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Tailoring the ligand structure to the reagent in the mandelamide-Ti (IV) catalyzed enantioselective addition of dimethyl- and diethylzinc to aldehydes

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Abstract

Amides derived from (*S*)-(+)-mandelic acid in the presence of titanium isopropoxide catalyze the enantioselective addition of dimethyl- and diethylzinc to aldehydes with good yields and ee up to 90%. Because of the modular character of the mandelamides, the structure of the ligand can be tailored to obtain the best results with each reagent. Thus, best results with dimethylzinc are obtained with *N*-benzyl mandelamide while *N*-(pyridin-2-yl) mandelamide is the best ligand for the addition of diethylzinc.

Keywords: Alkylation; Asymmetric catalysis; Organometallics; Dialkylzinc; Chiral alcohols; Titanium

1. Introduction

Enantioselective addition of diorganozinc reagents to aldehydes in the presence of a catalytic amount of chiral ligand is a convenient method for the synthesis of optically active secondary alcohols. Most diorganozinc reagents can be easily prepared, stored and, unlike other organometallic reagents, are compatible with many functional groups. Therefore, a multitude of chiral ligands that can enantioselectively catalyze this reaction have been developed [1]. Among them, *N*,*O*-ligands hold a prominent position: 1,2-aminoalcohols [2] have been mostly used, but the class includes 1,3- [3], and 1,4-aminoalcohols [4], as well as hydroxypyridines [5]. Furthermore, some of their derivatives such as iminoalcohols [6] and hydroxysulfonamides [7], usually in combination with titanium isopropoxide, have been used.

However, despite the large number of catalysts reported and the success obtained with many of them, the development of new ligands able to catalyze the addition of diorganozinc reagents to aldehydes keeps attracting the attention of many chemists [8]. On the other hand, from the hundreds of ligands for this asymmetric addition only a small number of them are obtained by simple synthetic methods. Therefore, stable ligands, prepared through short synthetic pathways from easily accessible starting materials and available in both enantiomeric forms, are still desirable. Furthermore, a modular system comprised of simple components would be valuable in order to gain quick access to a diversity of ligands, which is important since the efficiency of a particular ligand may depend on the diorganozinc reagent. The union of these components through an amide bond is a convenient method for this purpose (Fig. 1). Seto et al. have described modular ligands derived from aminoacids (AA) that incorporate both a tertiary amine and a carbamate or amide functional group [9]. Adolfsson et al. have reported modular oxazoline-amide ligands with different potential denticities [10]. Luis et al. have reported the use of nickel complexes from α-amino amides as catalysts in the enantioselective Et_2Zn addition to benzaldehyde [11].

Recently, we described the use of C_2 symmetric chiral bis(amino alcohol)oxalamides (Fig. 1) as catalysts for the addition of diethylzinc to aldehydes with moderate enantioselectivity [12]. Although the presence of C_2 symmetry is generally con-

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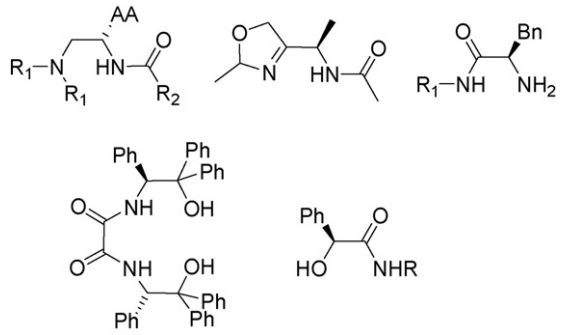


Fig. 1. Amide-containing ligands used for the addition of dialkylzinc to aldehydes.

sidered an advantageous structural feature [13], recent examples have shown the potential of C_1 symmetric ligands that, in some cases, can be more efficient than related C_2 systems [14] Accordingly, we proposed the use of C_1 symmetric hydroxyamides derived from chiral α-hydroxyacids and amines. These ligands are readily prepared from cheap and easily available sources, stable and storable, and present some structural features that make them very attractive in this respect. Thus, the presence of two groups with different coordinating capabilities, the hydroxyl and the N–H amide functionalities which can be both deprotonated, may favor the formation of strong metal complexes with a defined steric and electronic environment. Structural variety may be created by employing different hydroxyacids [15] and amines; furthermore, additional stereogenic centers and/or coordinating points to the metal ion can be introduced in the molecule through the appropriate selection of the R group in the amine. In a previous communication [16,17], we found that *N*-benzyl mandelamide catalyzed the addition of dimethylzinc to aldehydes with good yields and ee up to 90%. However, a low ee was obtained for the addition of diethylzinc to benzaldehyde under the same reaction conditions. Herein we will show that the structure of the mandelamide ligand can be modified and tailored to allow high enantioselectivity in the addition of diethylzinc to aldehydes, as well. We will report a full account for the addition of dimethyl- and diethylzinc to aldehydes using the proper mandelamide as chirality inducers for each reagent.

