | $R^1$ | $R^2$ | Yield (%)[a] | | Yield (%) | | $[\alpha]_D$ (deg)[b] |
| 1 | $CH_3$ | $CH_3$ | **4a** | (91) | **5a** | (93) | -42.6 |
| 2 | $CH_3$ | n-$C_3H_7$ | **4b** | (85) | **5b** | (79) | -24.5 |
| 3 | $C_2H_5$ | $C_2H_5$ | **4c** | (99) | **5c** | (83) | -25.7 |
| 4 | n-$C_6H_{13}$ | n-$C_4H_9$ | **4d** | (89) | **5d** | (90) | -26.6 |
| 5 | $PhCH_2$ | $CH_3$ | **4e** | (88) | **5e** | (99) | -8.0 |

a) Two-step overall yield from **3** and aldehydes. Isolated yield. b) Measured in acetone at room temperature.

Next, the Favorskii rearrangement of the optically active α-chloro α-sulfonyl ketones **5** was investigated. First, **5a** was treated with NaH (1.5 equiv.) in dry THF with benzylamine (1.5 equiv.) at room temperature for 2.5 h (Scheme 2). Clean reaction took place and the optically active β-sulfonyl amide **6a-1** was obtained in 82% yield as colorless crystals. The sulfonyl group of **6a-1** was reduced with 6% Na-Hg in methanol[5] at room temperature for 2 h to give optically active amide **7a-1** ($[\alpha]_D$ -14.36°) in 68% yield. Comparing the sign of the specific rotation of **7a-1** with that of synthesized (*S*)-(+)-*N*-Benzyl-2-methylbutanamide ($[\alpha]_D$ +16.96°), the absolute configuration of **7a-1** was unambiguously *R* and ee 85%.[6]

The mechanism of the asymmetric induction of the rearrangement is presumed as follows. As shown in Scheme 2, treatment of **5a** with a base gave cyclopropanone intermediate **B**. Coordination of the sulfone oxygen with sodium gave six-membered conformation **A** in the transition state for cyclization.[7]




Scheme 2

Table 2. Synthesis of Optically Active Amides 7 via the Asymmetric Favorskii Rearrangement of 5

| Entry | 5 | $R^3R^4NH$ | | 6 | | | | 7 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | $R^3$ | $R^4$ | Time h | | Yield[a] (%) | $[\alpha]_D$ deg | | Yield[a] (%) | $[\alpha]_D$ deg | ee (%) |
| 1 | 5a | $PhCH_2$ | H | 2.5 | 6a-1 | (82) | +1.25 | 7a-1 | (68) | -14.36 | 85[b] |
| 2 | 5a | $(CH_2)_5$ | | 2 | 6a-2 | (77) | +4.3 | 7a-2 | (74) | -19.51 | 70[b] |
| 3 | 5b | $PhCH_2$ | H | 2.5 | 6b-1 | (84) | -3.99 | 7b-1 | (88) | +1.22 | 50[c] |
| 4 | 5b | $PhCHCH_3$ | H[d] | 3 | 6b-2 | (64) | +35.0 | 7b-2 | (73) | +73.72 | 94[c] |
| 5 | 5c | $PhCH_2$ | H | 4 | 6c-1 | (51)[e] | -6.8 | 7c-1 | (74) | -1.66 | 83[c] |
| 6 | 5c | $PhCHCH_3$ | H[d] | 4 | 6c-2 | (59) | +35.84 | 7c-2 | (84) | +70.10 | 82[c] |
| 7 | 5d | $PhCH_2$ | H | 4 | 6d-1 | (78) | +8.04 | 7d-1 | (82) | +6.94 | 88[c] |
| 8 | 5d | $(CH_2)_5$ | | 22 | 6d-2 | (82) | +9.8 | 7d-2 | (85) | +1.93 | --[f] |
| 9 | 5e | $PhCH_2$ | H | 6 | 6e-1 | (71) | -36.85 | 7e-1 | (86) | -2.93 | 84[g] |
| 10 | 5e | $(CH_2)_5$ | | 24 | 6e-2 | (76) | -3.33 | 7e-2 | (76) | -18.41 | 90[g] |

a) Isolated yield. b) Calculated from specific rotation. See text. c) Calculated from HPLC using Waters Opti-Pak XC or TA or Nova-Pak Silica or Sumika Chemical Analysis Service Sumichiral OA-4600 column. d) (*R*)-(+)-1-Phenylethylamine. e) α,β-Unsaturated amide was obtained in 20% yield. f) The ee could not be determined. g) Calculated from $^1H$ NMR in the presence of $Eu(hfc)_3$.

The results for a synthesis of optically active **7** from **5** via the asymmetric Favorskii rearrangement are summarized in Table 2. The optical purity of **7** is generally good except for one example (entry 3). Unfortunately, as the ee of **6** could not be determined, the actual asymmetric induction of the Favorskii rearrangement is somewhat obscure at present. One of the main problems for the slight racemization is thought to occur in the reduction stage. For example, in reduction of **6a-1** with 6% Na-Hg in methanol for 24 h, instead of 2.5 h, the ee of **7a-1** was lowered to 39%.

It is noteworthy that **7b-1** and **7c-1** are enantiomeric with each other; namely, by appropriate selection of **3** and aldehyde, this synthetic procedure gives both enantiomers of α-alkyl amides **7**.

Further studies of these asymmetric Favorskii rearrangements and the application of this procedure in the synthesis of natural products are in progress.

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6. (*S*)-(+)-*N*-Benzyl-2-methylbutanamide was synthesized from (*S*)-(+)-2-methylbutylic anhydride (Aldrich) with benzylamine in THF at room temperature for 1 h in 97% yield ($[\alpha]_D$ +16.96°). Similarly, (*S*)-(+)-2-methylbutanoyl piperidine was obtained in 95% yield ($[\alpha]_D$ +27.95°). All specific rotations in this study were measured in acetone.
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