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Chiral amide from (1*S*,2*R*)-(+)-norephedrine alkaloid in the enantioselective addition of diethylzinc to aryl and heteroaryl aldehydes

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ABSTRACT

Chiral amide synthesized from (1*S*,2*R*)-(+)-norephedrine and furoic acid was found to catalyze the enantioselective ethylation of aromatic and heteroaromatic aldehydes to secondary alcohols with 99.8% enantioselectivity at 0 °C without the addition of a promoter such as titanium tetraisopropoxide.

1. Introduction

Catalytic asymmetric carbon–carbon bond formation is one of the most important research areas in organic synthesis.[1] Among the carbon–carbon bond formation reactions, the synthesis of optically active secondary alcohols via the addition of diethylzinc to aldehydes using catalytic amounts of chiral catalysts has attracted much attention because they are important intermediates in the synthesis of many naturally occurring compounds, biologically active intermediates, several synthetic drugs, and new materials with interesting optical properties.[2,3] The first highly enantioselective addition of an organometallic reagent to an aldehyde was reported by Mukaiyama et al. in 1979.[4] Several other catalysts were also used after this initial result, for example, DAIB by Noyori (ee upto 99%);[5a] quinine by Wynberg (ee upto 92%);[5b] methylephedrine by Buono (ee upto 81%)[5c]; aminoalcohol by Oguni (ee upto 98%)[5d] and diamide in combination with titanium tetraisopropoxide as an additive by Ohno (ee upto 99%);[5e] diamines[5f], and titanium alkoxides.[5g] Although many types of ligands can catalyze the dialkylzinc addition to aldehydes, such as the derivatives of chiral amino alcohols or amino acids such as norephedrine,[5d,6] proline,[7] valine, borneol,[5a,8] terpene,[9] and pyrrolidine[10] the derivatives of chiral amino alcohols were found to catalyse the reaction more efficiently. Diethyl zinc does not give spontaneous addition to aldehydes due to its non-polar character, originating from its linear sp-hybridized geometry.[11] A more polar (and reactive) bent compound may be obtained upon coordination of an electronegative group, or by reaction with a protic residue. Such a bent and activated complex can give addition to an aldehyde. If chiral activating ligands are used, induction may take place upon reaction with an aldehyde. The mechanism of diethylzinc addition to benzaldehyde is well known with β-amino alcohols as ligands. The amino alcohol acts as a Lewis base which activates the zinc reagent and forms a Lewis acidic zinc species, which activates the aldehyde. Upon treatment of an amino alcohol with an alkylzinc reagent, the nitrogen and oxygen donor atoms of the amino alcohol coordinate to the zinc atom, yielding a bifunctional catalyst which is capable of acting as an alkyl donor. The zinc atom in the five-membered chelate ring is a Lewis acid, which coordinates the aldehyde through the oxygen non-bonding orbital, and hence the carbonyl carbon atom is activated for nucleophilic attack.

Among the ligands that have been synthesized and applied in the diethylzinc addition reaction, ephedrine represents a class of compound. The naturally occurring enantiomerically pure β-amino alcohol ephedrine, has been shown to catalyze the addition of diethylzinc to benzaldehyde by Chaloner.[12] N-Alkylated derivatives of norephedrine have been reported by Soai et al.[13] to catalyze the diethylzinc addition to aliphatic and aromatic aldehydes with high asymmetric induction. It has been reported that the phenolic unit is crucial for stable catalytic activity and enantioselectivity. Furthermore, the *ortho*-substituent in the prochiral aldehydes causes the enantiomeric ratio to favor the (*R*)-enantiomer in contrast to the principal formation of the (*S*)-enantiomer.[14] In addition to amino alcohols, certain chiral hydroxyamides have recently been proven to be efficient promoters for this valuable asymmetric addition.[15] Knochel[16,2b] and Seebach have opened up new routes to functionalized dialkylzinc compounds, which favor the formation of 1-phenylpropanol in high enantiomeric excess. The use of such reagents opens up routes to more complex chiral alcohols in high enantiomeric purity and thus broadens the scope of this process. To the best of our knowledge there is no report of the diethylzinc addition to aldehydes catalyzed by amide derived from (1*S*,2*R*)-(+)-norephedrine alkaloid. There are some reports saying that amide functional group is more active in the asymmetric diethylzinc addition due to its rigidity.[17] However, there are only few reports on amide-based catalysts in asymmetric diethyl zinc addition to aldehydes. Hence we became interested in synthesizing norephedrine-derived amides. Herein we report the synthesis of new chiral amide synthesized from (1*S*,2*R*)-(+)-norephedrine and furoic

