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Preparation of new enantiopure atropisomeric b-aminoalcohols and their use in asymmetric catalysis: enantioselective addition of diethylzinc to aromatic aldehydes.

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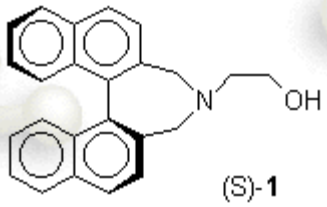
Abstract: A new class of enantiopure b-aminoalcohols having 1,1'-binaphthyl skeleton, and chiral only by atropisomerism, has been prepared and tested as catalytic precursors in the asymmetric addition of diethylzinc to aromatic aldehydes. The aldehydes were quickly and cleanly (99% yield) transformed in the corresponding alcohols with ee up to 87%.

Keywords: b-aminoalcohols, atropisomerism, 1,1'-binaphthyls, diethylzinc.

Introduction

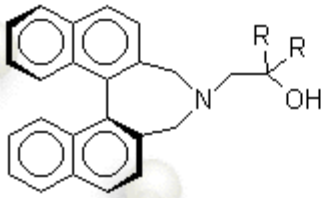
Enantiopure natural[1] and synthetic[2] aminoalcohols have found widespread application in asymmetric synthesis. In general these systems owe their chirality to the presence of stereogenic carbon atoms, and only recently aminoalcohols having either planar[3] or atropisomeric[4] chirality started to find a systematic investigation. So far the only report concerning atropisomeric b-aminoalcohols is due to Noyori,[5] who described the use of aminoalcohol (*S*)-**1** in the enantioselective addition of diethylzinc to benzaldehyde[2b,6], leading to the corresponding (*S*)-1-phenyl-1-propanol in 49% ee.



(S)-**1**

In a recent theoretical work Goldfuss and Houk[7] studied the structural features of (*S*)-**1** determining the stereoselectivity of the above reaction and explained the low enantioselectivity afforded by this ligand pointing out that "...the binaphthyl substituent at N does not efficiently distinguish the faces of the five-membered Zn-chelate ring. The lack of a substituent at C(O) eliminates significant repulsive interactions with the bulky $ZnEt_2$ moieties."

Taking into account the high efficiency showed by 1,1'-binaphthyl azepine ligands in asymmetric catalysis[8] and stimulated by the Houk observations,[7] we decided to start an investigation aimed at evaluating scope and limitations, as chiral catalysts, of atropisomeric b-aminoalcohols of general formula (*S*)-**2**. In this study the enantioselective addition of $ZnEt_2$ to aromatic aldehydes was chosen as benchmark reaction, in order to compare our results with the Noyori's work.



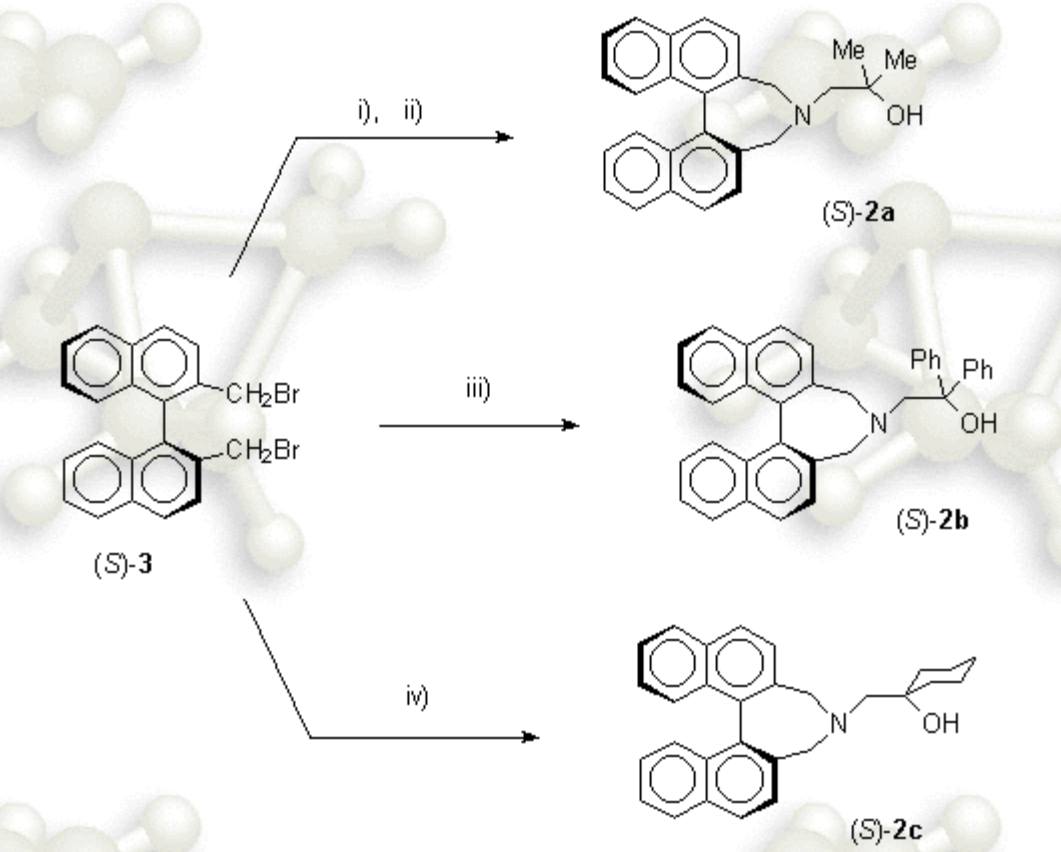
(S)-**2a** R = Me
(S)-**2b** R = Ph
(S)-**2c** R,R = -$(CH_2)_5$-