2. Experimental

2.1. Materials and analytical methods

Commercial reagents were used as purchased. Dichloromethane was distilled from CaH_2 and stored over 4A molecular sieves. All asymmetric reactions were carried out in dry glassware under argon atmosphere. Reactions were monitored by TLC analysis using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040–0.063 mm. Specific optical rotations were measured using sodium light (D line 589 nm). IR were recorded as liquid films in NaCl for oils and as KBr discs for solids. ^{1}H NMR were run at 299.95 MHz for ^{1}H and at 50.3 MHz for ^{13}C NMR, and referenced to the solvent as internal standard. The carbon type was determined by DEPT experiments. MS(EI) were run at 70 eV. Chiral GLC analyses were carried out in a Thermo Quest Trace GC 2000 series instrument equipped with a flame ionization detector using nitrogen (1 mL/min) as carrier gas, $T_{injector} = 220\,^{\circ}C$, $T_{detector} = 220\,^{\circ}C$. Chiral HPLC analyses were performed in an Agilent 1100 series instrument equipped with a refraction index detector. Retention times for GLC and HPLC are given in min.

2.2. General procedure for the synthesis of mandelamides *3a–e*

N,*N*′-Dicyclohexylcarbodiimide (7.5 g, 36.1 mmol) was added to a stirred solution of (*S*)-(+)-mandelic acid (**1**) (5 g, 32.9 mmol), amine **2** (32.9 mmol) and *N*-hydroxysuccinimide (4.2 g, 36.1 mmol) in anhydrous tetrahydrofuran (140 mL) at 0 °C under argon atmosphere. The cooling bath was removed and reaction mixture was stirred overnight, filtered and the cake of dicyclohexylurea was washed with THF (2 × 10 mL). The solvent was removed under reduced pressure, and the residue was dissolved with ethyl acetate. The solution was washed successively with saturated aqueous sodium carbonate, water, 1 M HCl (except in the case of **3d**), water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel eluting with hexane–ethyl acetate mixtures.

- 2.2.1. *N*-Benzyl-(*S*)-mandelamide (**3a**): 80% yield; physical and spectral data identical to those reported in the literature [16].
- 2.2.2. *N*-[(*R*)-1-Phenylethyl]-(*S*)-mandelamide (**3b**): 94% yield; physical and spectral data identical to those reported in the literature[16].
- 2.2.3. *N*-[(*S*)-1-Phenylethyl]-(*S*)-mandelamide (**3c**): 90% yield; physical and spectral data identical to those reported in the literature[16].
- 2.2.4. *N*-(Pyridin-2-ylmethyl)-(*S*)-mandelamide (**3d**): 74% yield; physical and spectral data identical to those reported in the literature[16].
- 2.2.5. *N*-[(2-Methoxyphenyl)methyl]-(*S*)-mandelamide (**3e**): 89% yield; mp 57-59 °C; $[\alpha]_D^{25}$ +56.7 (c 0.53, $CHCl_3$), $[\alpha]_D^{25}$ +48.1 (*c* 0.94, CH_3OH); IR *ν* 3338, 3064, 1659, 1531, 1494, 1244 cm^{-1}; MS(EI) 271 (M^+, 16), 253 (20), 121 (100); HRMS 271.1187, $C_{16}H_{17}NO_3$ required 271.1208; ^{1}H NMR ($CDCl_3$) *δ* 7.36–7.32 (m, 5H); 7.26 (td, *J* = 7.6, 1.6 Hz, 1H), 7.17 (dd, *J* = 7.5, 1.6 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 1H), 6.52 (br s, 1H), 5.00 (d, J = 3.3 Hz, 1H), 4.42 (AB system, 2H), 3.73 (s, 3H); ^{13}C NMR ($CDCl_3$) *δ* 171.9 (s), 157.4 (s), 139.5 (s), 129.4 (d), 128.9 (d), 128.6 (d), 128.4 (d), 126.8 (d), 125.6 (d), 120.5 (d), 110.2 (d), 74.0 (d), 55.1 (q), 39.6 (t).
- 2.2.6. *N*-(*tert*-butyl)-(*S*)-mandelamide (**3f**): 95% yield; physical and spectral data identical to those reported in the literature [16].

2.3. General procedure for the enantioselective addition of dimethylzinc to aldehydes:

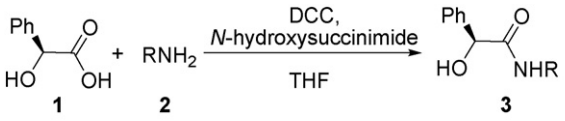
To a solution of ligand **3a** (48 mg, 0.2 mmol) in dry CH_2Cl_2 (5 mL) under Ar was added $Ti(OPr^i)_4$ (0.42 mL, 1.4 mmol). After 1 h, the reaction mixture was cooled to 0 °C and a 2 M solution of dimethylzinc in toluene (3 mL, 6 mmol) was added. After 30 min, the aldehyde (1 mmol) was added and stirring was continued at this temperature for 24 h. Then, the reaction was quenched with 1 M HCl (20 mL) (CAUTION! exothermic reaction, gas evolution), filtered and extracted with diethyl ether (3 × 15 mL). The organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Flash chromatography on silica gel eluting with hexane–diethyl ether mixtures gave the corresponding alcohol. Yields and ee are included in Table 2.