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acid and its catalytic application in the diethylzinc addition to prochiral aldehydes. We hope that the present ligand system may enhance the enantioselectivity by giving a more stable environment to the prochiral aldehydes compared to amino alcohols.

2. Results and discussion

The chiral amide was synthesized from (1*S*,2*R*)-(+)-norephedrine and 2-furoic acid (Scheme 1) using the well known mixed anhydride method with ethyl chloroformate as the activating reagent. Treatment of 2-furoic acid with ethylchloroformate in the presence of triethylamine in THF gave a mixed anhydride, which was subsequently reacted with (1*S*,2*R*)-(+)-norephedrine to give chiral amide **CL-1** in 80% yield.

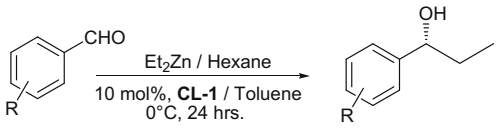
Asymmetric addition of diethylzinc to benzaldehyde was carried out using the **CL-1** as catalyst. It has been previously reported that the solvent plays an important role in controlling the activity of the chiral ligand for the diethylzinc addition to aldehydes[18,19] and toluene was found to be the best solvent. Thus the reaction was carried out with 5 mol % of the **CL-1** in toluene (Scheme 2). In order to study the effect of temperature on the reaction, the reaction was carried out at −77 °C, 0 °C, and 25 °C for 24 h. It was found that the reaction temperature had a significant influence on the conversion and the enantioselectivity of the catalyst. As the reaction temperature is increased from −77 °C to 25 °C, the product yield increases from 90% to 98%. The **CL-1** gave the product with 50% enantioselectivity at 0 °C, which was decreased to 40% at 25 °C. However, only the racemic product was obtained at −77 °C.

The effect of the catalyst concentration on the product yield and the enantioselectivity of **CL-1** was also studied at 0 °C for 24 h. Interestingly, the **CL-1** registered 99.8% enantioselectivity with 90% yield with 10 mol % of the **CL-1**. These results indicate that at 0 °C, 10 mol % of the **CL-1** in toluene, and a reaction time of 24 h are the best conditions to obtain the highest enantioselectivity and as a result they have been chosen for further studies. The optimization of reaction condition is given in Table 1.

Ligands with multidentate donors favor the formation of organometallic complexes, which possess well-organized spatial arrangements to give rise to good asymmetric induction in the catalytic process.[20] It is expected that a tridentate chiral ligand should confer more rigidity to the reactive zinc-chelate catalyst than a bidentate one, and thus may enhance the enantioselectivity of the addition reaction.[21] The ligand reported here is also tridentate in nature, capable of forming well-organized organometallic complexes with diethylzinc for the reduction of prochiral aldehydes.

The catalytic cycle for the addition of diethylzinc to benzaldehyde catalyzed by **CL-1** is shown in Figure 1. In the first step, the **CL-1** reacts with diethylzinc to yield monomeric alkylzinc complex **a**. This alkoxide can subsequently form mono-alkoxide diethylzinc complex **b** by reaction with another equivalent of diethylzinc. Transition state **c** clearly indicates that the aldehyde is attacked at the *re*-face to yield the chiral alkoxide **d**. On work-up, this alkoxide is converted into (*R*)-1-phenyl propanol **e**.

