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Aziridine sulfides and disulfides as catalysts for the enantioselective addition of diethylzinc to aldehydes†

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Received (in Corvallis, OR, USA) 4th June 2004, Accepted 1st July 2004
First published as an Advance Article on the web 14th September 2004

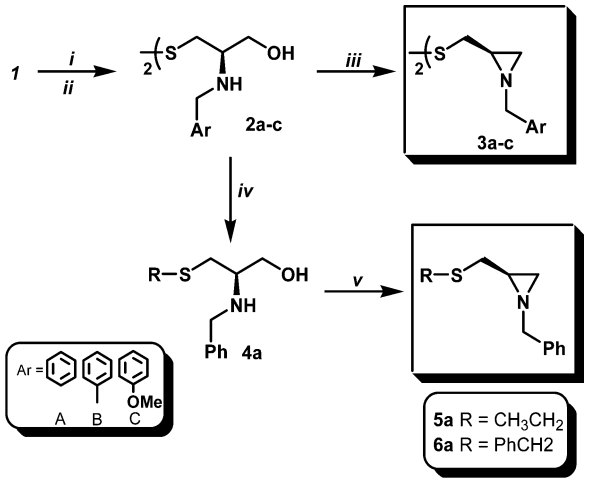
Chiral aziridine sulfides and disulfides were synthesized from readily available and inexpensive *R*-cysteine by a Mitsunobu reaction; their application in the addition of diethylzinc to aldehydes provides secondary alcohols with up to 99% *ee* and *S*-configuration.

Enantioselective carbon–carbon bond formation is one of the major challenges in organic synthesis. In recent years the catalytic enantioselective addition of dialkylzinc to aldehydes has attracted much attention because of its potential in the preparation of optically active secondary alcohols.[1] Most successful results have been obtained mainly by the use of chiral β-amino alcohols which cause catalytic asymmetric induction in the formation of the corresponding alcohols.[2] Recently, some reports exploring aziridines containing a β-amino alcohol moiety as effective chiral ligands in the asymmetric addition of diethylzinc to aldehydes have been published.[3] Furthermore, the efficient use of organochalcogen ligands has been recently reported for this purpose.[1b]

As part of our broader program to explore the preparation and use of chiral organochalcogen compounds in asymmetric catalysis,[4] we have shown previously that chiral aziridine sulfides are appropriate ligands for the palladium catalyzed allylic alkylation.[5]

In this paper, we give a preliminary account of our efforts towards the synthesis of *N*,*S* ligands as a new family of sterically and electronically adjustable chiral ligands and their application to the asymmetric addition of diethylzinc to aldehydes.

We have prepared the chiral aziridine disulfides **3a–c**, aziridine sulfides **5a** and **6a** from *R*-cysteine **1** in a few synthetic steps (Scheme 1). In the first step, *R*-cysteine was converted into disulfide amino alcohols **2a–c** by treatment with different aldehydes followed by $NaBH_4/I_2$ reduction[6] and air oxidation. Amino alcohols **2a–c** were then converted to chiral aziridines **3a–c** through a Mitsunobu reaction using DEAD and triphenylphosphine as reagents in a mild reaction.[7] Disulfide **2a** was reduced with $NaBH_4$ and alkylated, to give corresponding sulfide amino alcohols **4a**.[4e] Treatment of **4a** with DEAD and triphenylphosphine in THF afforded aziridine sulfides **5a** and **6a** with 69 and 61% yield respectively.



Scheme 1 *Reagents and conditions*: i) EtOH, ArCHO; ii) $NaBH_4/I_2$, THF then O_2; iii) THF, PPh_3, DEAD; iv) EtOH, NaOH, $NaBH_4$, RX; v) THF, PPh_3, DEAD.

With this sterically and electronically varied set of enantiopure organosulfur compounds in our hands, first we examined the efficiency of these compounds as chiral catalysts in the enantioselective addition of diethylzinc to benzaldehyde and the results are depicted in Table 1.

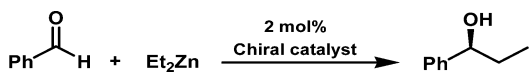
The ethylation of benzaldehyde in the presence of 2 mol% of catalyst **3a** gave the corresponding (1*S*)-phenylpropanol in a high yield (82%) and an enantiomeric excess of 87% (entry 1). It is noteworthy that the temperature has a considerable impact on the enantioselectivity. Carrying out the reaction at 0 °C for a longer reaction time, the *ee* has increased to 99% (entry 2). Ligands **3b** and **3c** were evaluated under the same experimental conditions. In the diethylzinc addition to benzaldehyde (entry 3) the catalyst **3b** provided comparable chemical yields and enantioselectivity to **3a**. Ligand **3c** afforded low enantioselectivity (entry 4).

When the ligands **5a** or **6a** were tested, the (1*S*)-phenylpropanol was obtained with moderate yields and *ee* (entries 5 and 7). An increase in the enantioselectivity was gained again by lowering the temperature to 0 °C for a longer reaction time (entries 6 and 8).

The results collected in Table 1 reveal that the disulfide catalysts **3a** and **3b** are highly efficient in the enantioselective addition of diethylzinc to benzaldehyde at 0 °C with a predominant formation of (1*S*)-phenylpropanol, and aziridine sulfides **5a** and **6a** give (*S*)-alcohols in a lower *ee*.

