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The synthesis of new optically active 2-methylquinoline derivatives and their application in the enantioselective addition of diethylzinc to aldehydes

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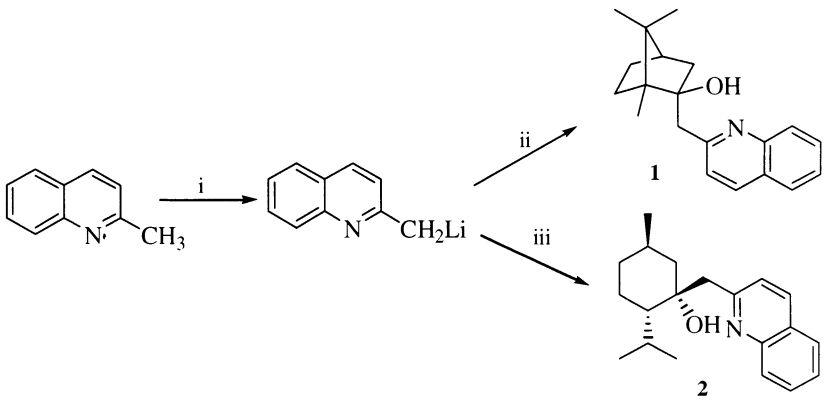
Abstract—Homochiral 2-methylquinoline derivatives have been synthesized and applied in the enantioselective addition of diethylzinc to aldehydes. Good yields and enantiomeric excesses of up to 91.4% were observed in these reactions. © 2001 Published by Elsevier Science Ltd.

1. Introduction

One of the most important and fundamental synthetic procedures for the establishment of carbon–carbon bond stereoselectivity is the enantioselective addition of organometallic reagents to aldehydes affording chiral secondary alcohols.[1] This structural feature is part of many natural products or can serve as an important synthetic precursor to various other functionalities, such as halide, amine, ester and ether. Effective enantioselective routes to *sec*-alcohols are therefore of great synthetic value.

The first reported enantioselective alkylation of aldehydes was performed by Betti, who obtained *sec*-alcohols with low enantioselectivity by treatment of benzaldehyde with methylmagnesium iodide in the presence of *N*,*N*-dimethylbornylamine.[2] A significant improvement has been achieved by using organozinc compounds as alkylating agents. Since uncoordinated organozinc compounds are virtually inert, the reaction requires a compound to coordinate to the metal atom to enhance nucleophilicity. Due to the increased reactivity of the reagent when it is involved in the coordinated complex, a catalytic amount of the coordinating ligand can be used. For this purpose, many chiral ligands, mostly with 1,2-functionalities, have been designed and synthesized.[3,4] Despite the variety of chiral ligands that have been synthesized, the design and development of cost-effective catalysts that exhibit



Scheme 1. *Reagents and conditions*: (i) BuLi, ether, 0°C; (ii) (+)-camphor, ether, 0°C; (iii) (−)-menthone, ether, 0°C.

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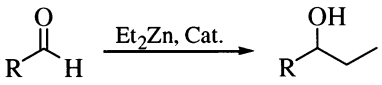

Scheme 2.

high reactivity and enantioselectivity remain an active research subject.

Several quinoline derived aminoalcohol[5] or (+)-camphor and (−)-menthone derived β-amino alcohols[6] have been synthesized and used in the enantioselective alkylation of aldehydes. However, to our knowledge, no chiral ligands derived from quinoline and (+)-camphor or (−)-menthone have been reported. Herein, we first report the syntheses of chiral ligands derived from 2-methylquinoline, (+)-camphor and (−)-menthone, and their applications in the enantioselective addition of diethylzinc to aldehydes.

2. Results and discussion

The syntheses of the chiral ligands **1** and **2** are shown in Scheme 1. 2-Methylquinoline was first lithiated with BuLi in ether at 0°C to give 2-quinolylmethyllithium,[7] followed by trapping with (+)-camphor or (−)-menthone to produce compounds **1** and **2** in nearly quantitative yields as single diastereoisomers, as shown by ^{1}H NMR analyses. The configurations shown in Scheme 1 are the same as those reported previously.[6]

The enantioselective addition of diethylzinc to aldehydes catalyzed by the synthesized chiral ligands **1** and **2** is shown in Scheme 2. It has been reported that the solvent has a great effect on the enantioselectivity and yield.[8] Therefore we first investigated the effect of solvent on the enantioselectivity of the addition of diethylzinc to benzaldehyde using ligand **1** as catalyst. The effect of temperature was also investigated, and the results of this study are shown in Table 1.