- 2.3.1. (*S*)-(−)-1-Phenyl-1-ethanol. GC (Supelco β-dex-225): $t_R = 24.2$, $t_S = 26.4$ ($T_{column} = 100$ °C).
- 2.3.2. (*S*)-(−)-1-(4-Chlorophenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 44.8$, $t_S = 47.4$ ($T_{column} = 120$ °C).
- 2.3.3. (*S*)-(−)-1-(4-Nitrophenyl)-1-ethanol. HPLC (Chiralcel OD-H): $t_R = 30.1$, $t_S = 31.8$ (hexane/^{i}PrOH 98:2, flow 1 mL/min).
- 2.3.4. (*S*)-(−)-1-(4-Methylphenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 36.9$, $t_S = 43.1$ ($T_{column} = 105$ °C).
- 2.3.5. (*S*)-(−)-1-(4-Methoxyphenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 34.1$, $t_S = 36.7$ ($T_{column} = 125$ °C).
- 2.3.6. (*S*)-(−)-1-(3-Chlorophenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 23.8$, $t_S = 24.2$ ($T_{column} = 100$ °C (5 min) to 200 °C at 3 °C/min).
- 2.3.7. (*S*)-(−)-1-(3-Nitrophenyl)-1-ethanol. HPLC (Chiralpack AD-H): $t_R = 23.6$, $t_S = 28.4$ (hexane/^{i}PrOH 98:2, flow 1 mL/min).
- 2.3.8. (*S*)-(−)-1-(3-Methylphenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 28.3$, $t_S = 31.3$ ($T_{column} = 105$ °C).
- 2.3.9. (*S*)-(−)-1-(3-Methoxyphenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 75.2$, $t_S = 75.6$ ($T_{column} = 90$ °C (60 min) to 200 °C at 5 °C/min).
- 2.3.10. (*S*)-(−)-1-(2-Chlorophenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 19.2$, $t_S = 19.0$ ($T_{column} = 100$ °C (5 min) to 200 °C at 3 °C/min).
- 2.3.11. (*S*)-(+)-1-(2-Nitrophenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 29.3$, $t_S = 28.8$ ($T_{column} = 100$ °C (5 min) to 200 °C at 3 °C/min).
- 2.3.12. (*S*)-(−)-1-(2-Methylphenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 62.8$, $t_S = 63.7$ ($T_{column} = 85$ °C).
- 2.3.13. (*S*)-(−)-1-(2-Ethylphenyl)-1-ethanol. GC (Supelco β-dex-225): $t_R = 87.2$, $t_S = 88.3$ ($T_{column} = 85$ °C).
- 2.3.14. (*S*)-(−)-1-(2-Methoxyphenyl)-1-ethanol. GC (Mega DETTBSIL β): $t_R = 43.6$, $t_S = 41.2$ ($T_{column} = 95$ °C (30 min) to 200 °C at 3 °C/min).
- 2.3.15. (*S*)-(+)-2-Undecanol. HPLC (Chiralpack AD-H): $t_R = 23.4$, $t_S = 22.9$ (hexane/^{i}PrOH 98:2, flow 0.25 mL/min).
- 2.3.16. (*S*)-(+)-4-Phenyl-2-butanol. GC (Supelco β-dex-225): $t_R = 57.9$, $t_S = 58.9$ ($T_{column} = 105$ °C).
- 2.3.17. (*S*)-(+)-1-Cyclohexylethanol. HPLC (Chiralpack AD-H): $t_R = 17.4$, $t_S = 16.7$ (hexane/^{i}PrOH 98:2, flow 0.5 mL/min), or GC (Supelco β-dex-225): $t_R = 27.0$, $t_S = 24.6$ ($T_{column} = 85$ °C).

2.4. Enantioselective addition of diethylzinc to aldehydes

To a solution of ligand **3d** (48 mg, 0.2 mmol) in dry toluene (5 mL) under Ar was added $Ti(OPr^i)_4$ (0.42 mL, 1.4 mmol). After 1 h, the reaction mixture was cooled to 0 °C and a 1.1 M solution of diethylzinc in toluene (2.7 mL, 3 mmol) was added. After 30 min, the reaction mixture was cooled to –10 °C and the aldehyde (1 mmol) was added and stirring was continued at this temperature until consumption of the starting material. Working up as described above followed by flash chromatography gave the corresponding alcohol. Yields and ee are included in Table 4.

