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Enantioselective Addition of Et_2Zn to Benzaldehyde Activated by Benzamides Containing the (*S*)-α-Phenylethyl Group

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Abstract. Application of atropisomeric ligands, i.e. 2-aminobenzamides **1a–e** and 2-sulfonamidobenzamides **2a–e**, in the addition of Et_2Zn to benzaldehyde afforded low to moderate enantioselectivities (up to 63% ee).
Keywords: atropisomers, benzamides, chiral ligands, diethylzinc, enantioselective addition.

Resumen. La aplicación de los ligantes atropoisoméricos, 2-aminobenzamidas **1a–e** y 2-sulfonamidobenzamidas **2a–e**, en la adición de Et_2Zn a benzaldehído condujo a enantioselectividades de bajas a moderadas (hasta 63% ee).
Palabras clave: atropoisómeros, benzamidas, ligantes quirales, dietilzinc, adición enantioselectiva.

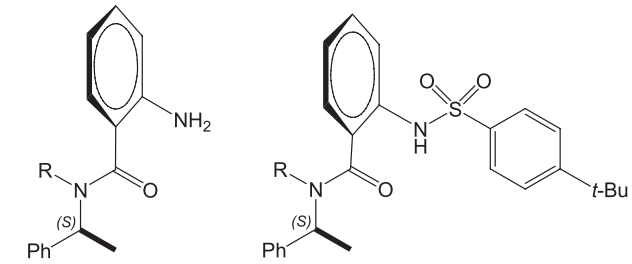
Introduction

Asymmetric C–C bond-forming reactions constitute a fundamental class of transformation in organic synthesis. One of the most useful reactions is the asymmetric addition of carbon-based nucleophiles to carbonyl groups [1-8]. The reaction of dialkylzinc reagents with aldehydes has been used as a model for this important class of reactions.

Compounds with chiral axes, such as BINOL and BINAP, have played an important role in the development of asymmetric catalysis and are considered privileged ligands [9]. These ligands are chiral due to restricted rotation about single bonds. The rotational barriers are sufficiently high to allow isolation and use of these ligands at high temperatures [10-13].

In contrast to atropisomeric biaryl ligands, efforts to perform catalytic asymmetric reactions with nonbiaryl atropisomers have met with little success, despite the ability of these compounds to control stereochemistry. It is apparent that the perpendicular architecture of atropisomeric anilides, benzamides, and naphthamides effectively exert control over the formation of new stereogenic centers [14-19].

One of the aims of our research is to prepare chiral ligands incorporating (*S*)-α-phenylethylamino group as chiral functionality, which has proven quite effective in asymmetric synthesis [20, 21]. Previously, we reported the synthesis and dynamics of atropisomeric 2-amino- and 2-(4-*tert*-butylphenylsulfonamido)-(*S*)-*N*-(α-phenylethyl)benzamides **1a–e** and **2a–e** [22]. Herein we disclose the application as ligands of **1a–e** and **2a–e** (Figure 1) in the enantioselective addition of $(Et)_2Zn$ to benzaldehyde.



1a, R = *i*-Pr
1b, R = $PhCH_2$
1c, R = (1-Naphthyl)CH_2
1d, R = (9-Anthracenyl)CH_2
1e, R = (*S*)-PhMeCH

2a, R = *i*-Pr
2b, R = $PhCH_2$
2c, R = (1-Naphthyl)CH_2
2d, R = (9-Anthracenyl)CH_2
2e, R = (*S*)-PhMeCH

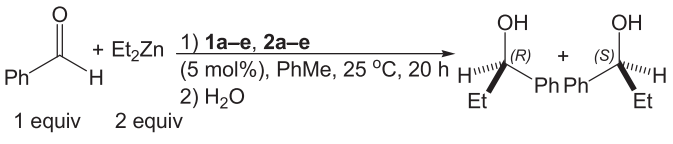
Fig. 1. 2-Substituted *N*-[(*S*)-α-phenylethyl]benzamides