In some cases where norephedrine-derived ligands were employed as a catalyst, it was found that the absolute configuration of the products is mainly controlled by the stereogenic centers of norephedrine on chiral ligands.[22]



Scheme 2. Diethylzinc addition to different aldehydes using **CL-1**.

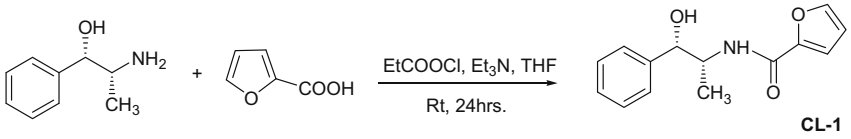
In order to account for the preferential formation of the (*R*)-isomer in the addition of diethylzinc to benzaldehyde using **CL-1** as catalyst, the possible transition state assemblies can be proposed as shown in Figure 2. As in the transition state models, the phenyl group present in the ligand exerts a steric effect with the phenyl group in benzaldehyde, thus favoring the transition state I over state II during the reaction. Due to the steric factor of the phenyl groups, the ethyl group of the second coordinating diethyl zinc molecule can only approach the *re*-face of the benzaldehyde.

Initially, the product alkoxide was formed as the alkylzinc alkoxide with the transfer of alkyl group to the *re*-face of the aldehyde, and the formation of a stable tetramer **a** is the driving force for the reconstitution of the catalyst which is believed to be monomeric **b**.[23] Finally, The main product, 1-phenyl propanol was obtained from the alkoxide after the acid work-up.

As generally observed in most of the asymmetric diethylzinc additions, by increasing the temperature, the less stereoselective pathway was more favorable.[21] This may be due to the free rotation possible when increasing the temperature, which leads to an unstable transition state during the reaction. This unstable transition state is responsible for the low enantiomeric excess of the product in such a manner that the addition of ethyl group to the carbonyl functional group of the aldehyde is not that specific. In our case, increasing the temperature from 0 °C to room temperature also caused the enantiomeric excess to decrease from 50% to 40%.

As discussed in the Introduction, the common additive that is employed to help facilitate the asymmetric addition of diorganozinc reagents to carbonyl substrates, is titanium tetraisopropoxide Ti(O-*i*Pr)$_4$. This reagent has become nearly ubiquitous in its application in this process, as it has been proven to be a powerful promoter of the diethylzinc addition reaction.[24–27] Walsh et al. demonstrated that there is a reaction between the Ti(O-*i*Pr)$_4$ and diethylzinc to give a reactive intermediate EtTi(O-*i*Pr)$_3$ that is likely to be the alkylating agent. An interesting aspect of Ti(O-*i*Pr)$_4$ in the diorganozinc addition reaction is the impact on the stereochemical outcome of the enantioselective addition. In rare cases of the diethylzinc addition to aldehydes, a reversal in enantioselectivity of the product can be observed in the presence of Ti(O-*i*Pr)$_4$.[28] This is due to the formation of different transition states mediated by either zinc or titanium.

In order to study the effect of promoter, the diethylzinc addition to benzaldehyde was carried out, in the presence of Ti(O-*i*Pr)$_4$. (*R*)-1-Phenyl propanol was formed in 99.8% ee with 90% yield, which is almost similar to the results obtained using **CL-1** without the use of promoter. This result indicates that our catalyst **CL-1** has the capability of controlling the catalytic activity with excellent enantioselectivity, without the addition of any promoters. Thus we decided to study the diethylzinc addition to other substituted benzaldehydes, salicylaldehydes, and heterocyclic aldehydes without the



Scheme 1. Synthesis of chiral ligand (CL)-**1** from (1*S*,2*R*)-(+)-norephedrine alkaloid.