The compounds (*S*)-**2a-c** present some interesting features: (a) They can be easily obtained from optically pure 2,2'-bis(bromomethyl)-1,1'-binaphthalene (*S*)-**3**, a compound which became easily available from enantiopure 2,2'-dihydroxy-1,1'-binaphthalene only very recently.[9] (b) They are chiral only for atropisomerism and the carbon atoms bearing both the hydroxy and the amino groups are not stereogenic. (c) Compound (*S*)-**2b** looks particularly interesting because it possesses the "magic" diphenylhydroxymethyl group[10] which has been shown to be an achiral feature useful to obtain high ee values.

Results and Discussion

Compounds (*S*)-**2a-c** were obtained by reacting (*S*)-**3** with the suitable aminoalcoholic precursors as reported in Scheme

Scheme



i) $H_2NCH_2COOCH_3 \cdot HCl$, Et_3N, THF (54%); ii) MeMgBr (2 eq.), THF (67%);
iii) $H_2NCH_2C(Ph_2)OH$, Et_3N, THF (93%); iv) 1-aminomethylcyclohexanol, Et_3N, THF (91%)

(*S*)-**2a** was prepared by reacting (*S*)-**3** with excess of glycine ethylester hydrochloride, in the presence of Et_3N, affording the corresponding binaphthyl aminoester in 54% yield, the latter was then reacted with 2.2 equiv. of MeMgBr giving (*S*)-**2a** in 67% yield. The same procedure did not give satisfactory results in the case of (*S*)-**2b**, so it was prepared by reaction of (*S*)-**3** with 1,1-diphenyl-2-aminoethanol (93% yield), in turn obtained by treatment of glycine ethylester hydrochloride with excess of phenylmagnesium bromide (52% yield). Finally, reaction of (*S*)-**3** with commercially available 1-aminomethyl-cyclohexanol smoothly afforded (*S*)-**2c** in 91% yield.
Aminoalcohols (*S*)-**2a-c** were then tested in the enantioselective addition of diethylzinc to aryl aldehydes using the experimental conditions reported in Table.

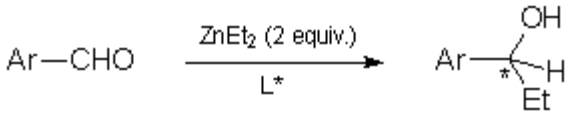


Table. Addition of $ZnEt_2$ to aryl aldehydes.

Run	Ar	L* [a]	Time	Temp.(°C)	Yield (%)[b]	ee %.[c] (C.A.)[d]
1	Ph	(*S*)-**2a**	14 h	20	97[e]	64 (*S*)
2	Ph	(*S*)-**2b**	30 min	25	99	87 (*S*)
3	Ph	(*S*)-**2c**	5 h	20	99	81 (*S*)
4	Ph	(*S*)-**2c**	16 h	0	99	78 (*S*)

5	Ph	(*S*)-**2c** [f]	16 h	20	99	75 (*S*)
6	*p*-$CH_3OC_6H_4$	(*S*)-**2b**	90 min	25	99	80 (*S*)
7	*p*-CNC_6H_4	(*S*)-**2b**	10 min	25	99	84[g] (*S*)[h]

a) 8% of aminoalcohol was used. *b*) Chromatographic (GLC) yield. No traces of benzylalcohol detected. *c*) Determined by HPLC on Chiralcel OD. *d*) Determined by elution order on Chiralcel OD.[6c] *e*) About 1% of benzylalcohol was detected. *f*) 3% of aminoalcohol was used. *g*) Determined by HPLC on Chiralcel OJ. *h*) Determined by comparison of optical rotation with literature value.[11]