Results and Discussion

The asymmetric addition of ethyl group to benzaldehyde was performed using 5 mol% of **1a–e** and **2a–e** in the presence of diethylzinc (2 equiv) in toluene at 25 °C for 20 h. While excellent yields were obtained, low to moderate enantioselectivities were observed (Table 1, entries 1 – 10, 76 – 96% yield and 1 – 61% ee). Best results were obtained with the sufonamido derivatives **2a–e**. Enantiomeric excess up to 61% was achieved with (*S*)-*N*-benzyl-2-(4-*tert*-butyl-benzenesulfonamido)-*N*-(α-phenylethyl)benzamide **2b** (Table 1, entry 7).

Contrary to our expectations, the use of ligands containing bulkier aromatic substituents did not improve the enantioselection. This may be explained by the conformation observed on the solid-state structure of benzamide **2c**. Benzamide **2c** acted

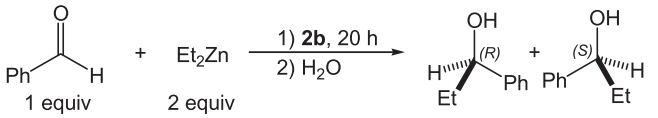
Table 1. Enantioselective Addition of Et_2Zn to Benzaldehyde.



Entry	Ligand	ee (yield)[a]	Conf.[a]
1	**1a**	3 (85)	(*R*)
2	**1b**	1 (90)	(*S*)
3	**1c**	1 (84)	(*R*)
4	**1d**	1 (87)	(*S*)
5	**1e**	12 (76)	(*S*)
6	**2a**	2 (95)	(*R*)
7	**2b**	61 (96)	(*R*)
8	**2c**	45 (94)	(*R*)
9	**2d**	27 (93)	(*R*)
10	**2e**	27 (80)	(*R*)

[a]The analyses for determining enantiomeric excess and configuration of the major enantiomer were performed after purification by flash chromatography on deactivated silica gel (SiO_2/Et_3N = 2.5% v/v; hexanes/EtOAc, 95/5) by HPLC with Chiralcel OD column under conditions reported previously [8], and were confirmed by optical rotation.

Table 2. Enantioselective Addition of Et_2Zn to Benzaldehyde in the presence of Chiral Ligand **2b**.



Entry	Ligand (mol%)	Solvent	T (°C)	ee (yield)[a]	Conf.[a]
1	5	hexane	25	63 (86)	(*R*)
2	20	hexane	25	58 (80)	(*R*)
3[b]	5	none	25	62 (90)	(*R*)
4	5	toluene	0	50 (80)	(*R*)
5[c]	5	toluene	25	9 (60)	(*R*)

[a]The analyses for determining enantiomeric excess and configuration of the major enantiomer were performed after purification by flash chromatography on deactivated silica gel (SiO_2/Et_3N = 2.5% v/v; hexanes/EtOAc, 95/5) by HPLC using a Chiralcel OD column under conditions reported previously [8], and were confirmed by optical rotation. [b]The reaction proceeded in highly concentrated conditions, with only 5 equiv of toluene. [c]This reaction was performed with $Et_2Zn/Ti(OiPr)_4$/benzaldehyde /**2b** (1.6/1.2/1.0/0.05).

also as molecule tweezer by electrostatic and aromatic pi-pi-stacking interaction with the solvent.[22] These observations might explain the decrease in enantioselection in the presence of benzamides **2c** and **2d** as ligands (Table 1, entries 7–9).