- 2.4.1. (*S*)-(−)-1-Phenyl-1-propanol. GC (Supelco β-dex-225): $t_R = 16.3$, $t_S = 16.4$ ($T_{column} = 100$ °C (5 min) to 200 °C at 3 °C/min).
- 2.4.2. (*S*)-(−)-1-(4-Chlorophenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 43.3$, $t_S = 44.3$ ($T_{column} = 125$ °C).
- 2.4.3. (*S*)-(−)-1-(4-Bromophenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 89.2$, $t_S = 90.5$ ($T_{column} = 120$ °C (5 min) to 200 °C at 1 °C/min).
- 2.4.4. (*S*)-(−)-1-(4-Nitrophenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 66.6$, $t_S = 67.3$ ($T_{column} = 100$ °C (5 min) to 170 °C at 3 °C/min).
- 2.4.5. (*S*)-(−)-1-(4-Methylphenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 20.0$, $t_S = 20.2$ ($T_{column} = 100$ °C (5 min) to 200 °C at 3 °C/min).
- 2.4.6. (*S*)-(−)-1-(4-Methoxyphenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 27.2$, $t_S = 27.4$ ($T_{column} = 100$ °C (5 min) to 200 °C at 3 °C/min).
- 2.4.7. (*S*)-(−)-1-(3-Chlorophenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 25.3$, $t_S = 25.5$ ($T_{column} = 100$ °C (5 min) to 200 °C at 3 °C/min).
- 2.4.8. (*S*)-(−)-1-(3-Nitrophenyl)-1-propanol. HPLC (Chiralpack AD-H): $t_R = 15.6$, $t_S = 16.1$ (hexane/^{i}PrOH 95:5, flow 1 mL/min).
- 2.4.9. (*S*)-(−)-1-(3-Methylphenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 28.5$, $t_S = 30.3$ ($T_{column} = 110$ °C).
- 2.4.10. (*S*)-(−)-1-(3-Methoxyphenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 31.6$, $t_S = 32.7$ ($T_{column} = 130$ °C).
- 2.4.11. (*S*)-(−)-1-(2-Chlorophenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 32.3$, $t_S = 31.6$ ($T_{column} = 135$ °C).
- 2.4.12. (*S*)-(−)-1-(2-Nitrophenyl)-1-propanol. GC (Supelco β-dex-225): $t_R = 45.6$, $t_S = 44.3$ ($T_{column} = 115$ °C).
- 2.4.13. (*S*)-(−)-1-(2-Methylphenyl)-1-propanol. GC (Mega DETTBSIL β): $t_R = 19.3$, $t_S = 19.6$ ($T_{column} = 100$ °C (5 min) to 200 °C at 3 °C/min).
- 2.4.14. (*S*)-(−)-1-(2-Methoxyphenyl)-1-propanol. HPLC (Chiralpack AD-H): $t_R = 13.0$, $t_S = 12.6$ (hexane/^{i}PrOH 95:5, flow 1 mL/min).
- 2.4.15. (*S*)-(+)-3-dodecanol. GC (Supelco β-dex-225): $t_R = 132.8$, $t_S = 133.8$ ($T_{column} = 95$ °C).



a: R = Bn
b: R = (*R*)-Ph(CH$_3$)CH-
c: R = (*S*)-Ph(CH$_3$)CH-
d: R = 2-Py-CH$_2$-
e: R = 2-MeO-C$_6$H$_4$-CH$_2$-
f: R = *t*-Bu

Scheme 1. Synthesis of mandelamides **3a**–**f**.

- 2.4.16. (*S*)-(+)-1-Phenyl-3-pentanol. GC (Supelco β-dex-225): $t_R = 73.1$, $t_S = 74.1$ ($T_{column} = 110\,^{\circ}C$).
- 2.4.17. (*S*)-(−)-1-Cyclohexylpropanol. GC (Supelco β-dex-225): $t_R = 33.1$, $t_S = 37.8$ ($T_{column} = 90\,^{\circ}C$).

3. Results and discussion

3.1. Preparation of the α-hydroxyamide ligands

A series of hydroxyamides **3** was prepared from (*S*)-(+)-mandelic acid (**1**) and primary amines **2**. The ligands were obtained in a one step procedure by coupling of the α-hydroxyacid and the amine in the presence of dicyclohexylcarbodiimide (DCC) and *N*-hydroxysuccinimide [18], in good yields and without the need for protecting the hydroxyl group (Scheme 1). Benzylamide **3a** was used as the lead ligand. Benzylamides **3b** and **3c** incorporate an additional stereogenic center in the molecule, while α-hydroxyamides **3d** and **3e** incorporate an additional potential coordinating group on the amino substituent. Finally ligand **3f** bears an aliphatic amine.

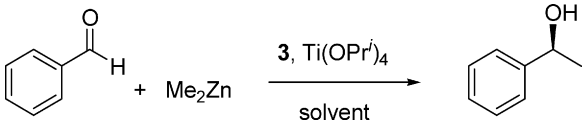
3.2. Enantioselective addition of dimethylzinc to aldehydes

Our first interest was the addition of dimethylzinc to aldehydes. The small number of studies in the addition of Me_2Zn to aldehydes, compared with Et_2Zn, is in part due to the lower reactivity of Me_2Zn, which was documented in the literature [19]. However, the chiral 1-hydroxyethyl moiety resulting from the addition of a methyl group to an aldehyde is found widespread in nature, and makes this reaction very interesting from a synthetic point of view [20].

