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New bis-steroidal axially chiral diols as ligands for the asymmetric addition of diethylzinc to aldehydes

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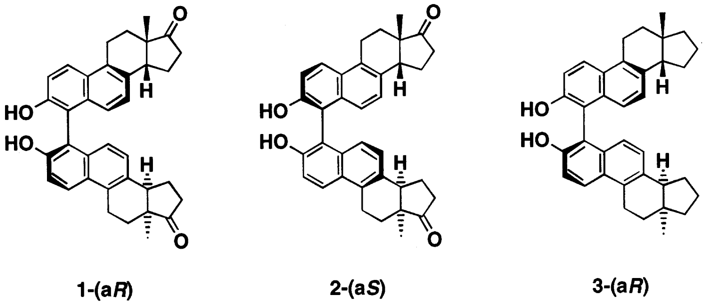
Abstract

New axially chiral steroidal binaphthols, prepared from estrone, were applied in the form of their Ti-alkoxides as catalysts for the addition of diethylzinc to aldehydes. The addition reactions proceeded with high yields and enantioselectivities up to 86%. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Axially chiral nonracemic binaphthyls have achieved an important place in asymmetric metal-catalyzed synthesis since it was shown that their diol or bis-phosphine derivatives can introduce high degrees of enantioselectivity in several chemical transformations, e.g. the Ti-alkoxide mediated addition of R_2Zn compounds to aldehydes, $LiAlH_4$ reductions, carbonyl ene reactions, aldol additions, cyanohydrin formation or hydrogenation reactions.[1–3] Therefore, the preparation of new chiral binaphthyl ligands is a subject of increasing interest. A recently synthesized new steroidal BINAP type phosphine ligand has been shown to provide excellent yields and high degrees of enantioselectivity in Ru-catalyzed hydrogenation reactions.[4] In the course of the preparation of the phosphine ligand the diastereoisomeric axially chiral binaphthols **1** and **2** (Scheme 1) have been isolated.



Scheme 1.

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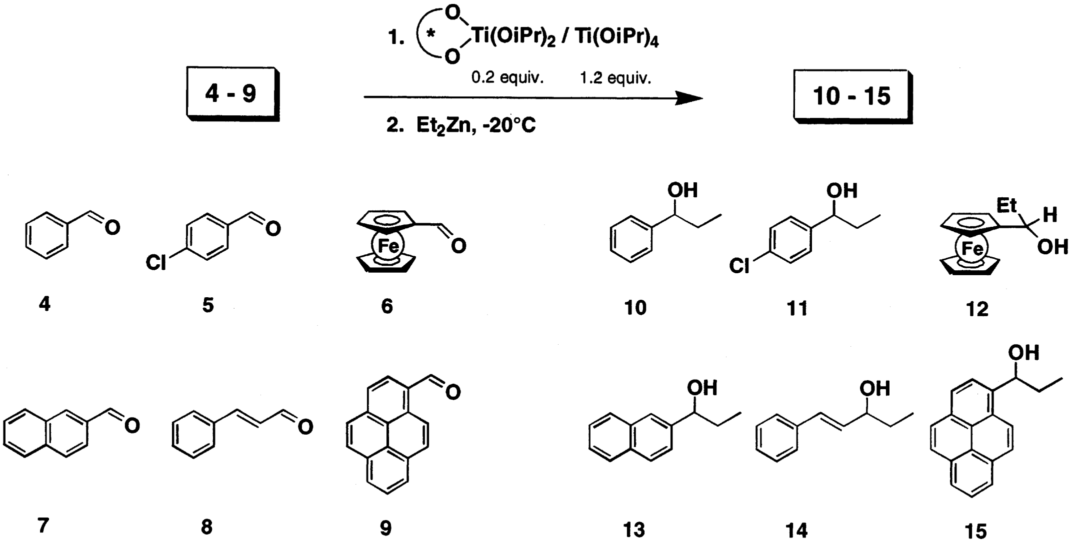
In this communication we describe, according to our interest in the application of chiral ligands for enantioselective addition of dialkylzincs to aldehydes,[5] the use of the new steroidal axially chiral binaphthols as catalysts for this purpose.

2. Results and discussion

The diastereoisomeric diols **1** and **2** were obtained from estrone in two steps in high yields, according to the recently published procedures.[4] The separation of the axially chiral diastereoisomers was achieved, as described, by column chromatography. For the synthesis of the two diastereoisomers of **3** (Scheme 1) additional synthetic steps were required and the separation of the axially chiral diastereoisomers proved difficult. This has also been described;[4] however, we were interested in obtaining at least one diastereoisomer without carbonyl groups in the framework. We could isolate in pure form only the (a*R*)-diastereoisomer. The determination of the absolute configuration of the ligands is based on CD investigations.[4,6]

The chiral Ti-alkoxides that were used as the catalysts for the enantioselective additions were prepared in situ by mixing equimolar quantities of Ti(O*i*Pr)$_4$ and binaphthols **1**, **2** or **3** in toluene at room temperature (see experimental details below). The exchange of the alkoxy groups proceeded very fast, resulting in a deep red colored chiral Ti-alkoxide solution.