As expected, the e.e. values were better when the reactions were run in non-polar solvents than in polar solvents. If a non-polar solvent was used, a solvent effect was detectable but not very significant. At 0°C the use of toluene, benzene, ether, hexane, benzene/hexane or toluene/hexane as solvents gave e.e.s ranging from 76.8 to 83.1% (entries 4–9). Toluene/hexane was found to be the preferred solvent for this addition reaction since it gave the best yield and enantioselectivity (entry 9).

The effect of temperature on the enantioselectivity of the reaction was also detectable, albeit not very large, with e.e. values tending to increase with decreasing temperature (entries 9–11). For convenience a temperature of 0°C was chosen and the toluene/hexane mixture (1:1, v/v) was adopted as the solvent system.

Next, we examined the effect of catalyst loading and the results are summarized in Table 2. It is interesting to find that the amounts of the two ligands have different effects on the e.e. values. When ligand **1** was used, the e.e. values of (*R*)-1-phenylpropan-1-ol increased by increasing the amount of catalyst. For example, the enantioselective addition of diethylzinc to benzaldehyde in toluene/hexane (1:1, v/v) catalyzed by either 5, 10, 15 or 20 mol% of ligand **1** afforded (*R*)-1-phenylpropan-1-ol in e.e.s of 72.2, 78.2, 82.2 and 83.1%, respectively (entries 1–4). When this reaction was catalyzed by 5, 10 or 20 mol% of ligand **2**, the (*S*)-isomer was produced in e.e.s of 64.5, 63.4 and 24.4%, respectively (entries 5–7). Other solvent systems such as benzene/hexane, benzene and toluene were examined for ligand **2** and similar results were obtained (entries 8–14). This phenomenon is not easy to understand, but it probably arises from a non-stereoselective ethyl transfer to aldehyde promoted by zinc coordination to the nitrogen atom of the catalyst.[9]

Using the optimized reaction conditions, the addition of diethylzinc to various aromatic and aliphatic aldehydes catalyzed by both chiral ligands **1** and **2** was examined, and the results are summarized in Table 3. It

Table 1. The effect of solvents and temperature on the asymmetric addition of diethylzinc to benzaldehyde with **1** as a catalyst[a]

Entry	Solvent	Temperature (°C)[b]	Yield (%)[c]	E.e. (%) (config.)[d]
1	Dichloromethane	0	73	48.7 (*R*)
2	Acetonitrile	0	69	51.7 (*R*)
3	THF	0	56	67.6 (*R*)
4	Toluene	0	95	76.9 (*R*)
5	Benzene	0	96	76.8 (*R*)
6	Ether	0	91	79.3 (*R*)
7	Hexane	0	95	77.6 (*R*)
8	Benzene/hexane (1:1)	0	94	80.9 (*R*)
9	Toluene/hexane (1:1)	0	96	83.1 (*R*)
10	Toluene/hexane (1:1)	rt	94	82.4 (*R*)
11	Toluene/hexane (1:1)	−20	93	86.4 (*R*)

[a] Catalyst/benzaldehyde/Et_2Zn = 0.2/1.0/2.0 (mmol).
[b] The reactions were completed at the indicated temperature for 4 h then warmed to rt gradually with stirring for 12 h.
[c] Based on isolated product.
[d] The e.e. values were determined by GLC.

Table 2. The effect of chiral ligands on the asymmetric addition of diethylzinc to benzaldehyde[a]

Entry	Ligand (mol%)	Solvent	Yield (%)[b]	E.e. (%) (config.)[c]
1	**1** (20)	Toluene/hexane (1:1)	96	83.1 (*R*)
2	(15)	Toluene/hexane (1:1)	94	82.2 (*R*)
3	(10)	Toluene/hexane (1:1)	94	78.2 (*R*)
4	(5)	Toluene/hexane (1:1)	91	72.2 (*R*)
5	**2** (20)	Toluene/hexane (1:1)	92	24.4 (*S*)
6	(10)	Toluene/hexane (1:1)	90	63.4 (*S*)
7	(5)	Toluene/hexane (1:1)	93	64.5 (*S*)
8	(20)	Benzene/hexane (1:1)	88	26.1 (*S*)
9	(10)	Benzene/hexane (1:1)	90	54.1 (*S*)
10	(5)	Benzene/hexane (1:1)	85	56.7 (*S*)
11	(20)	Benzene	91	41.4 (*S*)
12	(5)	Benzene	89	48.9 (*S*)
13	(20)	Toluene	93	48.7 (*S*)
14	(5)	Toluene	91	53.3 (*S*)