Table 1
Diethylzinc addition to benzaldehyde using **CL-1** as the catalyst[a]

S. no.	Ligand	Cat. amount	Temp (°C)	Yield[b] (%)	ee[c] (%)	Absolute configuration[d]
1	**CL-1**	5 mol %	−77 °C	90	0	—
2	**CL-1**	5 mol %	0 °C	98	50	(*R*)
3	**CL-1**	5 mol %	rt	91	40	(*R*)
4	**CL-1**	10 mol %	0 °C	90	99.8	(*R*)
5	**CL-1**	10 mol %	0 °C	90	99.8	(*R*)[e]

[a] The reaction was carried out in toluene, for 24 h.
[b] Isolated yield by column chromatography.
[c] Determined by HPLC analysis using chiralcel OD–H column.
[d] The absolute configuration was assigned by comparison of the sign of the specific rotation to the literature data.
[e] The reaction was carried out with Ti(O-*i*Pr)$_4$.

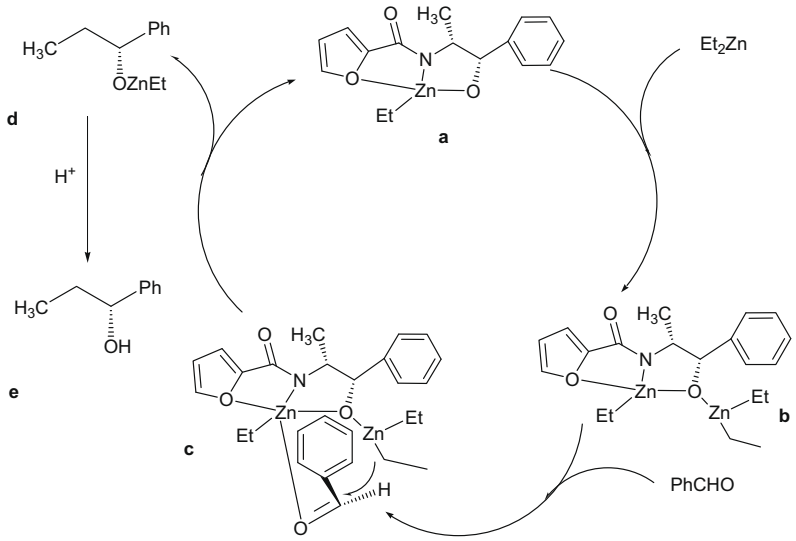


Figure 1. Catalytic cycle for the addition of diethylzinc to benzaldehyde catalyzed by **CL-1**.

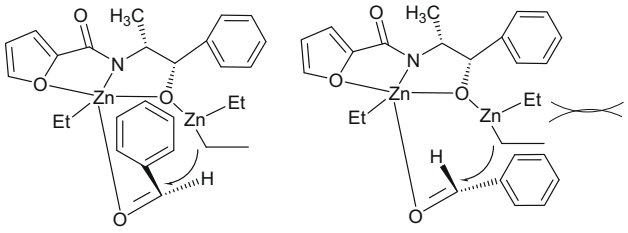


Figure 2. Transition state models I and II for **CL-1** as a catalyst.

addition of any promoters such as Ti(O-*i*Pr)$_4$, the results are given in Table 2.

The electronic effect of the substituents present in the benzaldehyde showed the same effect on the enantioselectivity which is observed generally. Aldehydes with electron-withdrawing groups (Table 2, entries 3, 4, 7, 8, and 9) are reduced with higher ee than aldehydes having electron-donating groups (Table 2, entries 5, 6, and 10). Among the nitro-substituted benzaldehyde, *o*-substituted aldehydes were reduced with less ee when compared to the *m*-substituted aldehydes, which in turn were reduced with less ee when compared to the *p*-substituted benzaldehydes (Table 2, entries 2, 3, and 4).[18] This may be due to the steric repulsion of the substituent and the ethyl group. As a result, the ethyl nucleophile can hardly approach the carbon atom of the carbonyl group of the aldehyde.

