# Stereoselective reaction of arylsulfanyl-stabilized homoenolates with aldehydes

COMMUNICATION
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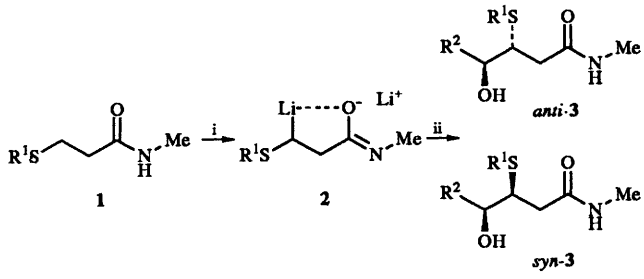
**The reaction of arylsulfanyl-stabilized lithium homoenolates with aromatic aldehydes gave *anti*-adducts with a high level of diastereoselectivity (up to 96% de) and fair enantioselectivity (up to 47% ee) in the presence of (−)-sparteine.**

Sulfur-stabilized carbanions play an important role in organic synthesis. Although such carbanions are easily generated, there have been only a limited number of reports on their use in enantioselective synthesis, with the exception of α-sulfinyl carbanions, which have a chiral sulfur atom. Recently, Hoppe and Kaiser[1] reported that *S*-alkyl thiocarbamate is enantioselectively deprotonated using (−)-sparteine[2] and Bu$^s$Li and can be trapped with $Me_3SiCl$ or $CO_2$ to give the adduct with 40–60% ee. To our knowledge, few reports are available on the diastereo- and enantio-selective reactions of arylsulfanyl-stabilized carbanions with aldehydes.[3] In this paper, we describe the stereochemical aspects of the reaction of arylsulfanyl-stabilized amide-homoenolates with aldehydes.

Amide-homoenolates **2** were chosen since the strongly chelated dianion ring was expected to result in high stereoselectivity.[4] Although arylsulfanyl-stabilized homoenolates could not be generated from 3-phenylsulfanyl- or 3-*p*-tolylsulfanyl-propanoic acid because of β-elimination,[5] arylsulfanyl-stabilized amide-homoenolates **2** were easily generated using 2.2 equiv. of BuLi in THF at −78 °C. The generated amide-homoenolates **2** were trapped with aldehydes (Scheme 1).[6]



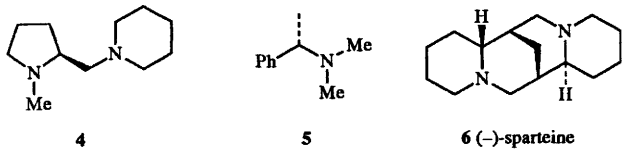

**Scheme 1** *Reagents and conditions:* i, 2.2 equiv. BuLi, THF, −78 °C; ii, $R^2CHO$

Reactions were carried out under various conditions using propanamide **1a** ($R^1$ = *p*-Tol) as shown in Table 1. When homoenolate **2a** was treated with benzaldehyde, only poor diastereoselectivity was observed (Table 1, entry 1). The use of the chiral amine ligand **4**[7] or **5** did not affect the diastereoselectivity nor cause appreciable levels of enantioselectivity (Fig. 1, Table 1, entries 2 and 3). Surprisingly, when (−)-sparteine **6** was used a high level of diastereoselectivity was observed with 28% ee† (Table 1, entry 4). The relative stereochemistry was determined by transformation of **3a** into lactones (*vide infra*),‡ and the enantioenrichment assay was done using a chiral HPLC column. We examined the effect of the amount of **6** in detail. The use of 2.2 equiv. of **6** was preferred for enantioselectivity, and the use of larger amounts of **6** was preferred for diastereoselectivity (Table 1, entries 4–7). When

**Table 1** Reactions of the amide-homoenolate **2a** with several aldehydes[a]

| Entry | Temp. (°C) | $R^2$ | Ligand (equiv.) | Yield (%) | *anti*:*syn* | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 | −78 | Ph | None | 96 | 58:42 | — |
| 2 | −78 | Ph | **4** (1.1) | 73 | 55:45 | 5 |
| 3 | −78 | Ph | **5** (4.4) | 43 | 56:44 | 1 |
| 4 | −78 | Ph | **6** (1.1) | 86 | 84:16 | 28 |
| 5 | −78 | Ph | **6** (2.2) | 85 | 87:13 | 36 |
| 6 | −78 | Ph | **6** (3.3) | 91 | 91:9 | 28 |
| 7 | −78 | Ph | **6** (0.6) | 89 | 80:20 | 16 |
| 8[c] | −78 | Ph | **6** (2.2) | 14 | 51:49 | 47 |
| 9 | −100 | Ph | **6** (2.2) | 82 | 95:5 | 30 |
| 10 | −78 | *o*-Tol | None | 93 | 63:37 | — |
| 11 | −78 | *o*-Tol | **6** (2.2) | 92 | 93:7 | 19 |
| 12 | −78 | Bu$^t$ | None | 60 | 24:76 | — |
| 13 | −78 | Bu$^t$ | **6** (2.2) | 50 | 37:63 | 18 |
| 14 | −78 | Bu | None | 85 | 45:55 | — |
| 15 | −78 | Bu | **6** (2.2) | 62 | 45:55 | 28 |

[a] All reactions were carried out using 2.2 equiv. of BuLi in THF. [b] The values of major adduct. [c] BuLi was added to the mixture of **1a**, **6** and benzaldehyde.




