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New *N,O*-heterocycles derived from (*R*)-cysteine as catalysts in the enantioselective diethylzinc addition

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Abstract

The synthesis of several β-amino alcohols derived from (*R*)-cysteine with morpholine and aza-crown ether structures is described. These ligands were tested in the addition of diethylzinc to benzaldehyde and enantiomeric excesses up to 92% were obtained.

After the primary work of Oguni et al.[1,2] on the addition of diethylzinc to benzaldehyde, many investigations have been carried out on this stereoselective C–C bond formation over the last 15 years. In this connection chiral amino alcohols, usually synthesized from α-amino acids, have shown to be effective catalysts.[3–5] Usually, the amino group of this type of ligand is secondary or tertiary. To the best of our knowledge *N,O*-heterocycles have never been applied in the enantioselective addition of dialkylzinc to aldehydes before. For this reason, we were encouraged to synthesize amino alcohols with a tertiary amino group as a part of an *N,O*-heterocycle.[6] Therefore, some of the new compounds presented in this paper are aza crown ethers since it is also well-known that chiral crown ethers are very good catalysts with high stereoselective induction in other C–C bond formation reactions.[7–9]

Starting from (*R*)-cysteine **1**, the amino alcohols **2a** and **2b** were prepared according to the following procedure (Scheme 1): after protection of the thiol as an *iso*-propyl thioether[10] and esterification of the amino acid, the addition of the appropriate Grignard reagent to this ester resulted in the formation of the amino alcohols **2a** and **2b**.[11]

Treatment of these compounds with the corresponding polyethyleneglycol diiodo derivatives in the presence of Na_2CO_3 in refluxing acetonitrile led, after chromatographic work-up, to the *N,O*-heterocycles **3**–**6** in moderate yields of up to 50%.[12]

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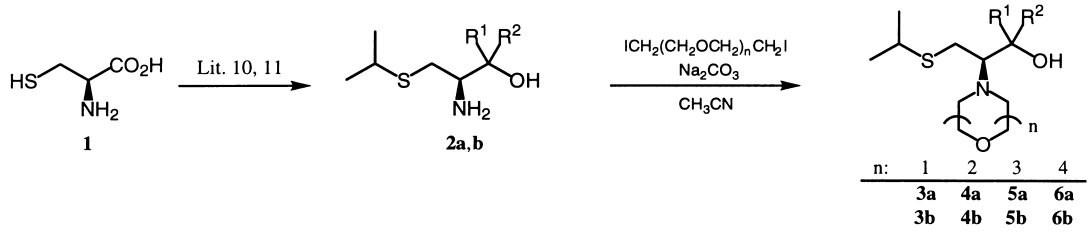

Scheme 1. (a) $R^1=R^2=C_2H_5$; (b) $R^1,R^2=-(CH_2)_4-$

Ligands **2–6** were tested in the enantioselective addition of diethylzinc to benzaldehyde. According to the typical procedure[13] the reaction was carried out at 22°C, for 48 h and at a catalyst concentration of 5 mol% (relative to benzaldehyde). The chemical yields were always in the range of between 78 and 85%.

As expected, the primary amino derivatives **2a–b** (Table 1, entries 1–2) induced low ees in the production of 1-phenylpropan-1-ol. However, the ee value drastically increased if the nitrogen atom was part of a morpholine ring: with ligands **3a** and **3b** (Table 1, entries 3–4) an ee of 92% and 71%, respectively was attained. Changing to bigger heterocycles, there appears to be a non-monotonic correlation between ring size and enantioselectivity: ee values decreased from six- to twelve-membered rings (Table 1, entries 3–8) but increased again for the aza-15-crown-5 **6a** and **6b** (Table 1, entries 9–10). Besides, although ees were very low in the presence of **5a** and **5b** (Table 1, entries 7–8), it is noteworthy that the dominant enantiomer has *S*-configuration in these cases.

Table 1
Enantiomeric excess of the addition of diethylzinc to benzaldehyde; product: 1-phenylpropan-1-ol

entry	catalyst	*e.e.* [%][a] (config.)
1	**2a**	23 (*R*)
2	**2b**	24 (*R*)
3	**3a**	92 (*R*)
4	**3b**	71 (*R*)
5	**4a**	48 (*R*)
6	**4b**	70 (*R*)
7	**5a**	5 (*S*)
8	**5b**	11 (*S*)
9	**6a**	33 (*R*)
10	**6b**	38 (*R*)

a) Determined by GC analysis (SGE Cydec-B, chiral); absolute configuration was detected *via* chiral GC analysis by comparison with authentic samples.

Further investigations including molecular modelling are in progress to understand the role of the aza polyoxa rings.

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