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Enantioselective diethylzinc addition to aldehydes using azetidine-derived chiral catalysts

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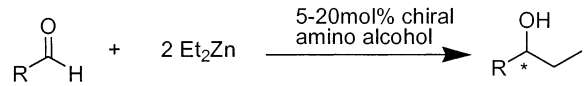
Abstract—High levels of enantioselectivity have been achieved in the diethylzinc addition to both aromatic and aliphatic aldehydes, employing readily available *N*-substituted-azetidinyl(diphenylmethyl)methanols as chiral catalysts.

One of the most extensively studied methodologies for asymmetric carbon–carbon formation is the nucleophilic addition of organometallic reagents to aldehydes, catalysed by appropriate chiral ligands. Employing this methodology for the reaction of aromatic aldehydes with diethylzinc catalysed by various chiral β-amino alcohols, 1-aryl-1-ethanols have been obtained in both excellent chemical yield and enantioselectivity[1] (Scheme 1). In contrast, however, the enantioselectivity for aliphatic aldehydes is usually considerably lower.[2]

In the course of our ongoing studies on the synthesis and application of small-ring functionalised heterocycles,[3–7] we recently described the application of *N*-tritylaziridinyl(diphenyl)methanol **1**[8a] and its polymer bound analogue[8b] as chiral catalysts in the diethylzinc reaction with aldehydes. As these catalysts proved to be very effective in the diethylzinc reaction, the question arose as to whether amino carbinols derived from azetidines would serve the same purpose. One example of such a ligand, viz. **2**, has been prepared from the non-proteinogenic amino acid azetidine-2-carboxylic acid.[9] This ligand showed excellent enantioselectivity for several aromatic aldehydes, but gave only moderate induction in the case of nonanal. Recently, a C_2-symmetric ligand **3** has been reported,[10] which showed similar



Scheme 1. Enantioselective addition of diethylzinc to aldehydes catalysed by a chiral amino alcohol.

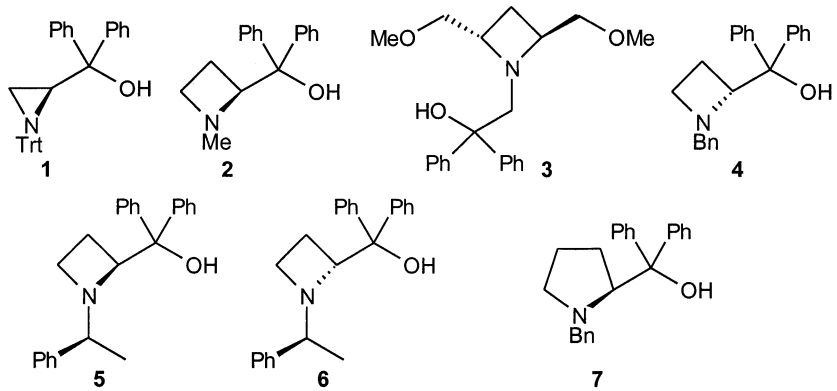


Figure 1. Small-ring heterocyclic amino alcohols used as chiral catalysts for the diethylzinc addition to aldehydes.

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Table 1. Enantioselective addition of diethylzinc to aromatic aldehydes catalysed by several small-ring heterocyclic amino alcohols

Entry	Aldehyde	Ligand	Yield (%)	*Ee*[a] (%)	Conf.[b]
1	Benzaldehyde	**2**	–	98	*S*[9]
2	Benzaldehyde	**3**	99	92	*S*[10]
3	Benzaldehyde	**4**	62	88	*R*
4	Benzaldehyde	**5**	75	35	*S*
5	Benzaldehyde	**6**	85	95	*R*
6	Benzaldehyde	**7**	92	72	*S*[12]
7	Anisaldehyde	**2**	–	100	*S*[9]
8	Anisaldehyde	**4**	91	>99	*R*
9	Anisaldehyde	**7**	94	79	*S*[12]
10	Anisaldehyde	**3**	92	92	*S*[10]
11	*p*-Cl-Benzaldehyde	**4**	80	96	*R*
12	Tolualdehyde	**4**	85	95	*R*

[a] Determined by chiral GC (Beta-DEX® 120 fused silica column by Supelco).
[b] Determined by comparison with the absolute optical rotation given in the literature.

behaviour. Bearing in mind that fine-tuning of the ligand structure may lead to substantial improvement of the enantioselectivity, we decided to test the potential catalysts **4**–**6** (see Fig. 1).

