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Ligands with cycloalkane backbones VIII. Steric effects in the ligand accelerated enantioselective alkylation of benzaldehyde☆

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Dedicated to Professor Dr Henri Brunner on the occasion of his 65th birthday

Abstract

Alkylation of benzaldehyde with diethylzinc was carried out in the presence of a series of (1*S*,2*S*)-2-(pyrazol-1-yl)cyclohexanols. Depending on the substituent at pyrazole, the 1-phenylpropanols were obtained with 18–97% yield and 2–76% enantiomeric excess. However, the increase in activity is not parallel to the increase in stereoselectivity, which supports the reaction mechanism, proposed by Noyori. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Chelate ligands; N-donor ligands; Alkylation; Enantioselective catalysis; Diethylzinc

1. Introduction

The enantioselective alkylation of aldehydes is a typical ligand accelerated catalysis. It opens up an access to chiral alcohols, which are versatile products and reagents in organic and pharmaceutical chemistry. Therefore, this reaction has been investigated for years, leading to a whole series of different combinations of chiral ligands and alkylating agents: sulfonamides [2] or binaphthols [3] and $TiOR_4$ with R_2Zn, secondary amines, BuLi and R_2Zn [4], aminonaphthols and R_2Zn [5], transition metal salene complexes and R_2Zn [6], hydroxy phosphine oxides and R_2Zn [7], and, as the most important combination, aminoalcohols and R_2Zn compounds. Secondary aliphatic β-amino alcohols bearing rigid ligand backbones have shown to give high activities and stereoselectivities [8]. However, the application of ferrocene derivatives [9] and γ- [10] and δ-amino alcohols [11] has also been reported.

The mechanism of the DAIB (*exo*-(dimethylamino)isoborneol) catalyzed alkylation of benzaldehyde with Et_2Zn, which gives the corresponding 1-phenylpropan-1-ol in quantitative yields with more than 99% ee, was elucidated by Noyori et al. [12]. Herein a zinc alkoxide of the type **A** is formed first (Scheme 1) by reacting the protic aminoalcohol with diethylzinc, which either stabilizes by dimerization (compound **B**), or by subsequent addition of one equivalent of benzaldehyde (compound **C**) or of a second molecule of diethyl zinc (compound **D**). All these species are in equilibrium in solution. Starting from **C** or **D**, the transition state **E** of the alkylation reaction is accessible wherein the stereochemical information is transferred.

The dimeric species **B** represents something like a resting state of the catalyst. Owing to the mechanism presented in Scheme 1, there are two different regimes wherein steric effects must be discussed: first, the generation of the reactive monomer **A**, which is in equilibrium with its dimeric congener **B**, and second, during the transfer of the ethyl group in the transition state of the reaction.

2. Results and discussion

Recently we synthesized a series of *trans* configured 2-(pyrazol-1-yl)cyclohexanols, chiral γ-amino alcohols of the type **1** (Scheme 2), which we use as chelating

