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Synthesis of a Scalemic β-Amino Disulfide from *(S)*-Phenylglycine and *(R)*-Styrene Oxide and Use as a Catalyst in Enantioselective Additions of Diethylzinc to Aldehydes

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Abstract: Two routes to the novel scalemic ß-amino disulfide **7** have been developed from *(S)*-phenylglycine and *(R)*-styrene oxide. The ß-amino disulfide **7** was used as a catalyst in the enantioselective addition of diethylzinc to aldehydes providing *(R)*-secondary alcohols in 39-80% ee.

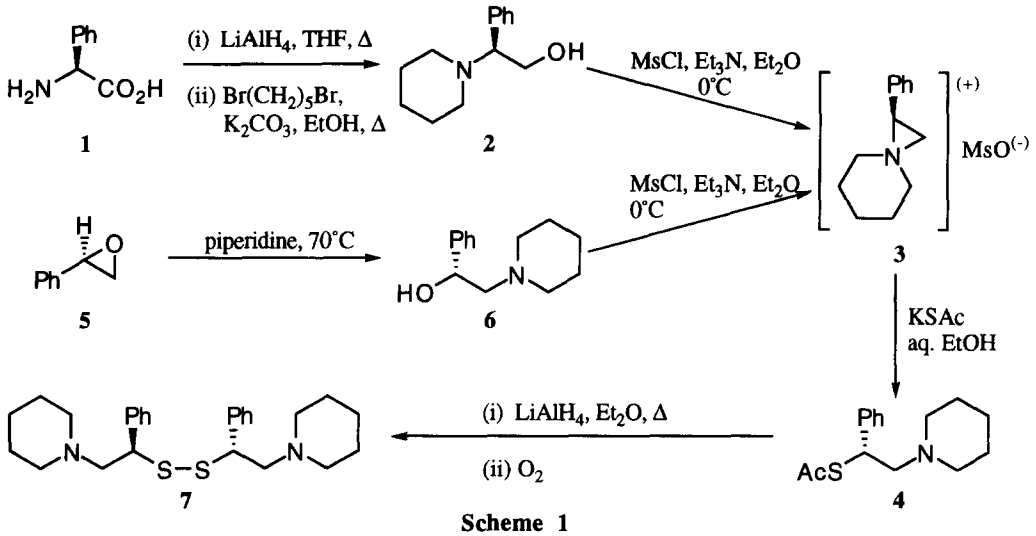
The presence of a sulfur chelation site in catalysts for enantioselective transition metal mediated carbon-carbon bond formation has been found to give rise to improved levels of enantioselectivity. In this context, scalemic amino arenethiolates[1] and thiosugars[2] have been shown to be effective catalysts in the copper(I) mediated enantioselective conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds. Recently, we have shown that an enantiopure β-amino disulfide gave improved enantioselectivity (50% ee) over the oxygen counterpart (6% ee) in the nickel(II) catalysed enantioselective conjugate addition of diethylzinc to chalcone.[3]

More significant improvements in enantioselectivities have been observed by the use of amino sulfur or selenium moieties in catalysts for the enantioselective addition of diethylzinc to aldehydes. In this context, β-amino thiols and disulfides derived from ephedrine were reported by Kellogg and co-workers to give improved ee's (≤ 90% ee) over the corresponding β-amino alcohol counterparts (≤ 64% ee) for the addition of diethylzinc to benzaldehyde.[4] These findings led to the subsequent development of β-amino thiols, disulfides and thioacetates synthesised from norephedrine and 2-amino-1,2-diphenyl-1-ethanol.[5] Derivatives of γ-amino arenethiols[6] and γ-amino arenediselenides[7] have also been shown to be effective catalysts for the enantioselective addition of diethylzinc to aldehydes.