For the optimization process we chose the reaction between Me_2Zn and benzaldehyde (Table 1). The reaction was initially performed with **3a** in dichloromethane solution at 0 °C using a commercially available solution of Me_2Zn (2 M in toluene). Under these conditions, no reaction was observed after 24 h (entry 1). The addition of 1.6 equivalents of titanium isopropoxide dramatically improved the result giving the expected product in 85% yield and 78% ee (entry 2). A screening of ligands was carried out under identical conditions. Ligands **3a** and **3e** gave the best results (entries 2 and 6, respectively). The presence of additional stereogenic centers as in ligands **3b** and **3c** reduced the stereoselectivity (entries 3 and 4). Similar results were obtained when the phenyl group was substituted by a pyridine ring (entry 5) or with ligand **3f** derived from an aliphatic amine (entry 7). Although ligands **3a** and **3e** gave similar results, ligand **3a** was preferred in account of the lower cost of the required amine. A change in the solvent from dichloromethane to toluene did not bring any improvement (entry 8). The effect of the temperature was studied next since it is known that the addition of dialkylzinc to aldehydes usually reaches a maximum ee at a certain temperature, which is called the inversion temperature [7,21]. When the reaction was carried out at −10 °C (entry 9) we observed a decrease in the reaction rate, which was incomplete after 40 h, while the ee was kept close to that obtained at 0 °C. On the other hand, at room temperature a decrease in ee to 74% was observed (entry 10). Accordingly the optimized reaction conditions for the addition of Me_2Zn to aldehyde involved the use of ligand **3a** and 1.6 equiv. of Ti(OPr^i)$_4$ in dichloromethane at 0 °C.

A number of aldehydes were subjected to these optimized conditions; the results are gathered in Table 2. Reasonable to

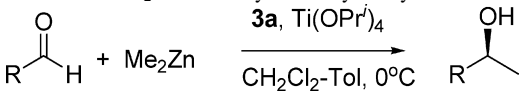
Table 1
Enantioselective addition of dimethylzinc to benzaldehyde. Optimization of the reaction conditions



Entry	Ligand **3**	Solvent	Reagent	T (°C)	t (h)	Yield (%)[a]	ee (%)[b]
1[c]	**a**	CH_2Cl_2	2 M Me_2Zn in toluene	0	20	–	–
2	**a**	CH_2Cl_2	2 M Me_2Zn in toluene	0	20	85	78
3	**b**	CH_2Cl_2	2 M Me_2Zn in toluene	0	20	47	49
4	**c**	CH_2Cl_2	2 M Me_2Zn in toluene	0	20	57	57
5	**d**	CH_2Cl_2	2 M Me_2Zn in toluene	0	20	65	19
6	**e**	CH_2Cl_2	2 M Me_2Zn in toluene	0	20	83	79
7	**f**	CH_2Cl_2	2 M Me_2Zn in toluene	0	20	69	35
8	**a**	Toluene	2 M Me_2Zn in toluene	0	20	87	75
9	**a**	CH_2Cl_2	2 M Me_2Zn in toluene	–10	40	60	79
10	**a**	CH_2Cl_2	2 M Me_2Zn in toluene	RT	20	90	74

[a] Isolated product.
[b] (*S*)-(−)-1-Phenylethanol as the major enantiomer. ee determined by GLC using a β-dex-225 column.
[c] Reaction carried out in the absence of titanium isopropoxide.

Table 2
Addition of Me_2Zn to aldehydes catalyzed by **3a** and titanium isopropoxide



Entry	Aldehyde	*t* (h)	Yield (%)[a]	ee (%)[b]
1	Benzaldehyde	20	85	78
2	*p*-Chlorobenzaldehyde	20	94	74
3	*p*-Nitrobenzaldehyde	20	92	49
4	*p*-Methylbenzaldehyde	20	83	82
5	*p*-Methoxybenzaldehyde	20	91	80
6	*m*-Chlorobenzaldehyde	20	79	66
7	*m*-Nitrobenzaldehyde	20	97	82
8	*m*-Methylbenzaldehyde	20	96	85
9	*m*-Methoxybenzaldehyde	20	90	78
10	*o*-Chlorobenzaldehyde	20	97	80
11	*o*-Nitrobenzaldehyde	20	82	85
12	*o*-Methylbenzaldehyde	20	75	89
13	*o*-Ethylbenzaldehyde	20	40	90
14	*o*-Methoxybenzaldehyde	20	95	85
15	Decanal	20	75	63
16	Dihydrocinnamaldehyde	24	70	61
17	Cyclohexanecarboxyaldehyde	24	33	55

[a] Yields refer to isolated products.
[b] *S* configuration for the major enantiomer in all the cases.