The active catalyst is most likely to be the corresponding ethylzinc thiolate, obtained from disulfide cleavage by diethylzinc as described by Kellogg.[9] However, this likely process was not

Table 1 Enantioselective addition of diethylzinc to benzaldehyde using 2 mol% of the chiral ligands **3a–c**, **5a** and **6a**[a]



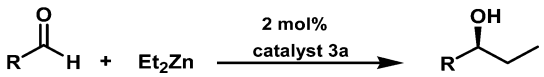
Entry	Catalyst	*t* (h)	*T* (°C)	Yield[b] (%)	*ee* (%) [config.][c]
1	**3a**	24	r.t.	82	87 [*S*]
2	**3a**	48	0	61	> 99 [*S*]
3	**3b**	48	0	60	> 99 [*S*]
4	**3c**	48	0	58	56 [*S*]
5	**5a**	24	r.t.	49	41 [*S*]
6	**5a**	48	0	42	65 [*S*]
7	**6a**	24	r.t.	46	37 [*S*]
8	**6a**	48	0	57	76 [*S*]

[a] Reactions were carried out in toluene. [b] Determined by GC analysis. [c] % enantiomeric excess was determined by chiral GC using a Hydrodex-β-3P column and comparison with the optical rotation reported.[8]

† Electronic supplementary information (ESI) available: spectroscopic data for all new compounds as well as detailed experimental procedures. See http://www.rsc.org/suppdata/cc/b4/b408537j/

DOI: 10.1039/b408537j

Table 2 Addition of diethylzinc to various aldehydes in the presence of 2 mol% of catalyst **3a**



Entry	Aldehyde	Yield[a] (%)	*ee* (%) [config.][b]
1	benzaldehyde	61	> 99 [*S*]
2	4-chlorobenzaldehyde	77	94 [*S*]
3	4-anisaldehyde	40	75 [*S*]
4	4-tolualdehyde	73	87 [*S*]
5	1-naphthaldehyde	55	89 [*S*]
6	pyridinecarboxaldehyde	92	97 [*S*][c]
7	phenylacetaldehyde	58	89 [*S*][c]
8	hexanal	62	86 [*S*][c]
9	decanal	61	40 [*S*][c]

[a] Determined by GC analysis. [b] % *ee* determined by chiral GC using a Hydrodex-β-3P column and comparison with the optical rotation reported.[8] [c] % *ee* determined by HPLC using Chiralcel OD column.

rigorously proven for our catalysts, but offers the future prospect of cutting the amount of catalyst required in half, if the thiol-form is applied.

In order to better investigate the reactivity of such ligands, the most efficient aziridine **3a** was used in the enantioselective addition of diethylzinc to various aromatic and aliphatic aldehydes. In all cases the reactions were performed in toluene at 0 °C and the results are summarized in Table 2.

All the reactions led to the predominant formation of the respective (*S*)-alcohols with different levels of enantiocontrol.

The highest *ee* for the diethylzinc addition to aromatic aldehydes were observed (*ee* from 75 to > 99% and yields ranging from 40 to 92%, entries 1–7). The catalytic diethylzinc addition to an aldehyde possessing an electron-withdrawing group at the aromatic ring proceeded with higher enantioselectivity than the addition to the aldehydes with an electron-donating group (entries 2–4), probably due to an electronic effect.[10] The addition reaction with pyridinecarboxaldehyde showed a similar result, but naphthaldehyde and phenylacetaldehyde showed low enantioselectivity compared to that of benzaldehyde (entries 5–7).

Additions to the less reactive and most often problematic aliphatic aldehydes gave distinct results. The tail-length of linear aliphatic aldehydes has a dramatic effect on the observed enantioselectivity. The best result was observed for diethylzinc addition to hexanal (86% *ee*, entry 8). A four carbon extension decreases dramatically the enantiomeric excess to 40% (entry 9).

The stereochemistry of the products is in accordance with the mechanistic rationalization described in the work of Noyori.[2c,8] Transition state structure **A** is favored over **B** because it avoids axial positioning of the aldehyde R-group and by this destabilizing 1,3 interactions between ethyl of zinc and the R-group [Fig. 1].

In summary, several inexpensive chiral aziridine sulfides and disulfides were synthesized in a straightforward synthetic route from commercial *R*-cysteine as the starting material. Preliminary results from studies of their behavior as ligands in the enantioselective addition of diethylzinc, showed a great catalytic potential.

Further studies are in progress in our laboratories concerning other metal-catalyzed asymmetric reactions and will be reported in due course.

We are grateful to the CAPES, CNPq and FAPERGS for financial support. E. F. A. thanks CAPES for a Ph. D. fellowship and M. W. P. thanks CNPq for a Master fellowship.

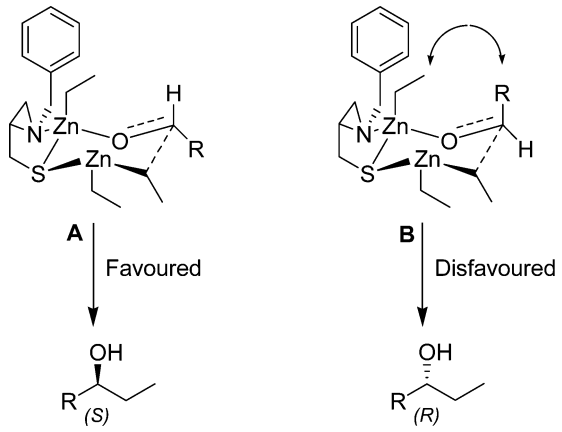


Fig. 1 Transition state model.

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