J. Chem. Sci. Vol. 126, No. 1, January 2014, pp. 151–158.

Chiral amide from (1*S*, 2*R*)-(+)-norephedrine and furoic acid: An efficient catalyst for asymmetric Reformatsky reaction

NALLAMUTHU ANANTHI and SIVAN VELMATHI*

Organic and Polymer Synthesis Laboratory, Department of Chemistry, National Institute of Technology, Tiruchirappalli 620 015, India
e-mail: velmathis@nitt.edu

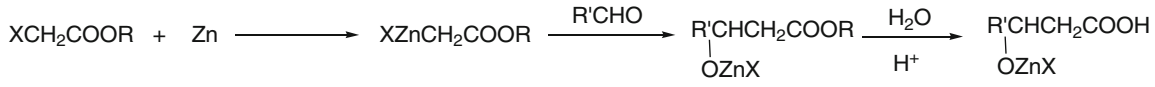
MS received 3 April 2013; revised 26 September 2013; accepted 29 September 2013

Abstract. Chiral amide derived from (1*S*, 2*R*)-(+)-norephedrine and 2-furoic acid was found to catalyse the asymmetric Reformatsky reaction between prochiral aldehydes and α-bromo ethylacetate with diethylzinc as zinc source. The corresponding chiral β-hydroxy esters were formed in 99% yield with over 80% enantiomeric excess. The presence of air was found to be essential for the effective C-C bond formation. The mechanism for the catalytic reaction was proposed.

Keywords. Asymmetric Reformatsky reaction; (1*S*, 2*R*)-(+)-norephedrine; 2-furoic acid; chiral amide; diethylzinc.

1. Introduction

Discovering remarkable stereoselectivity in the C-C bond formation reaction has been the prime objective of organic chemists. Organometallic reactions are among the superior processes for stereoselective bond formations, and Reformatsky-type reactions are one of the cornerstones.[1] Classical Reformatsky reaction involved a zinc-induced reaction between an α-halo ester and an aldehyde or ketone. Many processes have been developed using zinc.



There are more advantages in the Reformatsky reaction over classic aldol reaction in the sense that these reactions can be carried out under mild neutral conditions. It works for a type of stearically crowded ketones. The active ester enolate can be formed in the presence of highly enolizable aldehyde or ketone functionality. Both inter and intra molecular reactions are feasible and also a variety of electrophiles can be easily used.[2,3]

The product, chiral β-hydroxy esters are one of the most important intermediates in organic synthesis.[4,5] The Reformatsky reaction not only offers a convenient method for producing β-hydroxy esters and the corresponding unsaturated esters and acids, but also constitutes a method for lengthening the carbon chain. By proper choice of reactants, it is possible to branch the chain on the α-, β- carbon atoms. So far, various ligands such as diols,[6–8] carbohydrates,[9] dipeptides,[10] chiral diamines,[11] amino alcohols[12] and other chiral complexing agents have been thoroughly investigated.[13,14]

A general, enantioselective method affording β-hydroxyesters in high yield and *ee* remains elusive and selectivities above 70% *ee* are rare. Skarzewski *et al.* reported enantioselective Reformatsky reaction with ethyliodoacetate and achieved enantiomeric excess up to 96% using manganese Salen complex.[15] First enantioselective one-pot, three-component imino Refromatsky reaction was reported by Cozzi *et al.* in 2006, giving β-amino esters in moderate to good yields.[16] Cozzi reported enantioselective Reformatsky reaction with ketones using inexpensive and readily available

*For correspondence

[ClMn(salen)] as catalyst.[17] In literature, several modified Reformatsky reactions using other metals have also been reported.[18–20]

Among the class of ligands screened for asymmetric Reformatsky reaction, ephedrine- and norephedrine-derived ligands are very few. A representative study was reported by Soai *et al.*[21] in which chiral tertiary alcohols were obtained from aryl ketones in moderate enantioselectivity using N,N-dialkylnorephedrines as chiral ligands. Cozzi and Rivalta reported catalytic asymmetric Reformatsky reaction with ketones using ephedrine-derived ligand. They achieved enantiomeric excess up to 92%.[6] In 1996, Andres *et al.*[22] reported ephedrine-derived ligands produced in the asymmetric Reformatsky reaction between bromo-α,α-difluoroacetate and aldehydes. The corresponding β-hydroxy esters were formed with good enantiomeric excess for aromatic aldehydes and moderate *ee* for aliphatic aldehydes.