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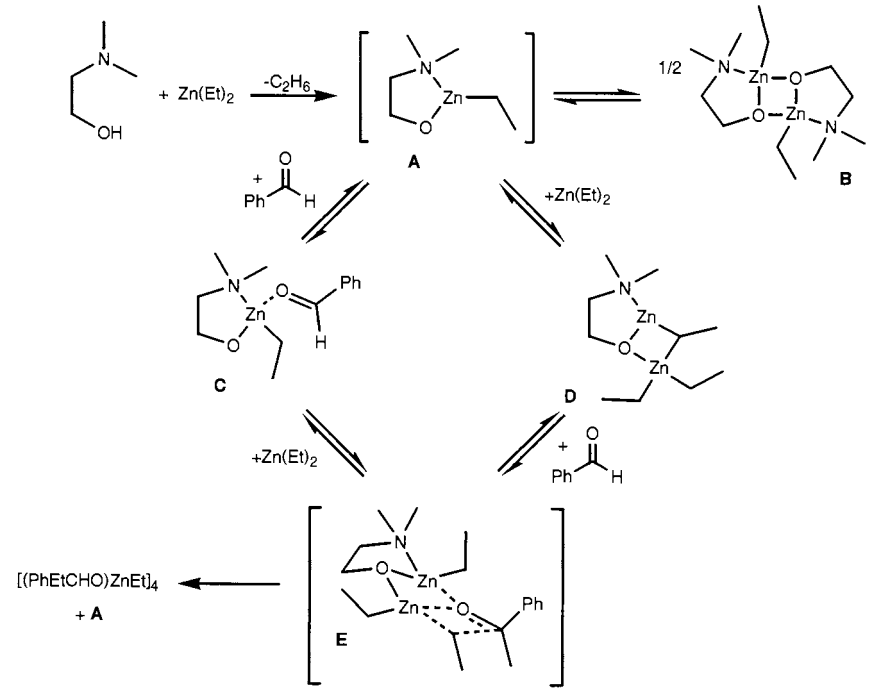
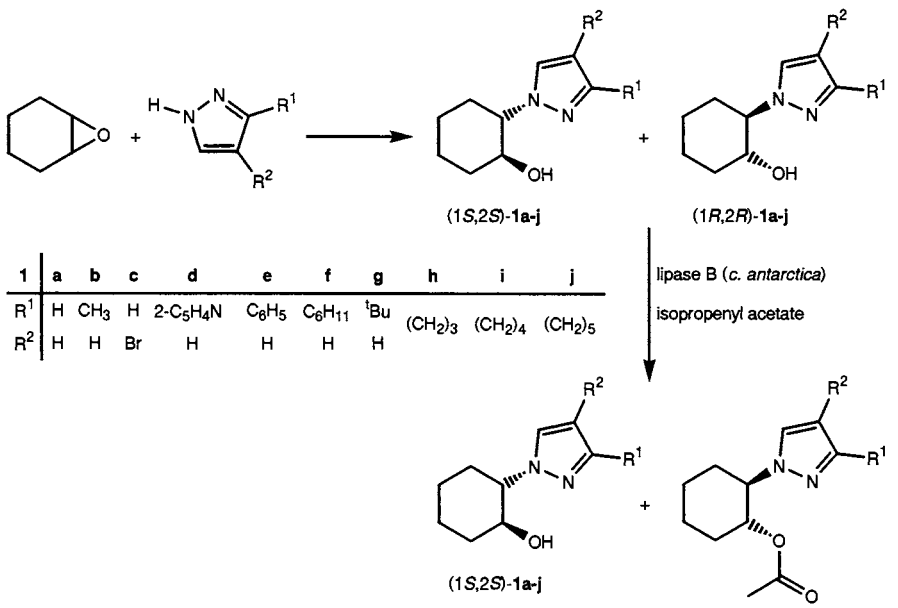
agents for transition metals and as starting compounds for the synthesis of other chiral ligands [13,14]. They are obtained as racemates by reacting pyrazole with epoxicyclohexane at elevated temperatures. Enzymatic kinetic resolution makes them accessible as enantiomerically pure compounds [13]. We decided to take these compounds for a detailed investigation on the steric influence of substituents on the performance of the asymmetric alkylation of benzaldehyde.

While rigid β-amino alcohols with aliphatic tertiary amino donors give high performances in terms of activity and stereoselectivity, γ-amino alcohols or systems bearing aromatic amines generally show up lower rates of conversion and decreased enantioselectivities. To our knowledge, no systematic preparative investigation on steric effects has yet been reported for the γ-amino alcohol catalyzed alkylation of benzaldehyde. In the present paper we show, that a destabilization of the

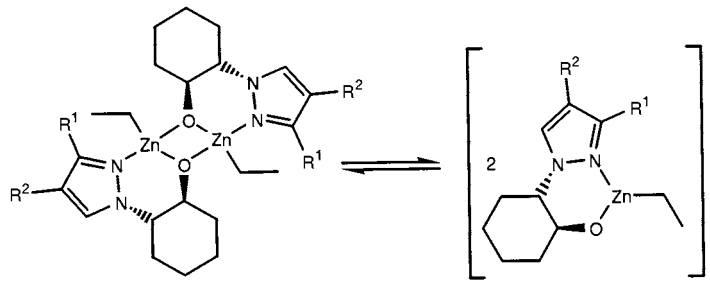


Scheme 1.



1	a	b	c	d	e	f	g	h	i	j
R^1	H	CH_3	H	2-C_5H_4N	C_6H_5	C_6H_{11}	^tBu	$(CH_2)_3$	$(CH_2)_4$	$(CH_2)_5$
R^2	H	H	Br	H	H	H	H			

Scheme 2.



Scheme 3.

dimer (increase in monomer concentration, higher catalytic activity) is possible already by introducing small substituents in the three-position of the pyrazole moiety. However, high stereoselectivities can only be obtained by much bulkier groups.