These ligands are readily accessible from the corresponding azetidinecarboxylic methyl esters, which are available in multigram quantities using methodologies previously developed in our laboratory.[11] Thus, treatment of methyl 2,4-dibromobutyrate with benzylamine in the presence of a co-base yields racemic methyl *N*-benzyl azetidine-2-carboxylate. Ammoniolysis using *Candida antarctica* lipase selectively converts the (*S*) ester into the corresponding amide, from which the remaining (*R*) ester can be easily separated. Similarly, treatment of methyl 2,4-dibromobutyrate with optically pure (*S*)-α-methylbenzyl amine, followed by chromatographic separation of the diastereoisomeric esters, gives the desired (*S*,*R*)- and (*S*,*S*)-methyl *N*-methylbenzylazetidine-2-carboxylates in optically pure form. Treatment of the three esters with phenylmagnesiumbromide leads to the potential catalysts **4**, **5** and **6**, respectively.

Application of catalyst **4** gave very high enantioselectivities for several substituted benzaldehydes (see Table 1).

We then tested the enantioselectivity of ligands **5** and **6**, to establish the influence of a second stereogenic centre. The enantioselectivity for these ligands is quite contrasting. For ligand **6**, a high *ee* of 95% was obtained whilst for the diastereomeric ligand **5**, an *ee* of only 35% was achieved. Clearly, this is a case of match/mismatch due to the presence of the second chiral centre. It should be noted, however, that despite this extra chiral centre, the absolute configuration of the secondary alcohols is solely determined by the configuration of the azetidine ring. It is interesting to compare the results obtained with these four-membered ring heterocyclic ligands with those for ligand **7**, derived from proline.[12] The more strained ring system clearly exhibits a better enantioselectivity, possibly due to the inherent conformational rigidity, which results in a better-defined environment around the prochiral reaction centre.

The best ligand, viz. **6**, was also tested with some aliphatic aldehydes. It was found that this catalyst is also very effective in the enantioselective addition of diethylzinc to these aliphatic aldehydes. Enantioselectivities ranging from 77 to 97% were obtained, which are similar to the ones previously observed with ligand **1**[8] and which can be classified as excellent for these aldehydes (see Table 2).

In conclusion, we have developed novel highly effective ligands for the enantioselective addition of diethylzinc to aldehydes. The results obtained with these ligands in the case of aromatic aldehydes are comparable to those reported for ligands **2** and **3**, whereas the effectiveness of catalyst **6** clearly exceeds that of ligand **2** in the case of aliphatic aldehydes. It should be noted that ligand **6** is readily available, in contrast to catalyst **2**, the synthetic accessibility of which is hampered by the high price and limited commercial availability of (*S*)-azetidine-2-carboxylic acid. Currently, we are investigating the application of the ligands **4**–**6** in other organometallic reactions, the results of which will be reported in due time.

Table 2. Enantioselective addition of diethylzinc to aliphatic aldehydes catalysed by azetidinol **6**

Aldehyde	Ligand	Yield (%)	*Ee*[a] (%)	Conf.[b]
Cyclohexane–carboxaldehyde	**6**	80	97	*R*
Isovaleraldehyde	**6**	45	90	*R*
Nonaldehyde	**6**	65	83	*R*[c]
Nonaldehyde	**2**	–	68	*S*
Butyraldehyde	**3**	94	65	*S*[10]
Undecylic aldehyde	**6**	80	77[c]	*R*[c]

[a] Determined by chiral GC (Beta-DEX® 120 fused silica column by Supelco).
[b] Determined by comparison with the absolute optical rotation given in the literature.
[c] Determined by ^{19}F NMR of Mosher's ester.[13]

The following procedure is representative: Ligand **4** (20 mol%) was dissolved in dry toluene (15 ml) and benzaldehyde (5 mmol) was added. The reaction mixture was cooled to 0°C before addition of diethylzinc (1.0 M in hexane, 10 mmol, 10 ml) and the resulting solution was stirred at room temperature overnight. The reaction mixture was quenched by addition of saturated ammonium chloride solution (5 ml) and the product was extracted with ether. The organic phase was dried over $MgSO_4$ and the solvents where removed in vacuo. The crude product was purified by column chromatography (Hex./EtOAc, 4:1 (v/v)).

Acknowledgements

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