Based on these results, we carried out the ethylation of benzaldehyde in the presence of atropisomeric ligand **2b** changing conditions such as solvent, amount of ligand and temperature (Table 2). Nevertheless, only slightly improvements were observed. Best enantioselectivity was achieved using hexane as solvent, at rt with 5 mol% ligand (Table 2, entry 1). Furthermore, increasing the amount of ligand from 5 to 20 mol% or decreasing the temperature from rt to 0 °C caused a decreased in the ee (Table 2, entries 2 and 4). Besides, in highly concentrated conditions [23], with only 5 equiv of toluene, afforded similar ee (Table 2, entry 3). Finally we proceeded to carry out the addition reaction following another protocol, in the presence of ligand **2b**, $(Et)_2Zn$ (1.6 equiv), and $Ti(OiPr)_4$ (1.2 equiv), in toluene at rt, however lower reactivity and enantioselectivity were observed (Table 2, entry 5).

We surmise that the benzamides might be bonded with the zinc atom by the oxygen atom of the carbonyl group and the nitrogen atom of the 2-amino or 2-sulfonamide group. These complexes might be analog to the previously reported with β-aminoalcohols involving dimeric complexes as Noyori's model [3,5]. There is no evidence on these zinc-ligand complexes and the mechanism thus far proposed is largely speculative.

In conclusion, the 2-amino- and 2-sulfonamidobenzamides **1a–e** and **2a–e** were used as atropisomeric ligands in the addition of Et_2Zn to benzaldehyde affording up to 63% ee with ligand **2b**. Further studies have to be made to formulate a working hypothesis for the mode in which these ligands function in the enantioselective reaction and design a second generation of atropisomeric benzamides.

Experimental Section

General Methods. All manipulations involving titanium(IV) isopropoxide and diethylzinc were carried out under an inert atmosphere. Titanium(IV) isopropoxide and benzaldehyde were distilled prior to use. NMR spectra were obtained on a Varian Mercury 200 MHz Fourier transform spectrometer at the Universidad de las Americas Puebla NMR facilities. ^1H NMR and spectra were referenced to tetramethylsilane; and and $^{13}C\{^1H\}$ NMR spectra were referenced to residual solvent.

Compounds. Benzamides **1a–e** and **2a–e** were prepared according to the literature procedure [22].

Diethylzinc Addition to Benzaldehyde. *Method A*. The ligands **1a–e** and **2a–e** (5 mol%) were weighed into the reaction vessel that was then purged with nitrogen, and diethylzinc (1.0 M toluene, 2.0 equiv, 0.94 mL) was added at rt. After 10 min, benzaldehyde (1.0 equiv, 0.47 mmol) was added neat. The homogeneous reaction mixture was stirred at rt. After 20 h, the reaction was quenched with water (5 mL), diluted with EtOAc, filtered through Celite, and the layers separated. The

aqueous layer was extracted with EtOAc (2 × 40 mL) and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on deactivated silica gel (Et_3N/SiO_2 = 2.5% v/v, hexanes : EtOAc / 95:5) to afford 1-phenyl-1-propanol. The analyses for determining enantiomeric excess were performed by HPLC using a Chiralcel OD column under conditions reported previously [8], and were confirmed by optical rotation.

Method B [24]. The compound **2b** (5 mol%, 12.4 mg) was weighed into the reaction vessel that was then purged with nitrogen. Diethylzinc (1.0 M toluene, 1.6 equiv, 0.75 mL) and titanium(IV) isopropoxide (1.0 M toluene, 1.2 equiv, 0.56 mL) were then added at rt. After 10 min benzaldehyde (1.0 equiv, 0.47 mmol) was added neat. The homogeneous reaction mixture was stirred at rt. After 20 h, the reaction was quenched with water (5 mL), diluted with EtOAc, filtered through Celite, and the layers separated. The aqueous layer was extracted with EtOAc (2 × 40 mL) and the combined organic layers washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash chromatography on deactivated silica gel (Et_3N/SiO_2 = 2.5% v/v, hexanes : EtOAc / 95:5) to afford 1-phenyl-1-propanol. The analysis for determining enantiomeric excess were performed by HPLC using a Chiralcel OD column under conditions reported previously [8], and were confirmed by optical rotation.

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