The alkylation of benzaldehyde with diethyl zinc in the presence of 8 mol% of (1*S*,2*S*)-2-(pyrazol-1-yl)cyclohexanol (**1a**) gave only 35% of the *S*-configured 1-phenylpropanol with just 41%ee after 3 h ($T = 0$°C, toluene). This reflects, together with the formation of benzylic alcohol (up to 23%), the low reactivity of the system. We assign this to the formation of a very stable dinuclear zinc complex (Scheme 3). Destabilization of this dimer by introduction of bulky substituents at the pyrazolyl fragment should therefore increase the monomer concentration and lead to higher reactivities and better chemo- and stereoselectivities. To prove this, *trans*-2-(pyrazol-1-yl)cyclohexanols bearing more or less bulky groups in the three-position of the pyrazole (**1a**, **b**, **1d**–**g**, Scheme 2), 3,4-cyclo annealed pyrazole moieties (**1h**–**j**) or a 4-bromo substituent (**1c**) were investigated. Table 1 shows the results of the catalytic alkylations obtained with these ligands.

Obviously, there is an increase of reactivity and chemoselectivity parallel to the steric demand of the substituents. While (1*S*,2*S*)-**1g** gave the *S*-configured product in 97% yield and 100% chemoselectivity, the unsubstituted derivative (1*S*,2*S*)-**1a** led to only 18% yield and remarkable amounts of benzylic alcohol were detected. The same feature was found in terms of stereoselectivity: again high enantiomeric excesses were observed when ligands with bulky side chains are used. Increasing temperature led to a decrease in stereoselectivity as expected. The performance of the alkylation also depends on the concentration of the chiral ligand. We applied different amounts of ligand (1*S*,2*S*)-**1j**. Obviously, the conversion drops with a decrease of ligand concentration (Table 2) but the stereoselectivity of the reaction is still quite good.

As shown in Table 1, the introduction of a simple methyl substituent in the three-position of the pyrazole (ligand **1b**) led to a remarkable increase in activity and chemoselectivity and gave a moderate enantiomeric excess of 53%. Comparing this result with the data of the other 3-alkyl substituted ligands **1f**,**g** implies, that the introduction of a methyl substituent sufficiently increases the activity of the system. However, substituents with an increased steric demand are required for better transfer of chirality, which should be relied to the geometry transition state. This also implies, that there is still a chance to obtain enantiomeric excesses higher than 80% with this type of ligands by further increasing the steric demand of the substituents without loosing activity. The same effects were observed when the size of the annealed rings in ligands **1h**–**j** was increased: the catalytic activity increased (yields: **1h**, 48%; **1i**, 92%) and reached some kind of a plateau (**1j**, 96%), showing that the rigid five membered ring cannot destabilize the dinuclear zinc complex in the way the more floppy six and seven membered rings do. On the other hand, the

Table 1
Catalytic alkylation of benzaldehyde with Et_2Zn in the presence of 5 mol% of (1*S*,2*S*)-**1a**–**j** (reaction time 7 h)

Ligand	(*S*)-1-Phenylpropanol		Benzylic alcohol (%)
	Yield (%)	ee (%)	
1a	18	2	8
1b	91	53	6
1c	82	38	0
1d	70	6	0
1e	52	32	0
1f	95	73	0
1g	97	76	0
1h	48	28	0
1I	92	52	0
1j	96	71	0

Table 2
Product formation in the presence of different concentrations of (1*S*,2*S*)-**1j** (reaction time 3 h)

1j (mol%)	(*S*)-1-Phenylpropanol		Benzylic alcohol (%)
	Yield (%)	ee (%)	
0.5	21	49	1
5	57	62	0
10	59	69	3