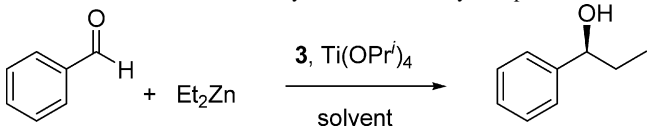
good yields and enantioselectivities are obtained with most of the aromatic aldehydes (entries 1–14). In general, there is only little dependence of the enantioselectivity on the electronic character of the substituents in *ortho*- (entries 10–14) and *meta*- (entries 6–9) substituted benzaldehydes. However, there is a dramatic decrease in the ee in the case of *p*-nitrobenzaldehyde (entry 3) with respect to other *p*-substituted benzaldehydes. In these cases, it appears that electron-donating substituents in the *para* positon increase the ee. On the other hand, *ortho*-substituted benzaldehydes give higher ee than either *meta*-substituted ones or *para*-substituted ones. The enantiomeric excesses found for aliphatic aldehydes (entries 15–17) were lower than for aromatic ones. Aliphatic aldehydes gave lower yields and enantiomeric excesses when the steric hindrance in the proximity of the carbonyl group increased.

3.3. Enantioselective addition of diethylzinc to aldehydes

Following a similar systematics as with Me_2Zn, the reaction between Et_2Zn and benzaldehyde was performed in dichloromethane at 0 °C, using a commercial 1 M solution of diethylzinc in hexanes. As with Me_2Zn, the reaction required the addition of 1.6 equivalents of $Ti(OPr^i)_4$ to proceed (Table 3, entry 2). Under these conditions ligand **3d** gave the best result (entry 5). It should be noted that ligand **3d** gave the lowest ee with dimethylzinc and that ligand **3a**, which was the best ligand for dimethylzinc, gave a low ee with diethylzinc. These results indicate the importance of a proper choice of the amine component of the ligand for each dialkylzinc reagent. A further improvement was observed when the Et_2Zn solution in hexanes was replaced by a toluene solution and when toluene was used as the only solvent (entries 8 and 9), indicating the importance of the solvent for the outcome of the enantioselective addition of diethylzinc to aldehydes, compared with dimethylzinc. The inversion temperature was near −10 °C (entry 10). At temperatures above or below this, the enantioselectivity of the reaction decreased (entries 11–12).

The catalytic system formed by ligand **3d**, titanium isopropoxide and diethylzinc was applied to a series of aromatic and aliphatic aldehydes under the optimized conditions. The results are shown in Table 4. In general good yields and ee were obtained with *para*- and *meta*-substituted aromatic

Table 3
Enantioselective addition of diethylzinc to benzaldehyde. Optimization of the reaction conditions



Entry	Ligand **3**	Solvent	Reagent	*T* (°C)	*t* (h)	Yield (%)[a]	ee (%)[b]
1[c]	**a**	CH_2Cl_2	1 M Et_2Zn in hexanes	0	24	10	4
2	**a**	CH_2Cl_2	1 M Et_2Zn in hexanes	0	24	70	51
3	**b**	CH_2Cl_2	1 M Et_2Zn in hexanes	0	24	59	36
4	**c**	CH_2Cl_2	1 M Et_2Zn in hexanes	0	24	62	44
5	**d**	CH_2Cl_2	1 M Et_2Zn in hexanes	0	4.5	97	68
6	**e**	CH_2Cl_2	1 M Et_2Zn in hexanes	0	24	88	61
7	**f**	CH_2Cl_2	1 M Et_2Zn in hexanes	0	24	62	32
8	**d**	CH_2Cl_2	1.1 M Et_2Zn in toluene	0	5	94	74
9	**d**	Toluene	1.1 M Et_2Zn in toluene	0	2.5	95	81
10	**d**	Toluene	1.1 M Et_2Zn in toluene	–10	2.5	94	86
11	**d**	Toluene	1.1 M Et_2Zn in toluene	–40	3.5	96	82
12	**d**	Toluene	1.1 M Et_2Zn in toluene	–60	24	60[d]	28
13	**d**	Toluene	1.1 M Et_2Zn in toluene	RT	2.5	65	74

[a] Isolated product.
[b] (*S*)-(−)-1-Phenylpropanol as the major enantiomer. ee determined by GLC using a β-dex-225 column.
[c] Reaction carried out in the absence of titanium isopropoxide.
[d] Conversion determined by GLC. Starting material unreacted 40%.

