Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 1, pp. 31-34, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 $6.00+0.00

0957-4166(93)E0038-X

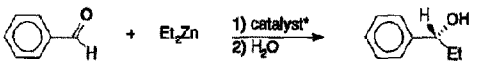
Sulfur Derivatives of Ephedra Alkaloids; New and Highly Efficient Chiral Catalysts.

Robert P. Hof, Martin A. Poelert, Nathalie C.M.W. Peper, Richard M. Kellogg*

Department of Organic and Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands

Abstract: Sulfur derivatives of ephedrine catalyze the 1,2-addition of diethylzinc to benzaldehyde in high enantiomeric excess. Disulfides and cyclic sulfide derivatives of these compounds serve the purpose very well, and the actual catalytically active species, containing zinc, has been extracted from the reaction mixture.

The pace of development in catalytic enantioselective synthesis is rapid.[1] An easy to perform and well documented reaction for testing the catalytic reactivity and enantiodifferentiating abilities of certain catalytic systems is the 1,2-addition of diethylzinc to aromatic aldehydes such as benzaldehyde (Eq. 1).[2]

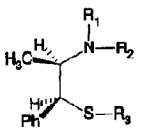


(R)-1-phenylpropanol

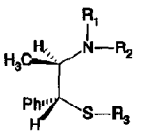
Eq. 1

Striking successes have been achieved using ß-amino alcohols as activators for this reaction, examples being ephedrine[3] and (-)-3-exo-(dimethylamino)isoborneol (DAIB),[4] which form the illustrated alcohol in excellent enantiomeric excess (e.e.).

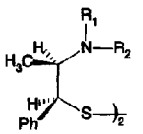
Many other chiral non-racemic ß-amino alcohols, both natural and synthetic, have been tested in this addition with varying success.[5] However, to the best of our knowledge, the use of sulfur analogs of these compounds, ß-amino thiols, has not been reported. The lack of straightforward synthetic routes to such compounds is undoubtedly one of the main reasons for this lack of activity. Recently, partly in conjunction with a long standing interest in the structure and reactivity of zinc thiolates as components of the active center of liver alcohol dehydrogenase,[6] we have developed a new, easy route to convert ephedrines to their sulfur analogs without racemization.[7] We find that these derivatives catalyze the reaction of Eq. 1 and, moreover, that enantiomeric excesses generally exceed those obtained with the corresponding ß-amino alcohols.[3] Also some unanticipated structural aspects have come to light.



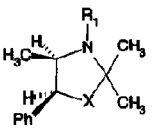
1



2



3



4

	R_1	R_2	R_3		R_1	R_2	R_3		R_1	R_2		X	R_1
1a	H	CH_3	H	**2a**	CH_3	COPh	H	**3a**	H	CH_3	**4a**	S	CH_3
1b	H	COPh	H	**2b**	CH_3	H	Ph	**3b**	CH_3	CH_3	**4b**	S	H
1c	CH_3	COPh	H					**3c**	CH_3	$CH(CH_3)_2$	**4c**	O	CH_3
1d	CH_3	H	Ph								**4d**	O	H
1e	CPh_3	H	Ph										
1f	CH_3	CH_3	Ph										

The results are summarized in Table 1. The sulfur derivatives **1a-f**, **2a,b**, **3a-c**, and **4a,b** have been examined as activators. Compounds of the series **1**, **3**, and **4** have the ephedrine (1*R*,2*S*) configuration whereas compounds **2** have the (1*S*,2*S*) configuration of pseudoephedrine.

Table 1

Entry	Compound	Conversion (% after 40 h)	e.e (%)	Benzyl alcohol (%)
1	**1a**.HCl	95	80 (*R*)	3
2	**1b**	94	3 (*R*)	<1
3	**1c**	28 (20 h)	23 (*R*)	<1
4	**1d**	43	0	<1
5	**1e**	0	0	-
6	**1f**	15 (20 h)	0	5
7	**2a**	59	51 (*S*)	<1
8	**2b**	34	0	<1
9	**3a**	75	86 (*R*)	4
10	**3b**	96 (20 h)	90 (*R*)	<1
11	**3c**	97 (20 h)	89 (*R*)	<1
12	**4a**	75	55 (*R*)	4
13	**4b**	>99	80 (*R*)	<1
14	**4c**	23	11 (*R*)	10
15	**4d**	48	12 (*S*)	9

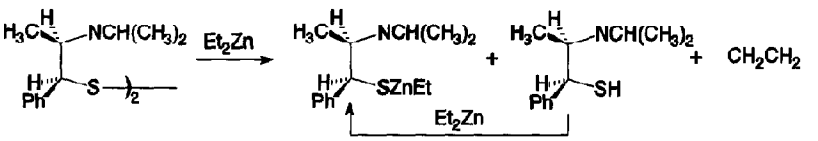
Enantiomeric excesses were determined on the crude reaction mixture using a Hewlett-Packard 5890A gas chromatograph equipped with a 50m WCOT fused silica capillary GC column coated with CP cyclodextrin-B-2,3,6-M-19 (Chrompack No. 7501) and a Hewlett-Packard HP 3396 Series II integrator. All reactions were performed in duplo and results agreed within experimental error (1%). Also enantioselectivity was shown not to be dependent on either catalyst concentration or progress of the reaction.