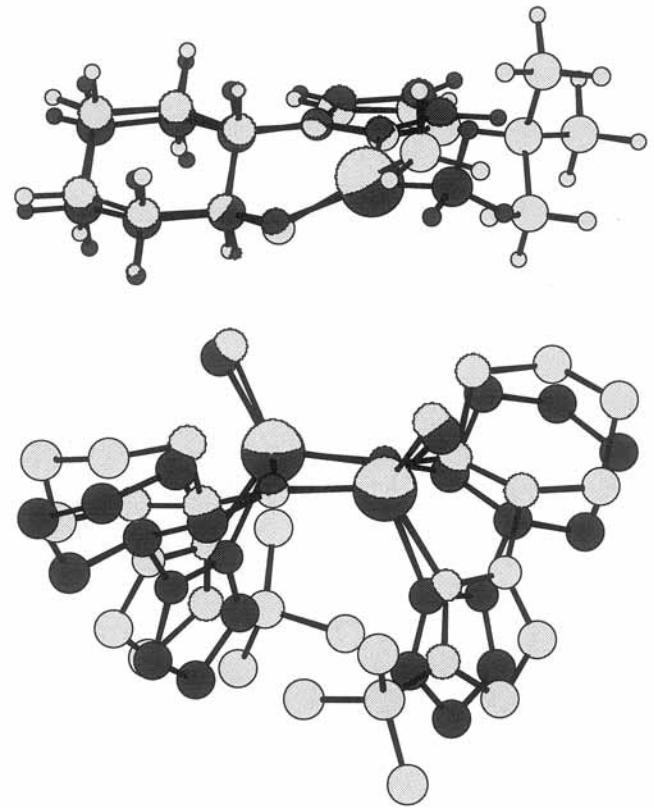


Fig. 1. Overlaid geometries of the monomers (top) of **1a** (bright) and **1g** (dark) and the dimers (bottom; hydrogen atoms omitted for clarity) *syn*-**1a** (bright) and *syn*-**1g** (dark).

stereoselectivity increased almost parallel to the ring size (ees: **1h**, 28%; **1i**, 52%; **1j**, 71%) proving a more and more pronounced stereodifferentiation in the transition state. Although its steric properties should somehow be comparable to the cyclohexyl derivative **1f**, the phenyl substituted ligand **1e** showed remarkably lower activities and stereoselectivities. This may be due to an electronic stabilization of the dinuclear zinc complex or due to some unfavorable π-interactions, either in the dinuclear complex or in the transition state. Switching from phenyl to a 2-pyridyl (**1d**) group, enhanced the activity of the system but led to an almost complete loss of stereoselectivity, which makes an interaction of the pyridyl moiety with the zinc center feasible. The high activity of **1c** can be explained by an electronic destabilization of the dinuclear complex owing to the electron withdrawing character of the 4-bromo substituent. However, the stereo differentiation of this system must be poor, since the essential substituent in the five-position is missing.

To give an impression on the stereochemical interactions of either a proton (like in **1a**) or a *t*-butyl group (as in **1g**) in the five-position of the pyrazole ring, we optimized the geometries of the monomeric and the homo- (*syn*) and heterochiral (*anti*) dimeric methylzinc complexes by quantum chemical calculations (the alkylation of benzaldehyde by dialkylzinc and aminoalcohols was recently matter of theoretical calculations of others [15]). With regard to the large numbers of heavy atoms in the dimers, we carried out these calculation with the HF method and a small set of basis functions (3-21G). Therefore, it makes no sense to discuss the resulting energies or the structures in detail. However it is clear, that the introduction of a *t*-butyl group (**1g**) leads to an increase of the dihedral angle C–Zn–N–C5 (C = carbon atom of the CH_3 group at Zn, N = nitrogen donor center of pyrazole, C5 = C5 of pyrazole) of the monomeric species from 28.1 (**1a**) to 53.6° (**1g**; Fig. 1, top). In the case of the homochiral dimer *syn*-**1g**, the steric interaction between the *t*-butyl group of one ligand and the cyclohexane ring of the other ligand is responsible for a repulsion of the ring systems away from the C_2 axis of the molecule compared to *syn*-**1a**.

3. Conclusion

To summarize, it could be shown that both, the catalytic activity and the stereoselectivity of the (1*S*,2*S*)-2-(pyrazol-1yl)cyclohexanols in the alkylation of benzaldehyde with diethyl zinc, depend on the steric demand of pyrazolyl donor site. However, the trends in activity and stereoselectivity are not complementary for these ligands. We are now going to look for the resolution of related ligands with more bulky substituents, which could not be performed by the enzymatic protocol we have worked out yet.

4. Experimental

The catalytic experiments were carried out under an inert gas atmosphere of nitrogen and with dried toluene as the solvent. The ligands applied herein were synthesized according to procedures described in the literature [13].

A general procedure: 0.7 ml (0.7 mmol) of a 1 M solution of $ZnEt_2$ in hexanes (Aldrich, 29,511-2) were added to a solution of one of the (1*S*,2*S*)-configured ligands (**1a**–**j**) in toluene at 0°C. Benzaldehyde (37.1 mg) was added after 30 min. The solution the was stirred for 7 h at 0°C and the reaction was quenched by addition of 3 ml of diluted HCl. The organic layer was separated, dried over $MgSO_4$ and the solvent was removed in vacuum at room temperature. The residue was re-dissolved in CH_2Cl_2 and analyzed by gaschromatography using a LIPODEX A column (Fa. Macherey&Nagel).

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