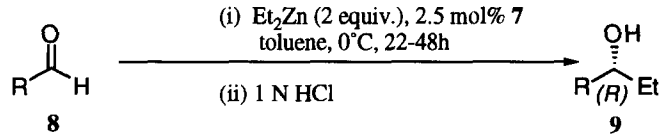
While the above findings for the diethylzinc addition to aldehydes represent significant advances in the generation of effective catalysts, these sulfur containing systems are derived from starting materials that are controlled substances, or toxic or expensive. Accordingly, we recently reported the use of a highly effective disulfide catalyst derived from L-proline.[8] However, we anticipated that disulfide catalysts derived from acyclic amino acids should also provide high enantioselectivities in the addition of diethylzinc to aldehydes. To this end a disulfide containing a phenyl group at the stereogenic centre was deemed to be appropriate and herein we report two independent syntheses from *(S)*-phenylglycine **1** and *(R)*-styrene oxide **5** of the disulfide **7**. Furthermore, we also report the use of the disulfide catalyst in the enantioselective addition of diethylzinc to a variety of aldehydes.

In the first route (Scheme 1), lithium aluminium hydride reduction of *(S)*-phenylglycine (74%) followed by alkylation (87%) with a slight excess of 1,5-dibromopentane afforded the amino alcohol **2**.[9] Mesylation of the amino alcohol **2** in ether afforded the crude aziridinium salt **3** which was directly treated with an excess of potassium thioacetate in water to provide the amino thioacetate **4** in 83% yield. Reduction of the amino thioacetate **4** with lithium aluminium hydride followed by aerial oxidation afforded the disulfide **7** in 65% yield.

An alternative synthesis of disulfide **7** was also carried out starting from *(R)*-styrene oxide **5**. Thus, using a procedure developed by Rossiter and co-workers,[10] *(R)*-styrene oxide **5** was ring opened with piperidine to afford the regioisomeric tertiary amine alcohol **6** in 82% yield. Treatment of the tertiary amine alcohol **6** with an excess of methanesulfonyl chloride and triethylamine afforded the crude aziridinium salt **3** which was directly converted into the amino thioacetate **4** in 60 % yield. This mesylation/thioacetate displacement proceeds with retention of configuration as the thioacetate anion opens the aziridinium salt **3** at the benzylic centre, this is in accord with the observations of Rossiter[10] for opening **3** with amine nucleophiles. The spectral characteristics (^1H, ^{13}C NMR and MS) of the amino thioacetates **4** were in complete agreement from both routes indicating that the mesylation/thioacetate displacement of the regioisomeric alcohols **2** and **6** afford only one regioisomeric β-amino thioacetate **4**. As before, reduction and aerial oxidation afforded the β-amino disulfide **7**.



Scheme 1



Scheme 2

With workable quantities of the disulfide **7** in hand we investigated the effectiveness of this catalyst in the enantioselective addition of diethylzinc to a range of aldehydes **8** (Scheme 2). As summarised in Table 1 under generalised conditions all the aldehydes afforded the corresponding *(R)*-secondary alcohols **9**. The highest enantiomeric excess of 80% was observed for the diethylzinc addition to 4-tolualdehyde (entry 3) and this

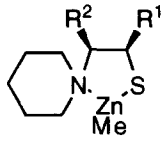
process has been shown to be more selective for other sulfur containing catalysts.[6,8] As with all catalysts for the diethylzinc addition to aldehydes, lower enantiomeric excesses are observed for the non aryl aldehydes (40 and 39% ee, entries 5 and 6, respectively).

Table 1 Enantioselective addition of diethylzinc to aldehydes in the presence of disulfide **7**[a]

Entry	R in RCHO	Yield (%)[b]	ee (%)[c]	config.[d]
1	Ph	69	61	*(R)*
2	4-ClC_6H_4	63	61	*(R)*
3	4-MeC_6H_4	78	80	*(R)*
4	2-Naphthyl	54	57	*(R)*
5	*(E)*-PhCH=CH	69	40	*(R)*
6	$PhCH_2CH_2$	30	39	*(R)*

[a] Reactions were carried out in toluene at 0°C for 22-48 h using two equivalents of Et_2Zn. [b] Isolated yields for chromatographically pure material. [c] Enantiomeric excesses determined by HPLC using a Daicel chiralcel OD column. [d] Absolute configuration determined from the elution order of the two enantiomers.[8]

The ee's observed for the 1-monosubstituted disulfide **7** are lower than those reported for other disulfides that are either *cis*-1,2-disubstituted[4,5], or are N,1-disubstituted.[8] The 1-monosubstituted disulfide **7** had been designed on the basis of the observations of Noyori *et al.* for β-amino alcohol catalysts for the dialkylzinc addition to aldehydes.[11] In this study Noyori had shown that while a *cis*-1,2-disubstitution pattern gives the best catalysts (≤98% ee), a 1-monosubstitution pattern can also give acceptable enantioselectivities (≤98% ee).