**4** **5** **6** (−)-sparteine

**Fig. 1**

BuLi was added to the mixture of **6**, **1a** and benzaldehyde, the best enantioselectivity (47% ee) was observed, but the yield and diastereoselectivity were poor (Table 1, entry 8). When the reaction was carried out at −100 °C, a lower ee value was observed with 2.2 equiv. of **6** (Table 1, entry 9). These results suggest that racemization of chiral **2a**, which is kinetically formed, takes place under the reaction conditions. We examined various deprotonating reagents (BuLi, Bu$^s$Li, Bu$^t$Li, a mixture of KH and BuLi), and the best deprotonating reagent was BuLi. We found also that the best procedure was to add **1a** to the precooled mixture of **6** and BuLi. Transmetallation was also investigated, using $ZnCl_2$, $MgCl_2$, $Ti(OPr^i)_4$ $Ti(OPr^i)_2Cl_2$ and $TiCl_4$, but none of the transmetallated enolates reacted with benzaldehyde.§ Reactions in other solvents ($Et_2O$, DME,

† We also tried to control the diastereo- and enantio-selectivity in the reaction of the α-sulfonyl carbanion derived from 3-phenylsulfonylpropanoic acid or *N*-methyl-3-phenylsulfonylpropanamide with benzaldehyde, but both selectivities were poor even using **6**. The reason for this is that the two oxygen atoms of the sulfonyl group prevent the tetrahedral lithium ion from chelating with the two nitrogen atoms of **6**.

‡ The absolute stereochemistry of *anti*-**3a** ($R^1$ = Ph) was 3*R*,4*S*. This was determined by optical rotation.[8]

§ Transmetallation sometimes improves the stereoselectivity.[9]

**Table 2** Reactions of the amide-homoenolates **2** with benzaldehyde

| Entry | 1 | $R^1$ | Method A[a] Yield (%) | Method A[a] dr[c] | Method B[b] Yield (%) | Method B[b] dr[c] | ee (%)[d] |
|---|---|---|---|---|---|---|---|
| 1 | **1b** | Ph | 79 | 50:50 | 90 | 83:17 | 32 |
| 2 | **1c** | *p*-$Bu^tC_6H_4$ | 84 | 50:50 | 64 | 91:9 | 42 |
| 3 | **1d** | *p*-$ClC_6H_4$ | 98 | 55:45 | 70 | 94:6 | 19 |
| 4 | **1e** | *p*-$MeOC_6H_4$ | 74 | 56:44 | 65 | 98:2 | 18 |
| 5 | **1f** | Mesityl | 74 | 54:46 | 59 | 93:7 | 20 |

[a] Method A: 2.2 equiv. of BuLi in THF at −78 °C. [b] Method B: 2.2 equiv. of BuLi and **6** in THF at −78 °C. [c] Ratio of less polar adduct: more polar adduct. The stereochemistry was not determined. [d] Values for major adducts.

toluene, Bu'OMe) did not show higher enantioselectivities and gave lower yields. Under optimum conditions (Table 1, entry 5), the reactions with several aldehydes ($R^2CHO$; $R^2$ = *o*-Tol, Bu, Bu') were examined. Although *o*-tolylcarbaldehyde exhibited the same diastereoselectivity as benzaldehyde (Table 1, entries 10 and 11), aliphatic aldehydes exhibited opposite and lower diastereoselectivities (Table 1, entries 12–15).

The effect of substitution on the aromatic ring $R^1$ was investigated as shown in Table 2. High levels of diastereoselectivity were observed by adding 2.2 equiv. of **6**. *para*-Substituents on the aromatic ring did give higher diastereoselectivities, but higher enantioselectivities were not always observed (Table 2, entries 2–5). The best diastereoselectivity was obtained by using **1e** (Table 2, entry 4, 96% de).

Transformation of adducts **3a** into lactones was also examined. Treatment of diastereoisomerically pure *anti*-**3a** ($R^2$ = Ph, *o*-Tol, Bu, Bu') with 4 equiv. of $CF_3CO_2H$ in $CH_2Cl_2$ gave diastereoisomerically pure *trans*-lactones in good yield. In the same manner, *syn*-**3a** ($R^2$ = Ph, *o*-Tol, Bu, Bu') gave diastereoisomerically pure *cis*-lactones. The relative stereochemistry of the lactones was determined by NOE experiments.[8]

## Experimental

**Typical procedure for the preparation of 3**

To a solution of (−)-sparteine **6** (2.2 mmol) in THF (5 $cm^3$), BuLi (2.2 mmol) was added dropwise at −78 °C. After 5 min, a solution of **1** [1 mmol in THF (10 $cm^3$)] was added dropwise. The reaction mixture turned yellow and was stirred for 0.5–1 h at −78 °C, after which the aldehyde (1.5 mmol) was added dropwise. In the case of aromatic aldehydes, the reaction mixture was stirred for 1–2 h at −78 °C, after which aq. HCl (2 mol $dm^{-3}$) was added. In the case of aliphatic aldehydes, the reaction temperature was allowed to rise to −10 °C and the mixture was stirred for 10–12 h, after which aq. HCl (2 mol $dm^{-3}$) was added. The reaction mixture was extracted with ethyl acetate and the extract was dried ($MgSO_4$) and concentrated under reduced pressure to afford a crude product, which was purified by flash chromatography with ethyl acetate–hexane as eluent. The diastereoisomeric ratios were determined by $^1H$ NMR (270 MHz) analysis of the crude product. The enantioenrichment assay was done using a chiral HPLC column (Daicel Chemical Industries, Ltd, Chiracel OJ) with propan-2-ol or ethanol in hexane as the mobile phase.

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