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Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by 14-hydroxylsubstituted morphinans

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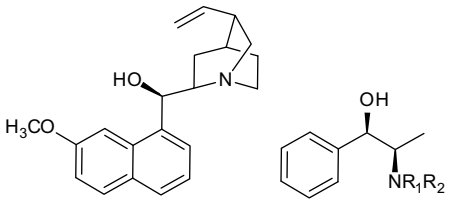
ABSTRACT

Enantioselective addition reactions of diethylzinc to aromatic aldehydes were performed with catalytic amounts of 14-hydroxylsubstituted morphine alkaloids. The reaction conditions such as catalyst loading, time and temperature were optimized to obtain the highest enantiomeric excess. Optically active secondary alcohols were synthesized with ee up to 95%.

1. Introduction

Chiral ligands are important tools for the synthesis of enantiopure organic compounds.[1] An easy to perform and well-documented reaction for testing the catalytic reactivity and enantiodifferentiating ability of certain catalytic systems is the addition of diethylzinc to aromatic aldehydes.[2] In particular, many chiral β-aminoalcohols, both natural and synthetic, have been tested in this addition with varying degrees of success. High enantioselectivities have been achieved by using compounds such as 3-exo-(dimethylamino) isoborneol (DAIB) or derivatives of ephedrine, norephedrine, quinine and other alkaloids (Fig. 1).[3–9] Chiral alkaloids have been extensively used in asymmetric synthesis.[10] However, morphine alkaloids have rarely been used as ligands in asymmetric reactions.



quinine and quinidine ephedrine and norephedrine

Figure 1. Alkaloids used as ligands in the enantioselective addition of dialkylzinc to aldehydes.

Wells et al. have reported the application of codeine and oxycodone modified platinum surfaces in the asymmetric hydrogenation of methyl pyruvate and butane-2,3-dione.[11] However, very low ee's of up to 15% were obtained.

Herein, we report the enantioselective alkylation of aromatic aldehydes by diethylzinc in the presence of catalytic amounts of 14-hydroxylsubstituted morphine alkaloids, oxycodone **1**, 14-hydroxy codeinone **2** and naltrexone **3** (Fig. 2). To the best of our knowledge, morphinans have not been used as chiral ligands for the enantioselective addition of dialkylzinc to aldehydes.

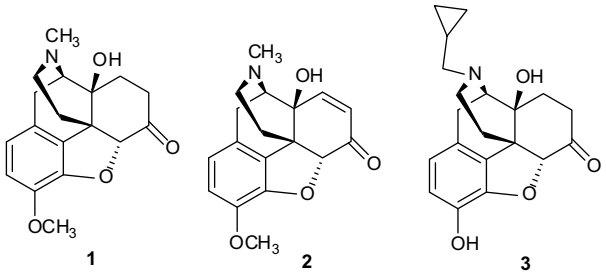


Figure 2.

2. Results and discussion

Chiral ligands **1**–**3** were synthesized according to the literature procedure.[12–15] Enantioselective addition of diethylzinc to aromatic aldehydes was investigated in the presence of catalytic amounts of **1**–**3** (Scheme 1).

First, the effect of temperature and catalyst loading on the reaction of diethylzinc to benzaldehyde was examined (Table 1). It was

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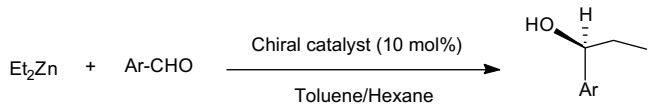


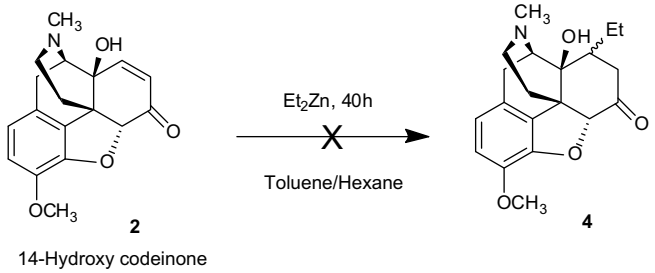
Scheme 1.

observed that lower temperatures and high catalyst loading gave higher enantioselectivities. A comparison between the abilities of all three catalysts under different conditions is summarized in Table 1. As shown, higher ee's were obtained using **1** and **3** at lower temperatures (Table 1, entries 5, 6, 16, and 17). It should be emphasized that the α,β-unsaturated carbonyl function of the ligand **2** was stable to diethylzinc under the reaction conditions. When a mixture of ligand **2** and 3 equiv of diethylzinc was stirred at room temperature for 40 h, compound **4** was not obtained (Scheme 2).

Table 1
Enantioselective addition of diethylzinc to benzaldehyde catalyzed by chiral ligands **1**–**3**

Entry	Ligand (mol %)	*T* (°C)	Additive	Yield[a] (%)	ee[b] (%)	Configuration[c]
1	**1** (1)	+10	—	35	—	—
2	**1** (5)	+10	—	45	9	(*S*)
3	**1** (10)	+10	—	55	35	(*S*)
4	**1** (10)	+10	Benzoic acid[d]	50	2	(*R*)
5	**1** (10)	−20	—	50	58	(*S*)
6	**1** (20)	−30	—	75	80	(*S*)
7	**2** (10)	+30	—	91	7	(*R*)
8	**2** (10)	+10	—	80	28	(*R*)
9	**2** (10)	+10	Benzoic acid[d]	75	66	(*S*)
10	**2** (10)	−20	Benzoic acid[d]	32	15	(*S*)
11	**2** (10)	+10	Phthalic acid[d]	72	33	(*S*)
12	**2** (10)	+10	Acetic acid[d]	75	17	(*S*)
13	**2** (10)	−10	—	41	50	(*R*)
14	**2** (10)	−30	—	43	53	(*R*)
15	**3** (10)	+10	—	75	71	(*S*)
16	**3** (10)	−20	—	65	80	(*S*)
17	**3** (20)	−30	—	60	89	(*S*)
18	**3** (10)	+10	$Ti(OPr^i)_4$[e]	55	16	(*R*)
19	**3** (10)	+10	Benzoic acid[d]	46	38	(*R*)