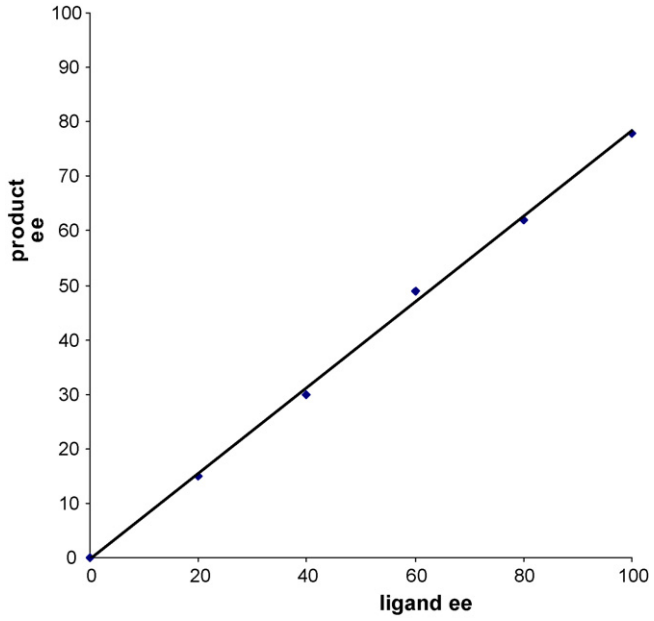
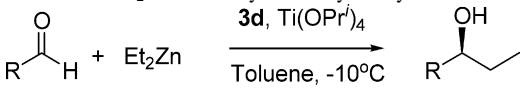


Fig. 2. Linear correlation for the addition of dimethylzinc to benaldehyde catalyzed by **3a**-titanium isopropoxide.

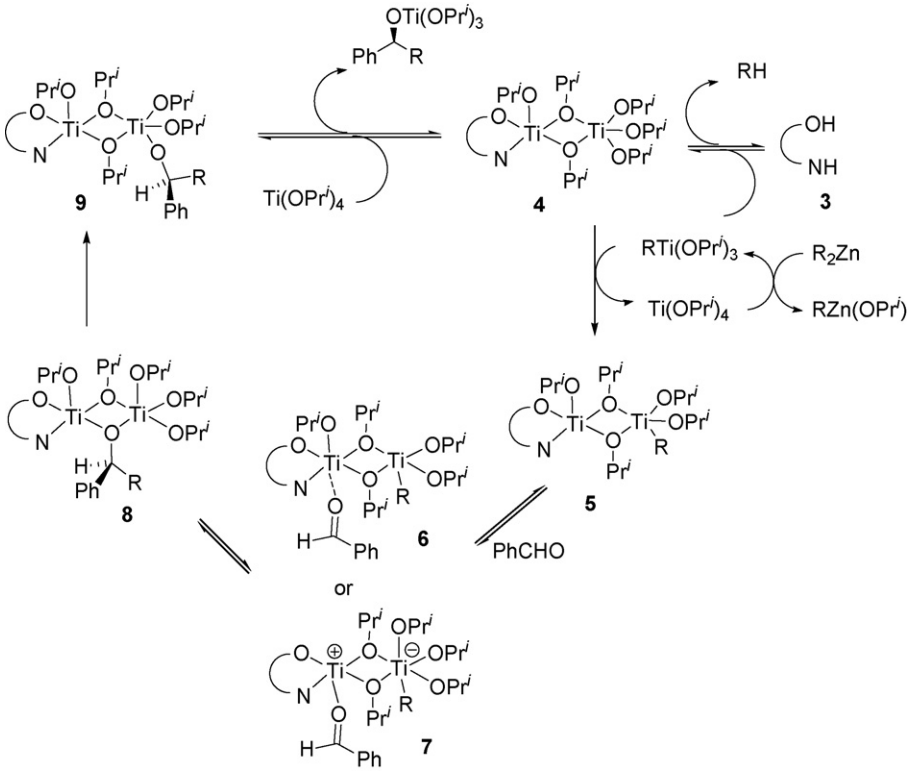
Table 4
Addition of Et_2Zn to aldehydes catalyzed by **3d** and titanium isopropoxide



Entry	Aldehyde	*t* (h)	Yield (%)[a]	ee (%)[b]
1	Benzaldehyde	2.5	94	86
2	*p*-Chlorobenzaldehyde	1.5	97	88
3	*p*-Bromobenzaldehyde	3	93	83
4	*p*-Nitrobenzaldehyde	4	88	62
5	*p*-Methylbenzaldehyde	5	97	79
6	*p*-Methoxybenzaldehyde	20	96	64
7	*m*-Chlorobenzaldehyde	4	97	86
8	*m*-Nitrobenzaldehyde	5	69	73
9	*m*-Methylbenzaldehyde	3.5	76	84
10	*m*-Methoxybenzaldehyde	5	97	80
11	*o*-Chlorobenzaldehyde	5	97	41
12	*o*-Nitrobenzaldehyde	5	66	32
13	*o*-Methylbenzaldehyde	20	90	44
14	*o*-Methoxybenzaldehyde	5.5	96	36
15	Decanal	4	84	88
16	Dihydrocinnamaldehyde	4	72	78
17	Cyclohexanecarboxyaldehyde	3	55	80

[a] Yields refer to isolated products.
[b] *S* configuration for the major enantiomer in all the cases.

aldehydes. In the case of *meta*-substituted benzaldehydes we found only small dependence of the enantioselectivity on the electronic character of the substituent, except in the case of *m*-nitrobenzaldehyde. This dependence was slightly more important in *para*-substituted benzaldehydes where the presence of strong electron-withdrawing (NO_2) or electron-releasing (MeO) groups brought about a significant decrease in the ee (entries 4 and 6). On the other hand, the presence of a substituent in the *ortho*- position caused a dramatic decrease in enantioselectivity, regardless of its electronic character (entries 11–14), indicating the importance of the steric hindrance in the proximity of the reactive center. These results are contrasted with those obtained in the addition of Me_2Zn for which *ortho*-



Scheme 2. Mechanistic proposal for the addition of dialkylzinc to aldehydes catalyzed by mandelamides **3**.