[a] The reactions were run at 0°C for 4 h and then warmed up to rt gradually with stirring for 12 h. Benzaldehyde/Et_2Zn = 1.0/2.0 (mmol).
[b] Based on isolated product.
[c] E.e. values were determined by GLC.

can be seen from the results that the enantioselectivity of the addition of diethylzinc to aldehydes with an electron donating group in the *para*-position of the aromatic ring is higher than to an aldehyde with an electron withdrawing group when catalysed by ligand **1** (entries 3, 7, 9, 11 and 13). However, the addition reactions catalysed by ligand **2** for all the substituted aromatic aldehydes occurred with low enantioselectivity (entries 2, 4, 6, 8, 10, 12, 14, 16 and 18) and for aliphatic aldehydes, the enantioselectivities of the reaction are generally low (entries 19–26).

From all the above results, it can be seen that ligand **1** induced (*R*)-enriched products and ligand **2** induced (*S*)-enriched products. It is recognized that the actual catalyst is in situ formed ethylzinc aminoalkoxide. When the ethylzinc aminoalkoxide **A** is formed from **1** and diethylzinc, the O-Zn linkage should be arranged to the *syn*-position of the norbornane skeleton (Fig. 1). Due to the steric repulsion between the 1-methyl of norbornane and the quinoline ring, the less hindered *Re*-face of the zinc atom might be more reactive towards the aldehyde oxygen leading to **TS-1**, and the (*R*)-enriched product was obtained. In contrast, when the ethylzinc complex **B** is formed from **2** and diethylzinc, the O-Zn linkage should be arranged to the *anti*-position of the menthol skeleton. Because of steric hindrance between the quinoline ring and the ethyl group on zinc, the less hindered side was the *Si*-face of the zinc atom, which coordinates with the aldehyde oxygen leading to transition state **TS-2**, and an (*S*)-enriched product was obtained. The extreme difference

Table 3. Enantioselective addition of diethylzinc to aldehydes[a]

Entry	Substrate	Ligand (mol%)	Yield (%)[b]	E.e. (%) (config.)[c]
1	Benzaldehyde	**1** (20)	96	83.1 (*R*)
2		**2** (5)	93	64.5 (*S*)
3	*p*-Chlorobenzaldehyde	**1** (20)	90	76.5 (*R*)
4		**2** (5)	87	53.9 (*S*)
5	*o*-Anisaldehyde	**1** (20)	95	80.2 (*R*)
6		**2** (5)	94	54.5 (*S*)
7	*p*-Anisaldehyde	**1** (20)	89	91.4 (*R*)
8		**2** (5)	93	63.9 (*S*)
9	*p*-Tolualdehyde	**1** (20)	93	83.5 (*R*)
10		**2** (5)	96	60.9 (*S*)
11	4-(Dimethylamino)benzaldehyde	**1** (20)	97	88.5 (*R*)[d]
12		**2** (5)	95	58.9 (*S*)[d]
13	3,4-Dimethoxybenzaldehyde	**1** (20)	90	86.8 (*R*)[d]
14		**2** (5)	91	56.0 (*S*)[d]
15	1-Naphthaldehyde	**1** (20)	94	89.3 (*R*)[d]
16		**2** (5)	87	72.5 (*S*)[d]
17	2-Naphthaldehyde	**1** (20)	90	78.6 (*R*)[d]
18		**2** (5)	93	64.3 (*S*)[d]
19	*trans*-Cinnamaldehyde	**1** (20)	92	74.5 (*R*)[d]
20		**2** (5)	93	69.1 (*S*)[d]
21	Nonylaldehyde	**1** (20)	70	38.5 (*R*)[e]
22		**2** (5)	74	40.4 (*S*)[e]
23	Dodecylaldehyde	**1** (20)	78	29.7 (*R*)[e]
24		**2** (5)	85	31.1 (*S*)[e]
25	Cyclohexanecarboxaldehyde	**1** (20)	83	42.7 (*R*)[e]
26		**2** (5)	89	44.2 (*S*)[e]

[a] The reactions were run at 0°C for 4 h and then warmed up to rt gradually with stirring for 12 h. Aldehyde/Et_2Zn = 1.0/2.0 (mmol).
[b] Based on isolated product.
[c] Except as noted, the e.e. values were determined by GLC.
[d] Determined by HPLC.
[e] Determined by GLC after acetylation.

in the reactivity between *Re*- and *Si*-face in the aminoalkoxide **A** results in a highly enantioselective formation of alcohols.