[a] GC yield on the mixture of the two enantiomers.
[b] Ee was determined by GC using a chiral capillary column (HP-Chiral).
[c] Absolute configuration of the major enantiomer was determined by comparison with authentic samples.
[d] 10 mol % of the acid were added.
[e] In the presence of 120 mol % of $Ti(OPr^i)_4$.



Scheme 2.

The addition of catalytic amounts (10 mol %) of benzoic acid in the reaction of diethylzinc to benzaldehyde with **2** led to a significant increase in the ee%, while with **1** and **3** led to a decrease in the enantioselectivity (Table 1, entries 4, 9, and 19). In each case, the product was obtained with an opposite configuration. Mass spectrometric studies showed that the by-product **4** was produced in situ in low yield in the presence of benzoic acid.

Although ligand **2** gave higher yields under the same conditions (+10 °C, 10 mol % of the catalyst for 40 h) than **1**, better ee's were obtained with ligands **1** and **3** (Table 1, entries 3, 8, and 15). Treatment of **3** with 120 mol % of titanium isopropoxide led to a significant decrease of the enantioselectivity with an opposite configuration (entry 18).

Therefore, ligands **1** and **3** were used as the catalysts of choice for the addition of diethylzinc to other aromatic aldehydes (Table 2). At first, the reactions were performed using 10 mol % of the catalyst in toluene at −20 °C.

As shown in Table 2, the electronic effects of the aromatic ring substituents also played an important role with regard to the enantioselectivity but not the yield of the reactions. Lower enantioselectivities were obtained in the presence of electron-donating substituted groups (Table 2, entries 8–10). The presence of *ortho* substituents lowered the enantioselectivity of the reactions (Table 2, entries 9–11).

Table 2
Enantioselective addition of diethylzinc to aromatic aldehydes catalyzed by ligands **1** and **3**[a]

Entry	Aldehyde	Ligand	Yield[b] (%)	ee[c,d] (%)
1	*p*-FC_6H_4CHO	**1**	83 (92)[e]	67 (81)[e]
2	*p*-FC_6H_4CHO	**3**	(84)[e]	(95)[e]
3	*p*-ClC_6H_4CHO	**1**	98 (95)[e]	68 (78)[e]
4	*p*-ClC_6H_4CHO	**3**	(97)[e]	(93)[e]
5	*p*-BrC_6H_4CHO	**1**	98 (88)[e]	66 (71)[e]
6	*p*-MeC_6H_4CHO	**1**	66	53
7	*p*-MeC_6H_4CHO	**3**	(73)[e]	(93)[e]
8	*p*-$MeOC_6H_4CHO$	**1**	70	32
9	*o,p*-$(MeO)_2C_6H_3CHO$	**1**	74	50
10	*o*-$MeOC_6H_4CHO$	**1**	87	32
11	*o*-ClC_6H_4CHO	**1**	97	45

[a] Conditions: −20 °C, 40 h and 10 mol % of ligand.
[b] Measured as conversion % by GC.
[c] Determined by capillary chiral GC analysis using the chiral column (HP-chiral).
[d] Absolute configuration was determined by comparing the sign of specific rotation.[16–19] The major enantiomer in all cases had the (*S*)-configuration.
[e] Values in parentheses are for conditions: −30 °C, 40 h and 20 mol % of ligand.

When the amount of ligand was increased to 20 mol %, and the temperature was decreased to −30 °C, the adduct was obtained in high yield and good enantiomeric excess (Table 1, entries 6, 17 and Table 2, entries 1–5, 7). Although ligand **1** gave higher yields than **3**, better enantioselectivities were obtained with **3** (Table 1, entries 6, 17 and Table 2 entries 1, 2).

3. Conclusion

In conclusion three morphinan ligands have been used for the first time in the enantioselective addition of diethylzinc to aromatic aldehydes. These results demonstrate that the chiral morphinan-based ligands are promising in asymmetric catalysis and deserve certainly more attention.

4. Experimental

4.1. General

Mass spectra were recorded on a FINNIGAN-MAT8430 mass spectrometer operating at an ionization-potential of 70 eV. Conversions were determined with a Hewlett-Packard HP-5890 GC instrument equipped with a flame ionization detector and a 30 m HP-1 capillary column, using nitrogen (2 mL/min) as carrier gas. The enantiomeric ratios were determined with the aforementioned apparatus using a 30 m WCOT fused silica capillary column (HP-chiral).

4.2. General procedure for the enantioselective addition of diethylzinc to benzaldehyde

The ligand (0.11 mmol) was placed in a test tube and dissolved in dry toluene (2 mL). The solution was stirred for 5 min. A 1.0 M solution of diethylzinc in *n*-hexane (2.2 mmol, 2.2 mL) was then added, and after the mixture had been stirred for 5 min, a solution of benzaldehyde (1.11 mmol) in dry toluene (1 mL) was added by syringe. The mixture was stirred at the appropriate temperature for 40 h. Saturated aqueous NH_4Cl was added (10 mL) and the mixture was extracted with ethyl acetate (3×20 mL). The collected organic phase was washed with water, dried over Na_2SO_4 and analyzed by GC, after suitable dilution.

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