In 1997, Zhang and Wu reported the enantioselective synthesis of β-hydroxy esters using chiral micelles.[23] They synthesised chiral micelles from (1*S*, 2*R*)-(+)-ephedrine and (8*R*, 9*S*)-(+)-cinchonine. These micelles provided the asymmetric micro environments for enantioselective β-hydroxy ester synthesis.

In an earlier report by our group,[24] chiral amide derived from (1*S*, 2*R*)-(+)-norephedrine and 2-furoic acid was proven to catalyse the asymmetric diethylzinc addition to prochiral aldehydes yielding the product chiral secondary alcohols in good yield and excellent enantioselectivity. Herein, we demonstrate for the first time, the application of the same chiral amide ligand in the asymmetric Reformatsky reaction with diethylzinc as zinc source.

2. Materials and methods

2.1 *General remarks*

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

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

Chiral ligand (CL) 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 anhydrous tetrahydrofuran (THF). To this, triethylamine (0.1 ml, 5 mmol) was added dropwise. Ethylchloroformate (0.7 ml, 5 mmol) in anhydrous 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, (1*S*, 2*R*)-(+)-norephedrine (0.936 g, 5 mmol) dissolved in anhydrous 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 sulphate. 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 colourless solid in 80% yield.

Melting point: 129–130°C. $[\alpha]_{589}{}^{30}$: +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, CHNH), 4.96 (d, $^3J = 2.0$, 1H, CHOH), 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, (100 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; high resolution mass spectroscopy (HRMS) Calculated for molecular formula $C_{14}H_{15}NO_3$: 245.1561; Found: 245.1565.

2.3 *Typical procedure for the asymmetric Reformatsky reaction of α-bromo ethylacetate to benzaldehyde*

To a solution of the CL (49 mg, 0.1 mmol) dissolved in dry tetrahydrofuran (1.5 mL), Et_2Zn 1M solution in hexane (2 mL, 4 mmol) was added dropwise at 0°C. To this reaction mixture, α-bromoethylacetate (0.22 mL, 2 mmol), was added at room temperature. Then, benzaldehyde (0.1 mL, 1 mmol) and diethylzinc 1M solution in hexane (2 mL, 4 mmol) was added simultaneously and the reaction mixture was stirred for 1 h at room temperature. Then, the reaction mixture was quenched with 2M HCl, the

solvent was removed by rotary evaporation. The aqueous layer was extracted with ethylacetate. The optically active (*R*)-ethyl-3-hydroxy-3-phenyl propanoate was obtained in 60% yield after purification by column chromatography with silica gel as an adsorbent using 98:2 hexane : ethyl acetate as an eluent. $\alpha]_{21}^{589} = +30.1^\circ$ (*c* 1.1, $CHCl_3$); Lit[25] *ee* 98% $[\alpha]_{21}^{589} = +44.0^\circ$ (*c* 1.013, $CHCl_3$) HPLC conditions: Chiralcel OD-H, 11.96 (major), 13.20 (minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector $\lambda = 254$ nm ^{1}H NMR (400 MHz, $CDCl_3$, 25°C), δ (ppm): 1.31 (t, $^3J = 6.6$ Hz, 3H, CH_3), 2.80 (oct, $^3J = 9$ Hz, 2H, CH_2), 3.57 (t, $^3J = 3.5$ Hz, 1H, CHOH), 4.14 (q, 2H, $^3J = 4.6$ Hz, CH_2), 5.56 (s, 1H, OH), 7.22 (m, $^3J = 7.2$ Hz, 5H, phenyl). ^{13}C NMR (100 MHz, $CDCl_3$, 25°C), δ (ppm): 14.11, 43.15, 61.20, 71.12, 127.24, 127.83, 128.70, 140.64, 144.04, 173.14; HRMS Calculated for molecular formula $C_{11}H_{14}O_3$: 194.2314; Found: 194.2317.

2.4 *(R)-ethyl-3-hydroxy-3-p-tolylpropanoate*

$[\alpha]_{21}^{589}$ −6.18° (*c* = 1, CH_2Cl_2), HPLC conditions: Chiralcel OD-H, 10.96 (major), 14.20 (minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector $\lambda = 254$ nm. ^{1}H NMR: 1.30 (t, 3H, $^3J = 6.6$ Hz, CH_3), 2.19 (s, 3H, CH_3), 2.61 (m, 2H, $^3J = 8.9$ Hz, CH_2), 4.12 (q, 2H, $^3J = 3.6$ Hz, CH_2), 4.64 (t, 1H, $^3J = 4.6$ Hz, CH), 5.17 (s, 1H, OH), 6.79–7.07 (m, 4H, $^3J = 7.3$ Hz, Ar-H) ^{13}C NMR: 14.13, 24.36, 43.31, 61.53, 71.26, 127.12, 129.20, 137.66, 173.33. HRMS Calculated for molecular formula $C_{12}H_{16}O_3$: 208.2554; Found: 208.2558.