In conclusion, we have demonstrated that chiral ligands **1** and **2** can be easily prepared from (+)-camphor and (−)-menthone, and that they are effective catalysts for the enantioselective addition of diethylzinc to aldehydes. Further work is in progress in this laboratory with the aim of expanding the use of these inexpensive chiral compounds to other enantioselective processes.

3. Experimental

3.1. General

All reactions were carried out under an Ar atmosphere. Melting points were measured on a Kofler melting apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-400 NMR spectrometer with TMS as an internal reference. Electron ionization mass spectra were obtained on a Hewlett–Packard HP5988A mass spectrometer. Positive ion FAB mass spectra as 3-nitrobenzyl alcohol matrix were recorded on a VG ZAB-HS mass spectrometer. Elemental analyses were performed on a Carlo–Erba-1106 elemental analyzer. Optical rotations were measured on a JASCO J-20C automatic polarimeter. Enantiomeric excess (e.e.) determination was carried out using GLC with a Chrompack CP-Chirasil-DEX CB capillary column on a Varian CP-3380 GC instrument with FID as detector and nitrogen as carrier gas or using HPLC with a Chiralcel OD column on a Varian SD-200 HPLC instrument with UV detector and hexane/2-propanol as eluent. The configuration establishment of the products was based on the comparison of the direction of specific rotation with known compounds. All solvents used were dried by standard methods and aldehydes were purified using standard, published methods before use.

3.2. The synthesis of 2-methylquinoline derived chiral ligands 1, 2

3.2.1. The synthesis of 2-methylquinoline derived chiral ligand 1. To a 100 mL flame-dried three-neck flask under an argon atmosphere were added 2-methylquinoline (1.34 mL, 10 mmol) and anhydrous ether (30 mL). This solution was cooled to 0°C and 2.4 M butyllithium in hexane (4.3 mL, 10.4 mmol) was added using a pressure-equalizing dropping funnel over 15 min with stirring. The cooling bath was removed and the solution was allowed to stir for 1 h while the temperature rose to ambient. A solution of (+)-camphor (1.51 g, 10 mmol) in ether (20 mL) was added over 15 min with vigorous stirring while the temperature cooled to 0°C. The mixture was stirred for additional 2 h and hydrolyzed with a saturated aqueous NH_4Cl solution. When decomposition was complete, the ether layer was separated, and the water layer was extracted with ethyl acetate (3×20 mL). The combined organic layers were

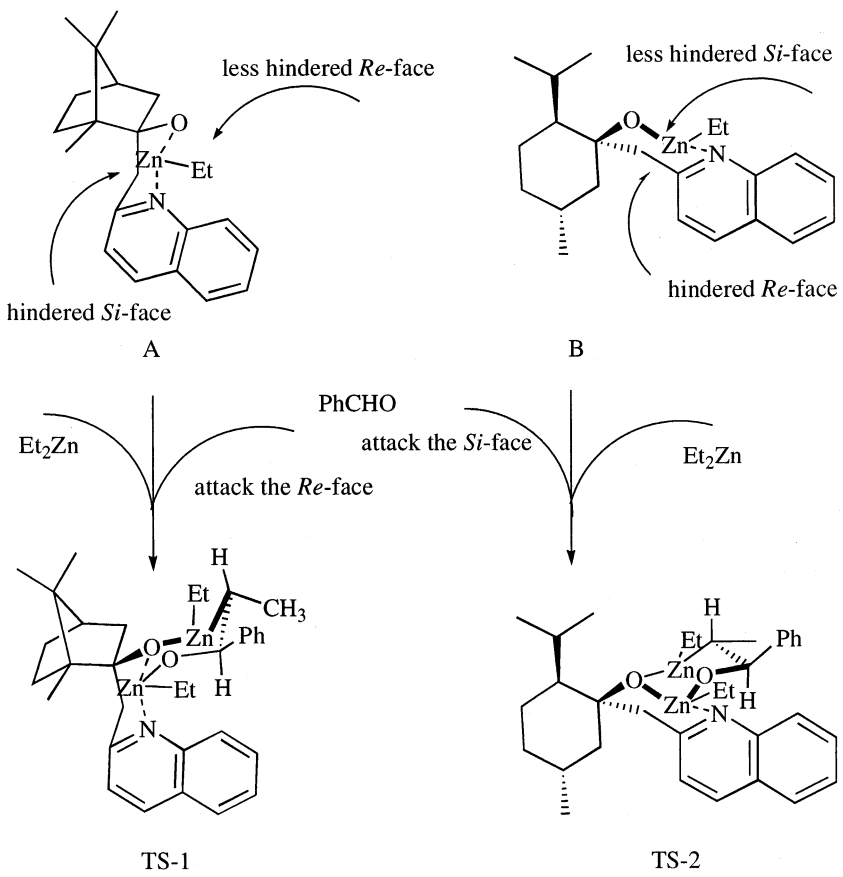

Figure 1.