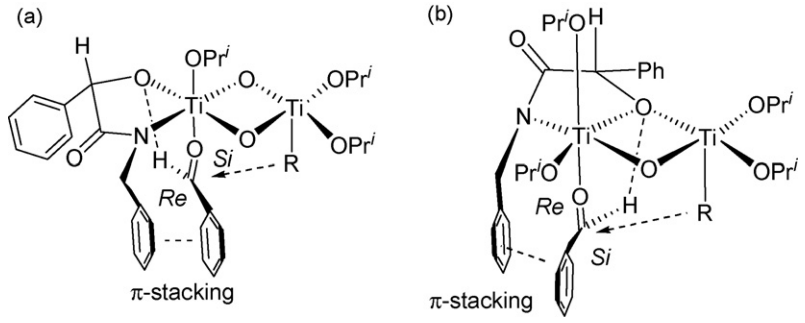


Fig. 3. Possible TS for the addition of dialkylzinc to aldehydes from the *Si* face of the aldehyde.

substituted benzaldehydes gave the highest enantioselectivities. Finally, aliphatic aldehydes gave high enantiomeric excesses with variable yields.

3.4. Mechanism and stereochemistry

In order to gain some insight into the mechanism of this reaction we performed non-linear effects studies for the addition of dimethylzinc to benzaldehyde catalyzed by **3a**-Ti(IV). A linear correlation between the ee of the product and the ee of the catalyst was observed (Fig. 2) indicating that dimeric species containing two units of mandelamide are not involved [22]. Linear correlations have been observed for several titanium promoted reactions with different ligands [7c].

According to this finding and based on studies carried out by Walsh [23] and Gau [24] we propose a plausible mechanism as shown in Scheme 2. The reaction of titanium isopropoxide with the chiral ligand **3** in the presence of the dialkylzinc reagent gives a dititanium complex **4**. This complex reacts with $RTi(OPr^i)_3$, generated from titanium isopropoxide and the dialkylzinc, to afford the precatalyst **5**. The coordination of the aldehyde to the more acidic titanium atom that is chelated to the chiral ligand results in the formation of the catalytic species **6** which is responsible for the facial enantiodiscrimination. Alternatively, a catalytic species **7** with a pentacoordinated cationic titanium atom may be considered, the benzaldehyde being coordinated in the same way [7c, 25]. After the addition of the alkyl group R to the carbonyl moiety, several successive interchanges of ligand on the titanium centers, including the interchange of the chiral alcoxide by isopropoxide, gives the product and renews the catalyst.

The reaction with either dimethyl or diethylzinc leads to the major alcohol having the *S* configuration regardless of the amide ligand **3** used as precatalyst. The stereochemical course of the reaction can be rationalized in terms of a bimetallic transition state, containing two titanium atoms, related to that proposed for the addition of dialkylzinc to carbonyl compounds using hydroxy sulfonamides, for which we propose two possible structures (a) and (b) that lead to the same product stereochemistry (Fig. 3) [7c, 24]. Coordination of the aldehyde to the titanium atom takes place *anti* to the apical isopropoxy group [24,26], which is directed toward the less hindered face of the five membered ring described by the octahedral titanium and the ligand, opposite to the mandelic acid phenyl group. The aldehyde is arranged in such a way that the *Si* face of the carbonyl group is exposed to the alkyl group which is transferred from the second titanium atom. This arrangement might be stabilized by a hydrogen bond between the ligand oxygen and the aldehyde hydrogen in a similar way as described by Corey and Lee for other enantioselective reaction [27], and by a π-stacking effect between the aldehyde aryl group and the benzyl substituent on the amido group of **3** [7c].

4. Conclusion

In summary, we have shown that readily available mandelamides, obtained in one step, are effective ligands for the enantioselective Ti(IV)-catalyzed addition of dimethyl- and diethylzinc. The reaction works with a number of aromatic and aliphatic aldehydes. Highest enantioselectivity for dimethyl- or diethylzinc addition requires a proper choice of the mandelamide ligand in each case. This is possible by changing the *N*-substituent of the mandelamide in these modular ligands. Thus, best results with dimethylzinc are obtained with *N*-benzyl mandelamide while *N*-(pyridin-2-yl) mandelamide is the best ligand for the addition of diethylzinc.

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