Tetrahedron: Asymmetry Vol. 4, No. 4, pp. 637-640, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

CATALYTIC ENANTIOSELECTIVE ADDITION OF DIETHYLZINC TO ALDEHYDES: APPLICATION OF A NEW BICYCLIC CATALYST

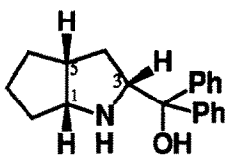
Sabine Wallbaum and Jürgen Martens*

Fachbereich Chemie der *Carl von Ossietzky* Universität Oldenburg
Ammerländer Heerstraße 114-118, D-2900 Oldenburg i.O.

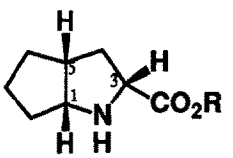
(*Received in UK 9 February* 1993)

Abstract : The optically active β-amino alcohol (1*R*,3*R*,5*R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane (1*R*,3*R*,5*R*)-**1** derived from a bicyclic proline analogue catalyzes the enantioselective addition of diethylzinc to various aldehydes. The resulting chiral secondary alcohols are obtained in high optical yields up to 100 % under mild reaction conditions. The bicyclic catalyst gives much better results than the corresponding (*S*)-proline derivative (*S*)-**4**.

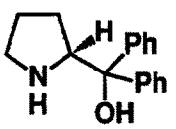
Amino acid-based chiral auxiliaries have attracted much attention over the last decade[1]. In particular structurally rigid pyrrolidine derivatives often lead to very high asymmetric inductions in organic syntheses[2]. One of the most studied processes in the field of asymmetric synthesis is the carbon-carbon bond forming reaction of organometallic reagents to carbonyl substrates in the presence of chiral ligands. In particular, increasing interest has recently been focused on the study of enantioselective additions of dialkylzinc to aldehydes[3]. *Oguni* and *Omi* found that optically active amino alcohols as ligands in such reactions not only accelerate but also direct the stereochemical outcome in the absolute sense[4].



(1*R*,3*R*,5*R*)-**1**



(1*R*,3*R*,5*R*)-**2** (R=H)
(1*R*,3*R*,5*R*)-**3** (R=CH_2Ph)



(*S*)-**4**

In the course of our studies to prepare new chiral auxiliaries from natural and unnatural α-amino acids we introduced (1*R*,3*R*,5*R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane[5] (1*R*,3*R*,5*R*)-**1** as a new efficient homogeneous catalyst for catalytic asymmetric borane reductions of prochiral ketones. In this paper we describe the application of (1*R*,3*R*,5*R*)-**1** as a new catalyst in the enantioselective addition of diethylzinc to aldehydes.

The precursor of the new catalyst is the bicyclic proline analogue (1*R*,3*R*,5*R*)-2-azabicyclo[3.3.0]octane carboxylic acid (1*R*,3*R*,5*R*)-**2**. This non proteinogenic α-amino acid is recovered from waste streams of the resolution step in the production of the highly potent angiotensin converting enzyme (ACE) inhibitor Ramipril[6]. The industrial production of (1*S*,3*S*,5*S*)-**2** is based on the optical resolution of the racemic benzyl ester derivatives (1*RS*,3*RS*,5*RS*)-**3** *via* diastereomeric salts with an enantiomerically pure chiral carboxylic acid. Thus, the unnatural amino acid **2** is advantageously accessible in two enantiomeric forms, (1*R*,3*R*,5*R*)-**2** and (1*S*,3*S*,5*S*)-**2**. Some new chiral auxiliaries based on (1*S*,3*S*,5*S*)-**2** and its enantiomer were synthesized in our laboratory previously[7].

(1*R*,3*R*,5*R*)-3-(Diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane (1*R*,3*R*,5*R*)-**1** is obtained *via* a *Grignard* reaction from the benzyl ester hydrochloride (1*R*,3*R*,5*R*)-**3**·HCl.

In order to examine the effect of the new catalyst the reaction of diethylzinc with benzaldehyde as the model substrate in the presence of β-amino alcohol (1*R*,3*R*,5*R*)-**1** under various reaction conditions was investigated.