washed with brine and dried over anhydrous Na_2SO_4, and the solvent was evaporated under reduced pressure. The crude product was purified by flash chromatography to give a white solid (2.80 g, 95% yield). Mp 88–89; $[\alpha]_D^{20}=-37.8$ (c 1.01, $CHCl_3$). ^1H NMR ($CDCl_3$, δ ppm): 0.56 (s, 3H), 0.64 (s, 3H), 1.17 (s, 3H), 1.10–1.15 (m, 1H), 1.41–1.49 (m, 2H), 1.52–1.58 (m, 1H), 1.71–1.78 (m, 2H), 2.14 (m, 1H), 3.17 (s, 2H), 6.75 (br, 1H), 7.33 (d, $J=8.4$ Hz, 1H), 7.51 (m, 1H), 7.69 (m, 1H), 7.80 (d, $J=8.4$ Hz, 1H), 8.01 (d, $J=8.2$ Hz, 1H), 8.12 (d, $J=8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 11.27, 21.04, 21.48, 22.23, 30.97, 45.07, 45.57, 47.53, 49.47, 52.50, 81.45, 122.91, 126.08, 126.67, 127.50, 128.71, 129.75, 136.71, 146.68, 161.27; MS m/z (EI): 295 (M^+), 280, 185, 143; positive ion FAB mass spectra m/z: 296 (M^++H). Anal. calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53; N, 4.74. Found: C, 81.23; H, 8.44; N, 4.89%.

3.2.2. The synthesis of 2-methylquinoline derived chiral ligand 2. Prepared from 1.53 g of (–)-menthone in a similar manner to that described above to give a white solid (2.67 g, 90% yield). Mp 137–138; $[\alpha]_D^{20}=-61.6$ (c 1.14, $CHCl_3$); ^1H NMR ($CDCl_3$, δ ppm): 0.66 (d, $J=6.5$ Hz, 3H), 0.95 (d, $J=6.5$ Hz, 3H), 1.02 (d, $J=6.5$ Hz, 3H), 0.87–0.91 (m, 1H), 1.10–1.12 (m, 1H), 1.24–1.27 (m, 1H), 1.44–1.48 (m, 1H), 1.61–1.70 (m, 4H), 2.36 (m, 1H), 3.14 (d, $J=13.8$ Hz, 1H), 3.47 (d, $J=13.8$ Hz, 1H), 5.30 (br, 1H), 7.43 (d, $J=8.4$ Hz, 1H), 7.53 (m, 1H), 7.71 (m, 1H), 7.91 (d, $J=8.4$ Hz, 1H), 7.99 (d, $J=8.4$ Hz, 1H), 8.24 (d, $J=8.4$ Hz, 1H). ^{13}C NMR ($CDCl_3$, δ ppm): 18.47, 21.40, 22.69, 24.00, 28.31, 26.98, 36.08, 47.89, 48.22, 51.33, 75.60, 124.29, 126.67, 127.49, 128.53, 129.22, 130.36, 137.24, 147.84, 162.53. MS m/z (EI): 297 (M^+), 282, 254, 240, 212, 143; positive ion FAB mass spectra m/z: 298 (M^++H). Anal. calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.67; H, 9.24; N, 4.93%.

3.3. General procedure for the asymmetric addition of diethylzinc to benzaldehyde

To a solution of ligand **1** (0.20 mmol) in toluene (2 mL) and hexane (2 mL) at 0°C was added a 1.0 M solution (2 mL, 2.0 mmol) of diethylzinc in hexane. After stirring for 30 min at 0°C, freshly distilled benzaldehyde (1 mmol) was added. The reaction mixture was stirred for 4 h at 0°C then allowed to warm to room temperature gradually with stirring for 12 h. After the addition of 1N HCl (10 mL), the phases were separated. The water layer was extracted with ethyl acetate (5 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. After purification by flash chromatography, the enantiomeric excess was determined by GLC.

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