Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 10, pp. 1529–1530, 1997

Printed in Great Britain
PII: S0957-4166(97)00150-X
0957-4166/97 $17.00 + 0.00

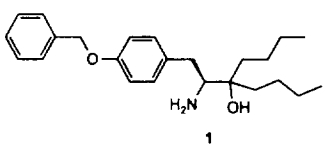
Novel ligands derived from *S*-tyrosine for the enantioselective addition of diethylzinc to aldehydes

Juliane Beliczey, Guido Giffels, Udo Kragl * and Christian Wandrey
Forschungszentrum Jülich GmbH, Institut für Biotechnologie, 52425 Jülich, Germany

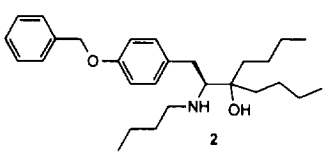
Abstract: (*S*)-2-N,N-dibutylamino-3-butyl-1-[4-(4-phenylmethoxy)-phenyl]heptan-3-ol **3** based on (*S*)-tyrosine has been synthesised. For the diethylzinc addition to both aliphatic and aromatic aldehydes, high enantiomeric excesses up to 95% were obtained. © 1997 Elsevier Science Ltd

Reactions for asymmetric carbon–carbon bond formation have been of interest for many years. One important reaction that leads to optical active secondary alcohols is the addition of diethylzinc to aldehydes[1–4]. The asymmetric induction can be achieved with among other compounds, chiral β-amino alcohols. While enantiomeric excesses (ee's) up to >99% can be achieved with aromatic aldehydes, in the reaction with aliphatic aldehydes ee's >90% are seldom obtained[3]. Therefore the aim of our work has been to synthesise chiral amino alcohols which lead to high ee's particularly with aliphatic aldehydes. Within the scope of our activities including research on polymer enlarged ligands in enantioselective homogeneous catalysis[5,6] ligands being based on tyrosine have been investigated. The hydroxy group remote from the asymmetric center involved in the catalysis offers the opportunity to bind the ligand to soluble polymers in an easy way[7], which allows its utilisation in a membrane reactor[5].

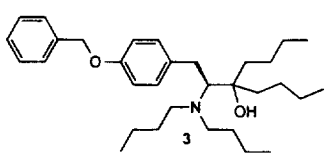
For inductors derived from (L)-valine it has been shown[8,9] that an increasing number of aliphatic substituents in the ligand procures high ee's with aliphatic aldehydes. Also it is known[4] that for N,N-dialkylnorephedrine the n-butyl group is most suitable. The transfer of this observation to the tyrosinol system led to the ligands **1**, **2** and **3**[10].



1



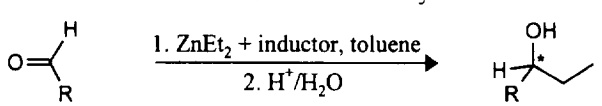
2



3

1 was prepared by Grignard addition of butylmagnesiumbromide to tyrosinethylester and benzylation of the phenolic hydroxy function. Alkylation with iodobutane in the presence of potassium carbonate procured **2** and **3**.

All three inductors have been used in the addition of diethylzinc to benzaldehyde (Table 1).



In the case of the complete alkylation of the amino function the stereoselectivity of the reaction is reversed. The special merits of ligand **3** are high activity and enantioselectivity. The utilisation of **3** in the reaction with various aldehydes gave the following results (Table 2):

* Corresponding author. Tel: +49-2461-616772; Fax: +49-2461-613870; Email: u.kragl@kfa-juelich.de

Table 1. Enantioselective addition of $ZnEt_2$ (2 eq) to PhCHO in presence of 10 mol% inductor in toluene

Inductor	Temp. [°C]	ee [%][a]	Config.	Conversion [%][a]	Time [h]	Selectivity [%][b]
1	0	81.8	S	93	31	99
2	0	7	S	66	31	97
3	0	93	R	100	10	100
3	rt.	92	R	100	5	100

[a] determined by GC on a chiral β-cyclodextrine phase;
[b] as side reaction the reduction of the aldehyde to the primary alcohol can take place.

Table 2. Enantioselective addition of $ZnEt_2$ (2 eq) to aldehydes in presence of 10 mol% **3** in toluene

Aldehyde	ee [%][a]	Conversion [%][a]	Time [h]	Selectivity [%][b]
Hexanal	86	100	48	not det.
Heptanal	86	100	48	not det.
p-Chlorobenzaldehyde	95	98	5	100
Benzaldehyde	93	98	8	100

[a, b] see Table 1.

Especially the enantiomeric excesses achieved with the aliphatic aldehydes are remarkable. For the addition of diethylzinc to hexanal with **3** as ligand an ee of 86% was reached which is similar to the highest value reported so far[4**] for this aldehyde.

3 was also bound to a soluble polystyrene derivative enabling retention by a membrane, and utilised in the reaction with benzaldehyde under same conditions. The reaction proceeded with the same selectivity and stereoselectivity as found for the free ligand. The conversion reached 70% after 10 h.

Acknowledgements

This work was supported by the Deutsche Forschungsgemeinschaft-SFB 380: "Asymmetrische Synthesen mit chemischen und biologischen Methoden"

References

1. Kitamura, K.; Okoda, S.; Suga, S.; Noyori, R., *J. Am. Chem. Soc.*, **1989**, *111*, 4028–4036.
2. Chaloner, P. A.; Langadianou, E., *Tetrahedron Letters*, **1990**, *31*, 5185–5188.
3. Soai, K.; Niwa, S., *Chem. Rev.*, **1992**, *92*, 833–856.
4. Soai, K.; Yokoyama, S.; Hayasaka, T., *J. Org. Chem.*, **1991**, *56*, 4264–4268. **88% with N,N-diphenylnorephedrine for heptanal as determined by optical rotation.
5. Kragl, U.; Dreisbach, C., *Angew. Chem Int. Ed. Engl.*, **1996**, *35*, 642–644; *Angew. Chem.*, **1996**, *108*, 684–685.
6. Dreisbach, C.; Wischnewski, G.; Kragl, U.; Wandrey, C., *J. Chem. Soc., Perkin Trans. 1*, **1995**, 875–878.
7. Itsuno, S.; Sakurai, Y.; Ito, K.; Maruyama, T.; Nakahama, S.; Fréchet, J. M. J., *J. Org. Chem.*, **1990**, *55*, 304–310.
8. Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L., *J. Org. Chem.*, **1994**, *59*, 4680–4682.
9. Delair, P.; Einhorn, C., *Tetrahedron*, **1995**, *51*, 165–172.
10. Compound **3** ^{1}H-NMR (400 MHz, $CDCl_3$): δ=0.6–0.94 (12H), 0.98–1.65 (21H), 2.01–2.93 (6H), 2.93–3.05 (1H), 4.93–5.07 (2H), 6.78–6.95 (2H), 7.0–7.19 (2H), 7.22–7.43 (5H).

(Received in UK 10 March 1997)