2.5 *(R)-ethyl-3-hydroxy-3-(4-ethoxyphenyl)propanoate*

$[\alpha]_{21}^{589}$ −4.3° (*c* = 1, CH_2Cl_2), HPLC conditions: Chiralcel OD-H, 12.07 (major), 15.89 (minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector $\lambda = 254$ nm. ^{1}H NMR: 1.30 (t, 3H, $^3J = 6.6$ Hz, CH_3), 1.35(t, 3H, $^3J = 6.3$ Hz, CH_3), 2.60 (m, 2H, $^3J = 3.7$ Hz, CH_2), 4.01 (q, 2H, $^3J = 3.6$ Hz, CH_2), 4.12 (q, 2H, $^3J = 3.7$ Hz, CH_2), 5.14 (t, 1H, $^3J = 4.5$ Hz, CH), 5.23 (s, 1H, OH), 6.71–7.11 (m, 4H, $^3J = 7.3$ Hz, Ar-H). ^{13}C NMR: 14.10, 14.81, 43.18, 61.30, 64.60, 71.26, 114.62, 127.70, 132.28, 156.90, 173.24. HRMS Calculated for molecular formula $C_{13}H_{18}O_4$: 238.2812 found: 238.2814.

2.6 *(R)-ethyl-3-hydroxy-3-(2-nitrophenyl)propanoate*

$[\alpha]_{21}^{589}$ 25.2° (*c* = 1, CH_2Cl_2), 87% *ee*. HPLC conditions: Chiralcel OD-H, 8.77 (major), 13.00 (minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector $\lambda = 254$ nm. ^{1}H NMR: 1.29 (t, 3H, $^3J = 6.6$ Hz, CH_3), 2.60 (m, 2H, $^3J = 6.2$ Hz, CH_2), 4.12 (q, 2H, $^3J = 3.6$ Hz, CH_2), 5.10 (t, 1H, $^3J = 4.5$ Hz, CH), 5.18 (s, 1H, OH), 7.40–8.05 (m, 4H, $^3J = 7.3$ Hz, Ar-H). ^{13}C NMR: 14.21, 42.14, 61.30, 66.55, 124.34, 128.23, 128.43, 135.42, 147.24, 173.26. HRMS Calculated for molecular formula $C_{11}H_{13}NO_5$: 239.2257 found: 239.2260.

2.7 *(R)-ethyl-3-hydroxy-3-(3-nitrophenyl)propanoate*

$[\alpha]_{21}^{589}$ −32.8° (*c* = 2, CH_2Cl_2), 90% *ee*. HPLC conditions: Chiralcel OD-H, 14.32 (Major), 16.05 (Minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector $\lambda = 254$ nm. ^{1}H NMR: 1.29 (t, 3H, $^3J = 6.6$ Hz, CH_3), 2.60 (m, 2H, $^3J = 6.2$ Hz, CH_2), 4.12 (q, 2H, $^3J = 3.6$ Hz, CH_2), 5.10 (t, 1H, $^3J = 4.5$ Hz, CH), 5.18 (s, 1H, OH), 7.55–8.29 (m, 4H, $^3J = 7.3$ Hz, Ar-H). ^{13}C NMR: 14.11, 43.12, 61.33, 70.15, 122.44, 123.27, 129.43, 133.22, 141.14, 148.21, 173.24. HRMS: Calculated for molecular formula $C_{11}H_{13}NO_5$ 239.2257 Found: 239.2261.

2.8 *(R)-ethyl-3-hydroxy-3-(4-nitrophenyl)propanoate*

$[\alpha]_{21}^{589}$ −20.3° (*c* = 1, CH_2Cl_2), 76% *ee*. HPLC conditions: Chiralcel OD-H, 15.03 (Major), 17.08 (Minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector $\lambda = 254$ nm. ^{1}H NMR: 1.29 (t, 3H, $^3J = 6.6$ Hz, CH_3), 2.60 (m, 2H, $^3J = 6.3$ Hz, CH_2), 4.12 (q, 2H, $^3J = 3.6$ Hz, CH_2), 5.10 (t, 1H, $^3J = 4.6$ Hz, CH), 5.18 (s, 1H, OH), 7.60–8.20 (m, 4H, $^3J = 7.3$ Hz, Ar-H). ^{13}C NMR: 14.21, 43.14, 61.30, 71.30, 124.24, 128.13, 146.34, 172.96. HRMS: Calculated for molecular formula $C_{11}H_{13}NO_5$ 239.2257, Found: 239.2259.