It was noted that aldehydes that contain an electron-donating oxygen atom have a significant negative influence on this reaction, especially in ee value (Table 2, entries 5, 10, and 12) which could be attributed to the additional coordination of the oxygen atom of the substituent with diethylzinc. Similarly, heterocyclic aldehydes (Table 2, entries 11 and 12) are reduced with less ee. This may be due to the binding of the ring heteroatom (N and O) in the substrate with the second zinc atom. Therefore, the reactivity and enantioselectivity of the chiral ligand were weakened to a certain extend.

Unlike the other aromatic aldehydes, 4-hydroxy, 3-methoxy benzaldehyde alone gave the (*S*)-isomer in which case the addition of diethylzinc takes place in the *si*-face of the aldehyde. This may be due to the steric hindrance caused by the presence of the hydroxy and methoxy groups at the 4- and 3-position, respectively (Table 2, entry 10).

3. Conclusion

In conclusion, the norephedrine-derived catalyst **CL-1** was synthesized and found to alkylate prochiral aldehydes in the diethylzinc addition to give the (*R*)-isomer specifically (except for 4-hydroxy 3-methoxy benzaldehyde) in up to 99.8% ee. The stereochemical outcome of this diethylzinc addition to aldehydes can be explained by taking the model of the transition state formed during the reaction. This catalyst is advantageous in such a way that it can be synthesized in one step. Both enantiomers of norephedrine are available. We have also demonstrated that the **CL-1** is also capable of alkylating salicylaldehyde and heterocyclic aldehydes to produce the corresponding optically active heterocyclic alcohols, which are the essential building blocks of many

Table 2
Diethylzinc addition to different aldehydes using **CL-1**[a]

S. no.	Aldehyde	% Yield[b]	% ee[c]	Absolute configuration[d]
1	Benzaldehyde	90	99.8	(*R*)
2	*o*-Nitro benzaldehyde	70	68	(*R*)
3	*m*-Nitro benzaldehyde	82	95	(*R*)
4	*p*-Nitro benzaldehyde	92	85	(*R*)
5	*p*-Methoxy benzaldehyde	90	30	(*R*)
6	*p*-Methyl benzaldehyde	90	76	(*R*)
7	*p*-Chloro benzaldehyde	95	99.8	(*R*)
8	Salicylaldehyde	23	99.8	(*R*)
9	5-Chloro salicylaldehyde	46	99	(*R*)
10	4-Hydroxy 3-methoxy benzaldehyde	20	20	(*S*)
11	Pyrrole-2-carboxaldehyde	99	53	(*R*)
12	Furfural	96	10	(*R*)

[a] The reaction was carried out in toluene, for 24 h at 0 °C.
[b] Isolated yield by column chromatography.
[c] Determined by HPLC analysis using chiralcel OD-H column.
[d] The absolute configuration was assigned by comparison of the sign of the specific rotation to the literature data.

biologically active compounds. In addition, the novel catalyst is an additive which is capable of alkylating the prochiral aldehydes in excellent enantioselectivities of up to 99.8% with 90% yield without any promoters.

4. Experimental

4.1. General remarks

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ with a BRUKER AMX-400 MHz instrument using TMS as an internal standard. Commercial Precoated Silica Gel (Merck 60F-254) plates were used for TLC. 60–120 mesh Silica Gel was used for Column Chromatography. Specific rotations were recorded with a Rudolph Autopol IV polarimeter. Enantiomeric excess was determined with a Shimadzu 2010A HPLC instrument (Chiral column:Chiral Cel OD–H, Mobile Phase: 98:2 Hexane/*i*-PrOH, flow rate:0.5 min ml, UV detector λ = 254 nm). FTIR spectra were recorded with a Perkin Elmer–DXB spectrometer. Melting points were determined with a Kherea digital melting point apparatus and are uncorrected.