The results collected in the Table can be summarized as follows:
(1) In the presence of catalytic amounts of compounds (*S*)-**2a-c** diethylzinc smoothly and cleanly adds to benzaldehyde providing 1-phenyl-1-propanol in high chemical yield: the aldehyde is entirely converted and not even traces of benzylalcohol (a byproduct of this reaction) can be found. (2) (*S*) chirality of the binaphthyl compound always induces the prevailing formation of the (*S*)- alcohol. (3) Reduction of the amount of the ligand from 8 to 3% determines only a small reduction of enantioselectivity (from 81% to 75%) (compare runs 3 and 5). (4) The reduction of temperature (from 20°C to 0°C) slows down the reaction but does not enhance the enantioselectivity (compare runs 3 and 4). (5) It is really interesting to note that simply acting on the nature of the groups R we were able to increase the enantioselectivity from 49% (Noyori value with (*S*)-**1**[5]), to 64% [(*S*)-**2a**], to 81% [(*S*)-**2c**], to 87% [(*S*)-**2b**]. In other words, making suitable structural modification (without inserting further elements of chirality) on the original Noyori's ligand (*S*)-**1** we showed that high values of enantioselectivity can be obtained also using catalysts having only atropisomeric chirality and which do not possess any stereogenic carbon atom. Previous experimental[6] and theoretical[7] investigations showed that the absolute configuration of C(O) primarily determines the stereochemical outcome of the b-aminoalcohol catalyzed reaction. In the present case the chiral environment created by the 1,1'-binaphthyl nucleus is transmitted through all the molecule and affects the events occurring at the N-Zn-O moiety, where all the steps of the enantioselective formation of the alcohol take place. The transmission of chirality from the binaphthyl moiety to the C(O) is demonstrated by the diastereotopicity (revealed by ^{1}H NMR chemical shifts) of the R substituents on this carbon. As a consequence, even if this carbon atom is not stereogenic, it can be defined as chirotopic, following the Mislow and Siegel definition.[12] The concept of chirotopicity has been recently exploited by Knochel et al.[13] to prepare a new class of chiral ligand for asymmetric synthesis. The possibility of this long range control of chirality depends on the nature of the substituents at the C(O) atom: it is low for R = H, higher for R = Me, and reaches a maximum value for R = Ph. In the latter case the presence of the "magic" diphenylhydroxymethyl group allows the maximum enantioselectivity thus confirming the efficiency of this achiral moiety in asymmetric catalysis.[10]
The most efficient ligand (*S*)-**2b** was used in the enantioselective addition of $ZnEt_2$ to *p*-substituted aryl aldehydes with either electrondonating (-OCH_3) or electronwithdrawing (-CN) groups. The reaction for *p*-methoxybenzaldehyde is slower (90 min) than for benzaldehyde (30 min), while a very quick reaction (less than 10 min!) is observed for *p*-cyanobenzaldehyde: this can be clearly related to the more electrophilic character of the carbonyl group of *p*-cyanobenzaldehyde with respect to the *p*-methoxybenzaldehyde.[14] By contrast the ee of the product is independent of the nature of the substrate. This result seems to contradict a recent report[4b] where the enantioselectivity increases with reactivity, but is in complete agreement with other investigations[6] reporting that the enantioselectivity is mainly determined by steric factors.

Conclusions

We have clearly demonstrated that enantiopure atropisomeric aminoalcohols having the structure of (*S*)-**2** can act as efficient promoter of the enantioselective addition of $ZnEt_2$ to aryl aldehydes. This result is important from a practical point of view (a new class of efficient promoters is available) but also from a more speculative point of view: these compounds owe their chirality only to the atropisomerism of the binaphthyl nucleus and do not have any stereogenic

carbon atom. It is interesting to note that this investigation fully confirms the theoretical analysis of Goldfuss and Houk[7] about the need of substituents at C(O) in order to achieve higher enantioselectivity. We are convinced that the present experimental results may stimulate further investigation aimed at clarifying the correlation between structure and catalytic activity of aminoalcohol precatalysts. Work is now in progress to study also the efficiency of compounds (*S*)-**2a-c** in other asymmetric reactions.

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