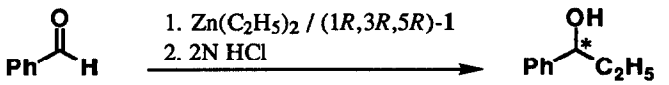


Table 1: Enantioselective addition of diethylzinc to benzaldehyde in the presence of catalyst (1*R*,3*R*,5*R*)-**1** and (*S*)-**4** under various reaction conditions.

entry	catalyst	catalyst concentration [mol%]	1-phenylpropan-1-ol: temperature [°C]	1-phenylpropan-1-ol: optical yield* [%]
1	(1*R*,3*R*,5*R*)-**1**	10	– 20	100 (*R*)
2	(1*R*,3*R*,5*R*)-**1**	10	20	100 (*R*)
3	(1*R*,3*R*,5*R*)-**1**	5	20	99 (*R*)
4	(*S*)-**4**	5	20	24 (*S*)
5	(1*R*,3*R*,5*R*)-**1**	1	20	45 (*R*)
6	(1*R*,3*R*,5*R*)-**1**	10	30	97 (*R*)
7	(1*R*,3*R*,5*R*)-**1**	10	40	93 (*R*)
8	(1*R*,3*R*,5*R*)-**1**	10	50	93 (*R*)

*.) The optical yield was calculated from the maximum rotation $[\alpha]_D^{\alpha} = -45.45$ (c = 5.15, chloroform) for (*S*)-1-phenyl-1-propanol[8].

In a typical procedure 20 mmol of a 1.1 M solution of diethylzinc in abs. toluene was added to a solution of the respective amount of catalyst (1*R*,3*R*,5*R*)-**1** in dry toluene at –20° C under an inert atmosphere. The mixture was allowed to reach room temperature and treated with 20 mmol of the respective aldehyde, then the resulting mixture was stirred for 48 h at room

temperature. The reaction was quenched with 2N hydrochloric acid, the organic layer was separated, and the aqueous layer was extracted with diethyl ether. The combined organic layers were washed with 3.7 % sodium hydrogen sulfite solution, concentrated sodium hydrogen carbonate solution and water. After drying the solvent was evaporated under reduced pressure and the residue was distilled under vacuum. The catalyst could be recovered from the aqueous layer. After storage at low temperatures the catalyst-hydrochloride (1*R*,3*R*,5*R*)-**1**·HCl can be filtered off, worked up and reused.

As can be seen from Table 1 the new β-amino alcohol (1*R*,3*R*,5*R*)-**1** serves as an efficient catalyst at a wide range of temperature. Even at 50 °C an optical purity of 93 % was reached. In each case (*R*)-1-phenylpropan-1-ol was formed preferentially. We also investigated the influence of the catalyst concentration on optical yields. The new catalyst works even well when only 5 mol% were applied to the reactions. It is interesting to remark that under identical reaction conditions (5 mol% catalyst, room temperature) the corresponding (*S*)-proline derivative (*S*)-2-diphenylhydroxymethyl)-pyrrolidine[9] (*S*)-**4** gave (*S*)-1-phenylpropan-1-ol with 24 % *op* only (entry 4). This could be due to steric influence being less efficient with the monocyclic catalyst compared to the bicyclic analogue. With 1 mol% catalyst concentration the optical yield decreased (entry 5). In the following all reactions were carried out at room temperature with 5 mol% catalyst concentration.

The new bicyclic catalyst (1*R*,3*R*,5*R*)-**1** was applied sucessfully to the addition of diethylzinc to various aromatic and aliphatic aldehydes. Results are summarized in Table 2.

Table 2: Enantioselective addition of diethylzinc to various aldehydes in the presence of 5 mol% (1*R*,3*R*,5*R*)-**1** at room temperature.

		chiral alcohol	
entry	aldehyde	chemical yield [%]	optical yield* [%]
1	2-naphtaldehyde	98	87 (*R*)[a]
2	furan-2-aldehyde	98	67 (*R*)[b]
3	4-chlorobenzaldehyde	98	99 (*R*)[c]
4	4-methylbenzaldehyde	87	100 (*R*)[d]
5	heptanale	78	66 (*R*)[e]
6	isovaleraldehyde	22	86 (*R*)[f]

*.) The optical yields were calculated from optical rotations based on the following maximum rotations of each alcohol: a.) $[\alpha]_D^{22} = -26.6$ (c = 3.35, benzene) for (*S*)-1-(2-naphthyl)propan-1-ol in 97 % ee[10], b.) $[\alpha]_D^{21} = +12.6$ (c = 2.09, chloroform) for (*R*)-1-(2-furyl)propan-1-ol in 95 % ee[11], c.) $[\alpha]_D = +23.7$ (c = 5.05, benzene) for (*R*)-1-(4-chlorophenyl)propan-1-ol in 90 % ee[12], d.) $[\alpha]_D = -39.2$ (c = 1, benzene) for (*S*)-1-(4-methylphenyl)propan-1-ol[13], e.) $[\alpha]_D^{24} = +9.07$ (c = 7.2, chloroform) for (*S*)-3-nonanol in 88 % ee[14], f.) $[\alpha]_D^{21} = -20.3$ (c = 5.25, ethanol) for (*R*)-5-methyl-hexan-3-ol[15].