The enantioselective addition of Et$_2$Zn to aldehydes **4**–**9** was performed as described by Seebach et al.[7] (see experimental details below and Scheme 2). Alcohols **10**–**15** were formed in high yields with moderate to high enantioselectivity (Table 1). The induced enantioselectivity by the addition of Et$_2$Zn to the same aldehyde is comparable for both ligands **1** and **2**. It is interesting to note that, whereas the additions catalyzed with the (a*R*)-**1** ligand were relatively fast, the transformations with ligand (a*S*)-**2** were slower (see Table 1). The behavior of the diastereoisomeric ligands **1** and **2** as enantiomers, due to the axial chirality, is reflected in the absolute configuration of the isolated products (Table 1). This is in accordance with the resulting observations with the corresponding phosphine ligands.[4] Compound **3** catalyzed the addition of Et$_2$Zn to benzaldehyde, which proceeds with excellent yield and within a relatively short reaction time. However, the observed enantioselectivity was lower than with ligand **1**.



Scheme 2.

Table 1
Addition of Et$_2$Zn to aldehydes **4**–**9** catalyzed by diols **3a** and **3b**

Entry	Aldehyde	Ligand	Time (h)	Product (yield%)[a]	$[\alpha]_D^{20}$ (*c*, solvent)	Optical purity[b] (%)
1	**4**	**1**	14	**10** (98)	+36.7 (*c* 2.2, hexane)	78 (*R*)[c]
2	**5**	**1**	24	**11** (92)	+19.6 (*c* 5.0, benzene)	70 (*R*)[d]
3	**6**	**1**	18	**12** (97)	−28.4 (*c* 1.1, benzene)	49 (*R*)[e]
4	**7**	**1**	20	**13** (92)	+16.3 (*c* 3.4, benzene)	61 (*R*)[f]
5	**8**	**1**	50	**14** (90)	+3.8 (*c* 2.7, CHCl$_3$)	60 (*R*)[g]
6	**9**	**1**	18	**15** (91)	+52.0 (*c* 0.7, CHCl$_3$)	86[h]
7	**4**	**2**	20	**10** (98)	−38.6 (*c* 2.2, hexane)	82 (*S*)[c]
8	**5**	**2**	60	**11** (82)	−19.2 (*c* 5.0, benzene)	68 (*S*)[d]
9	**6**	**2**	96	**12** (55)	+29.5 (*c* 1.1, benzene)	51 (*S*)[e]
10	**7**	**2**	120	**13** (68)	−14.9 (*c* 3.4, benzene)	56 (*S*)[f]
11	**8**	**2**	96	**14** (95)	−2.8 (*c* 2.7, CHCl$_3$)	44 (*S*)[g]
12	**9**	**2**	48	**15** (93)	−52.0 (*c* 0.7, CHCl$_3$)	86[h]
13	**4**	**3**	17	**10** (95)	+27.0 (*c* 2.2, hexane)	57 (*R*)[c]

[a] Yields of isolated products (after Kugelrohr distillation or column chromatography).

[b] Determined by polarimetry based on the maximum values for the specific rotations of the corresponding enantiomers.

[c] For (*S*)-(−)-**10** $[\alpha]_D^{20} = -47$ (*c* 2.2, hexane) for 98% ee in Fluka catalogue 1999/2000, p. 1142.

[d] For (*S*)-(−)-**11** $[\alpha]_D^{22} = -28.2$ (*c* 5.01, benzene) for 100% ee in Ref. 8.

[e] For (*R*)-(−)-**12** $[\alpha]_D^{20} = -57.5$ (*c* 1.0, benzene) for >96% ee in Ref. 9.

[f] For (*S*)-(−)-**13** $[\alpha]_D^{22} = -26.6$ (*c* 3.35, benzene) for 97% ee in Ref. 8.

[g] For (*S*)-(−)-**14** $[\alpha]_D^{20} = -6.3$ (*c* 2.70, CHCl$_3$) for 100% ee in Ref. 8.

[h] For **15** $[\alpha]_D^{20} = -60.1$ (*c* 0.72, CHCl$_3$) for 95% ee of unknown configuration.[10]

In conclusion, we obtained some new Ti-alkoxide catalysts, based on bis-steroidal axially chiral diols, which induced a moderate to high enantioselectivity in the addition of Et$_2$Zn to aldehydes.

A typical experimental procedure is as follows. All operations were carried out under an argon atmosphere in dried and distilled solvents. A 0.082 g (0.085 ml; 0.29 mmol) sample of Ti(O*i*Pr)$_4$ was added to a suspension of 0.140 g (0.28 mmol) of ligand (**1**, **2** or **3**) in 8 ml of toluene and the mixture was stirred until a clear, deep-red solution formed. All volatiles were distilled off under high vacuum (0.001 torr), and the residue was dissolved in 10 ml of toluene. To this solution 1.40 mmol of the corresponding aldehyde **4**–**9** and 1.68 mmol of Ti(O*i*Pr)$_4$ were added, and the mixture was stirred for 40 min at rt. It was cooled to −20°C and 2.52 mmol of Et$_2$Zn (1 M solution in toluene) was added. The mixture was stirred at −20°C until completion of the reaction (monitored by TLC), then the reaction was quenched with saturated aq. NH$_4$Cl solution, filtered through a pad of Celite, extracted with Et$_2$O (with CH$_2$Cl$_2$ for **15**), and dried (Na$_2$SO$_4$). After evaporation of the solvent the residue was chromatographed (hexane/Et$_2$O) or distilled to afford the corresponding alcohol **10**–**15**.

Acknowledgements

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