4.2. Synthesis of *N*-((1*S*,2*R*)-1-hydroxy-1-phenylpropan-2-yl)furan-2-carboxamide CL-1

Compound **CL-1** was prepared according to the following procedure. 2-Furoic acid (0.561 g, 5 mmol) taken in a round-bottomed flask flushed with nitrogen gas was dissolved in dry THF. To this, triethylamine (0.1 ml, 5 mmol) was added dropwise. Ethylchloroformate (0.7 ml, 5 mmol) in dry THF was slowly added into the flask at 0° C and stirred for 30 min. After the formation of a white precipitate, that is, the highly reactive anhydride, norephedrine (0.936 g, 5 mmol) dissolved in dry THF cooled to 0 °C was added dropwise into the reaction mixture and the stirring was continued for 24 h. The reaction mixture was then filtered. The solvent was removed by rotary evaporator, and the residue was dissolved in ethylacetate. The organic layer was washed with water, followed by saturated sodium bicarbonate and finally with brine and dried over anhydrous sodium sulfate. The crude product was purified by column chromatography with silica gel as the adsorbent and 90:10 hexane/ethylacetate as the eluent. The amide was obtained as a colorless solid in 80% yield. Melting point: 129–130 °C. $[\alpha]_{30}^{589} = +70.4$ (*c* 0.125, $CHCl_3$); FTIR (cm^{-1}): 3289 (–OH), 3042 (–NH), 2872 (–CH), 1679 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C), δ (ppm): 1.1 (d, ^3J = 6.8 Hz, 3H, CH_3), 3.33 (br s, 1H, OH), 4.5 (sep, ^3J = 7.9 Hz, 1H, C*H*NH), 4.96 (d, ^3J = 2.0, 1H, C*H*OH), 6.51 (t, ^3J = 1.6, 1H, CH), 6.56 (d, ^3J = 8.8 Hz, 1H, CH), 7.13 (d, ^3J = 3.6 Hz, 1H, CH), 7.32–7.37 (m, 5H, phenyl), 7.44 (s, 1H, NH); ^{13}C NMR, (400 MHz, $CDCl_3$, 25 °C), δ (ppm): 14.21, 50.65, 76.2, 112.16, 114.57, 126.24, 127.53, 128.20, 140.64, 144.04, 147.67, 158.64; MS(EI) 245 (M^+, 55%), 227 (100%), 197 (9%), 158 (20%).

4.3. Typical procedure for the asymmetric addition of Et_2Zn to benzaldehyde

To a solution of the **CL-1** (24.5 mg, 0.1 mmol) dissolved in dry toluene (1.5 ml), Et_2Zn (2 ml, 1 M solution in hexane) was added dropwise at 0 °C. After the mixture was stirred for 1 h, benzaldehyde (0.1 ml, 1 mmol) was added, and the reaction mixture was again stirred for 24 h at 0 °C. Then the reaction mixture was quenched with 2 M HCl and extracted with chloroform. The optically active 1-phenyl propan-1-ol was obtained in 90% yield after purification by column chromatography with silicagel as adsorbent using 98:2 hexane/ethyl acetate as eluent.

4.4. Typical Procedure for the asymmetric addition of Et_2Zn to benzaldehyde with $Ti(O\text{-}iPr)_4$

To a solution of ligand **CL-1** (24.5 mg, 0.1 mmol) dissolved in toluene (1.5 mL), $Ti(O\text{-}iPr)_4$ (1 ml, 1 mmol) was added dropwise and was stirred for 30 min. Then Et_2Zn (2 ml, 1 M solution in hexane) was added dropwise at 0 °C. After the mixture was stirred for 1 h, benzaldehyde (0.1 ml, 1 mmol) was added, and the reaction mixture was again stirred for 24 h at 0 °C. Then the reaction mixture was quenched with 2 M HCl and extracted with chloroform. The optically active 1-phenyl propan-1-ol was obtained in 90% yield after purification by column chromatography with silicagel as an adsorbent using 98:2 hexane/ethyl acetate as an eluent.

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