In each case the (*R*)-configured secondary alcohol was obtained. The best optical yields were obtained with aromatic aldehydes. Thus, the reaction of 4-chlorobenzaldehyde and 4-methylbenzaldehyde afforded the corresponding carbinols in excellent optical purities (99% *op* respectively 100% *op*). The heterocyclic carbonyl compound furan-2-aldehyde was converted into the corresponding carbinol with 67% *op*. With aliphatic aldehydes the highest optical yield (86% *op*) was achieved when isovaleraldehyde was applied to the reaction with diethylzinc. The long chain aldehyde nonanal gave a moderate result (66% *op*) only.

It has been shown that the bicyclic β-amino alcohol (1*R*,3*R*,5*R*)-3-(diphenylhydroxymethyl)-2-azabicyclo[3.3.0]octane (1*R*,3*R*,5*R*)-**1** serves as an efficient homogeneous catalyst in enantioselective additions of diethylzinc to aldehydes. Further studies in order to improve the optical yields are under investigation.

Acknowledgements : Thanks are due to Schering AG, Hoechst AG, Degussa AG and the Fonds der Chemischen Industrie for support.

References

1. J. Martens, *Top. Curr. Chem.* **1984**, *125*, 165.
2. (a) J. Martens, *Chem.-Ztg.* **1986**, *110*, 169. (b) K. Drauz, A. Kleemann, J. Martens, *Angew. Chem.* **1982**, *94*, 590; *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 584. (c) D. Enders, H. Eichenhauer, *Chem. Ber.* **1979**, *112*, 2933. (d) M. Asami, H. Ohno, S. Kobayashi, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1978**, *51*, 1869. (e) S. Terashima, S. Jew, K. Koga, *Chem. Lett.*, **1977**, 1109.
3. Reviews: (a) K. Soai, S. Niwa, *Chem. Rev.*, **1992**, *92*, 833. (b) R. Noyori, M. Kitamura, *Angew. Chem.* **1991**, *103*, 34; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 49. (c) R. Noyori, S. Suga, K. Kawai, S. Okada, M. Kitamura, N. Oguni, M. Hayashi, T. Kaneko, Y. Matsuda, *J. Organomet. Chem.* **1990**, *382*, 19.
4. N. Oguni, T. Omi, *Tetrahedron Lett.* **1984**, *25*, 2823.
5. S. Wallbaum, J. Martens, *Tetrahedron: Asymmetry* **1991**, *2*, 1093.
6. (a) H. Metzger, R. Maier, C. Sitter, H. O. Stern, *Arzneim.-Forsch./Drug Res.* **1984**, *34 (II)*, 1402. (b) H. H. Donaubauer, D. Mayer, *Arzneim.-Forsch./Drug Res.* **1988**, *38 (I)*, 14. (c) R. Henning, U. Lerch, H. Urbach, *Synthesis* **1989**, 265. (d) H. Urbach, R. Henning, *Heterocycles* **1989**, *28*, 957.
7. (a) J. Martens, S. Lübben, R. Bhushan, *Tetrahedron Lett.* **1989**, *30*, 7181. (b) J. Martens, S. Lübben, *Arch. Pharm. (Weinheim)* **1991**, *324*, 59. (c) J. Martens, S. Lübben, *Liebigs Ann. Chem.* **1990**, 949. (d) J. Martens, S. Lübben, *Tetrahedron* **1991**, *47*, 1205.
8. R. H. Pickard, J. Kenyon, *J. Chem. Soc.* **1914**, *105*, 1115.
9. (a) U. Kraatz, German Patent DE 3609152 A1, **1987**. (b) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551.
10. M. Watanabe, S. Araki, Y. Butsugan, *J. Org. Chem.* **1991**, *56*, 2218.
11. T. Kametani, M. Tsubuki, Y. Tatsuzaki, T. Honda, *J. Chem. Soc., Perk. Trans. I* **1990**, 639.
12. S. Niwa, K. Soai, *J. Chem. Soc., Perk. Trans. I* **1991**, 2717.
13. P. A. Chaloner, S. A. R. Perera, *Tetrahedron Lett.* **1987**, *26*, 3013.
14. K. Soai, S. Yokoyama, T. Hayasaka, *J. Org. Chem.* **1991**, *56*, 4264.
15. J. L. Coke, R. S. Shue, *J. Org. Chem.* **1973**, *38*, 2210.