10 R^1 = Ph, R^2 = H
11 R^1 = Ph, R^2 = Me
12 R^1 = Ph, R^2 = Ph
13 R^1 = H, R^2 = Ph

In order to rationalize our results, a molecular mechanics[12] analysis of the postulated active species[4] for the phenyl substituted piperidinyl methylzinc derivatives **10-13** was carried out. Interestingly, these calculations showed that for the 1-phenyl derivative **10**, derived from disulfide **7**, that the stereodifferentiating phenyl group is directed away from the zinc (Zn-H-1' distance = 4.8Å). Since the zinc centre is the key reacting centre for this catalyst, and on the basis of the calculated transition state for β-amino alcohol zinc catalysts[13] then it would be anticipated from these modelling results that **10** would not be a highly enantioselective catalyst. The methylzinc derivative **11**, based on the ephedrine disulfide catalyst of Kang *et al.*,[5a] also gave a minimum energy conformation with the 1-phenyl group directed away from the zinc. However, the C-2 methyl group of **11** is directed over the five membered ring (Zn-H distance of 2.8 Å) and appears to be the effective stereodifferentiating group. A similar finding was observed for the methylzinc compound **12**, based on the disulfide of Kang *et al.*,[5b] where the C-2 phenyl group, apparently, is the effective blocking group (Zn-H-1' distance 2.6 Å) while the C-1 phenyl group is directed away from the zinc. In the light of these observations we also carried out molecular mechanics calculations on the C-2 phenyl substituted catalyst **13**. These studies indicated that the C-2 phenyl group in **13** was directed over the five membered ring (Zn-H-1' distance 2.4 Å) to provide an effective blocking group. Thus, these modelling studies indicate that for phenyl substituted

piperidinyl systems **10-13** the key stereodifferentiating substituent is located at C-2, this is in line with the results presented above as well as those of Kang *et al.*[5]

In summary, the scalemic β-amino disulfide **7** has been prepared from *(S)*-phenylglycine **1** in 4 steps and in 34.7% overall yield. A second synthesis of disulfide **7** was also carried out and this was achieved in 3 steps and 32% overall yield from *(R)*-styrene oxide **5**. The disulfide **7** was used as a catalyst in the enantioselective addition of diethylzinc to aldehydes. The enantioselectivity (39-80% ee) was found to be lower than other reported disulfides and this was postulated to be due to the absence of a stereodifferentiating group at C-2. In the light of the molecular mechanics calculations we are currently investigating the syntheses of other chiral β-amino sulfides catalysts with stereogenic centres at C-2.

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9. All new compounds gave satisfactory IR, ^{1}H NMR, ^{13}C NMR and elemental analysis and/or HRMS. The quoted yields are for homogeneous (≥95%) materials isolated by chromatography or kugelrohr distillation or recrystallization. Selected data: *(R)*-**7** $[\alpha]_D^{20}$ -131 (c=1, $CHCl_3$); found MH^+ 441.2388 $C_{26}H_{37}N_2S_2$ requires MH^+ 441.2398; δ_H (270 MHz) 7.32-7.11 (m, 5H, ArH), 3.67-3.58 (t, J = 7.4 Hz, 1H, H-1), 2.95-2.74 (AB of ABX, J = 13.2, 2.95, 2.7 Hz, 2H, C-2 CH_2), 2.38-2.29 (m, 4H, 2xCH_2N), 1.59-1.19 (m, 6H, 3xCH_2); δ_C (67.8 MHz) 141.0, 128.8, 128.6, 127.5 (all ArC), 63.3 (C-2), 54.7 (C-2',6'), 52.8 (C-1), 24.5 (C-3',5'), 22.9 (C-4'); ν_{max} (CCl_4) 3032, 2939, 1460, 1267, 1118.
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