Thiol **1a**, the sulfur analog of (1*R*,2*S*) ephedrine, (the HCl salt is used to prevent oxidation to disulfide) affords 1-phenylpropanol in excellent yield and 80% e.e. (entry 1) compared to a reported e.e. of 66% for ephedrine.[3] Steric effects are important; **1e** (entry 5) in which the amine is substituted by a trityl group fails to react. Replacement of the free thiol group (compounds **1d-1f** and **2b**) by phenylsulfide leads to both diminished reactivity and complete loss of optical activity in the product (entries 4, 5, 6, 8). Derivatives **1b**, **1c** (entries 2, 3) in which nitrogen is acylated, react reasonably well but the e.e.'s of 1-phenylpropanol are only modest.

Acylated pseudoephedrine derivative **2a** (entry 7) provides a considerably better result than the ephedrine analog **1c** (entry 3). Unfortunately other derivatives in this series with a free thiolate are not available.

The series **3a-c** (entries 9-11) represents an unusual case. For **3b** and **3c** the free thiols are difficult to maintain pure owing to sensitivity to oxidation (**1a** is the thiol form of **3a**). These *disulfides* provide by far the best results; the e.e.'s of 1-phenylpropanol hover around 90%, more or less independent of the substitution pattern on nitrogen. Note that **3a** (entry 9) provides a better result than **1a** (entry 1). The e.e.'s for these reactions did not respond to increased concentrations of $(C_2H_5)_2Zn$; for amino alcohols this effect can be significant.[8]

We believe that the disulfide bond is cleaved *in situ* by excess $(C_2H_5)_2Zn$ as indicated in Eq. 2. This



Eq. 2

conclusion is based on the observation that treatment of (sterically quite hindered) **3c** with $(C_2H_5)_2Zn$ followed by aqueous work-up afforded an oil, the ^1H- and ^{13}C-NMR spectra of which indicate the presence of both the skeleton of **3b** as well as an ethyl group. This material also contains Zn and is *catalytically active*; when added to diethylzinc and benzaldehyde in toluene solution it induces the formation of 1-phenylpropanol in 86% e.e.. Attempts to establish the structure of this catalyst await the formation of good crystals.

The series **4a**, **4b** provides good results (entries 12, 13) but obviously does not fit into the established picture of diethylzinc additions; the thiolate group is alkylated. In sharp contrast the corresponding oxygen analogs **4c**, **4d** (entries 14, 15) are only sluggishly reactive and afford poor e.e.'s.

Four aspects of this work deserve extra note. First, in contrast to results described for ephedrine derivatives, the e.e.'s are virtually unresponsive to changes in the benzaldehyde/diethylzinc/catalyst ratio. This suggests the virtually complete formation of the active catalyst rather than an equilibrium between the catalyst and its components. Second, the active catalyst, at least for the case of sterically congested **3c**, is remarkably stable

surviving treatment with water. Once suitable crystals are available a structural determination will be carried out. Third, the excellent results for thiazolidines **4a**, **4b** (good reactivity and e.e's) are difficult to place in the common mechanistic picture in which zinc thiolates (analogous to zinc alkoxides, from ephedra alcohols) are involved. Although the ligands **4a**, **4b** undergo about 50% degradation during reaction no conclusive evidence for either reductive cleavage of the C-S bond by $(C_2H_5)_2Zn$ or ring opening to an iminium ion, which is subsequently attacked by $(C_2H_5)_2Zn$, has been garnered. Fourth, we note that absolute configurations of 1-phenylpropanol follow the general rule that the configuration at the benzylic carbon of the ephedra derivative determines that of the product.[9]

Acknowledgement: R.P.H. is supported by the Dutch National Scientific Foundation, administered through the office for Chemical Research. M.A.P. has been supported by DSM/Andeno in Venlo.

Experimental:

To a solution of 1 mmol of catalyst in 10 mL dry toluene was added 4 mL 1M diethylzinc under a nitrogen atmosphere. After stirring for 2 h the mixture was cooled to -20°C and 0.3 mL benzaldehyde (20 mmol) was introduced. The mixture was stirred at room temperature and aliquots of approximately 0.3 ml were periodically taken and filtered over 2 cm of silica which was washed with 2 mL of CH_2Cl_2. An aliquot of this solution (0.5 μL) was analyzed by means of chiral GC to calculate both conversion (using response factors) and enantioselectivity.

References:

1. For example; Chem. Rev. 92, No. 5, **1992** which is devoted to enantioselective synthesis.
2. Representative references:
   a) Soai, K.; Niwa, S., Chem. Rev., 92, 833, **1992.**
   b) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y., J. Organomet. Chem., 382, 19, **1990.**
3. Chaloner, P. A.; Renuka Perera, S. A., Tetrahedron Lett., 28, 3013, **1987.**
4. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R., J. Am. Chem. Soc., 108, 6071, **1986.**
5. a) Smaardijk, A. A.; Wynberg, H., J. Org. Chem., 52, 135, **1987.**
   b) Soai, K.; Ookawa, A., J. Chem. Soc. Chem. Commun., 412, **1986.**
6. Kaptein, B.; Barf, G.; Kellogg, R. M.; Van Bolhuis, F., J. Org. Chem., 55, 1890, **1990.**
7. Poelert, M. A.; Hof, R. P.; Peper, N. C. M. W.; Kellogg, R. M., Heterocycles, accepted for publication.
8. Chaloner, P. A.; Langadianou, E., Tetrahedron Lett., 31, 5185, **1990.**
9. Corey, E. J.; Hannon, F. J., Tetrahedron Lett., 28, 5233, **1987.**

(*Received in UK* 17 *November* 1993)