2.9 *(R)-ethyl-3-hydroxy-3-(2-hydroxyphenyl)propanoate*

$[\alpha]_{21}^{589}$ −17.2° (*c* = 1.1, CH_2Cl_2), 64% *ee*. HPLC conditions: Chiralcel OD-H, 14.85 (Major), 17.52 (Minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector $\lambda = 254$ nm. ^{1}H NMR: 1.29 (t, 3H, $^3J = 6.6$ Hz, CH_3), 2.60 (m, 2H, $^3J = 6.2$ Hz, CH_2), 4.12 (q, 2H, $^3J = 3.6$ Hz, CH_2), 5.10 (t, 1H, $^3J = 4.6$ Hz, CH), 5.18 (s, 1H, OH), 6.66–7.20 (m, 4H, $^3J = 7.2$ Hz, Ar-H), 9.83 (s, 1H, OH). ^{13}C NMR: 14.21, 43.44, 61.34, 65.40, 116.23, 121.64, 129.13, 154.34, 173.16. HRMS: Calculated for molecular formula $C_{11}H_{14}O_4$: 142.1026, Found: 142.1030.

2.10 *(R)-ethyl-3-hydroxy-3-(1H-pyrrol-2-yl)propanoate*

$[\alpha]_{21}^{589}$ −8.6° (c = 1, CH_2Cl_2), 48% *ee*. HPLC conditions: Chiralcel OD-H, 13.97 (Major), 17.97 (Minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector λ = 254 nm. ^{1}H NMR: 1.29 (t, 3H, ^3J = 6.6 Hz, CH_3), 2.60 (m, 2H, ^3J = 6.2 Hz, CH_2), 4.12 (q, 2H, ^3J = 3.6 Hz, CH_2), 4.99 (s, 1H, NH), 5.10 (t, 1H, ^3J = 4.6 Hz, CH), 5.18 (s, 1H, OH), 6.06–6.40 (m, 3H, ^3J = 7.3 Hz, Ar-H). ^{13}C NMR: 14.11, 43.84, 61.30, 70.46, 106.03, 108.33, 117.86, 133.20, 173.26. HRMS: Calculated for molecular formula $C_9H_{13}NO_3$: 183.200, Found: 183.203.

2.11 *(R)-ethyl-3-hydroxy-3-(thiophen-2-yl)propanoate*

$[\alpha]_{21}^{589}$ −20.3° (c = 1, CH_2Cl_2), 53% *ee*. HPLC conditions: Chiralcel OD-H, 15.03 (Major), 17.08 (Minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector λ = 254 nm. ^{1}H NMR: 1.29 (t, 3H, ^3J = 6.6 Hz, CH_3), 2.60 (m, 2H, ^3J = 6.2 Hz, CH_2), 4.12 (q, 2H, ^3J = 3.6 Hz, CH_2), 5.10 (t, 1H, ^3J = 4.6 Hz, CH), 5.18 (s, 1H, OH), 6.62–6.96 (m, 3H, ^3J = 7.2 Hz, Ar-H). ^{13}C NMR: 14.11, 43.84, 61.30, 70.46, 125.53, 126.33, 126.86, 143.60, 173.06. HRMS: Calculated for molecular formula $C_9H_{12}O_3S$: 200.2568 found 200.2571.

2.12 *(R)-ethyl-3-(furan-2-yl)-3-hydroxypropanoate*

$[\alpha]_{21}^{589}$ −17.2° (c = 1.1, CH_2Cl_2), 45% *ee*. HPLC conditions: Chiralcel OD-H, 14.85 (Major), 17.528 (Minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector λ = 254 nm. ^{1}H NMR: 1.29 (t, 3H, ^3J = 6.6 Hz, CH_3), 2.60 (m, 2H, ^3J = 6.2 Hz, CH_2), 4.12 (q, 2H, ^3J = 3.6 Hz, CH_2), 5.10 (t, 1H, ^3J = 4.6 Hz, CH), 5.18 (s, 1H, OH), 6.18–7.40(m, 3H, ^3J = 7.3 Hz, Ar-H). ^{13}C NMR: 14.11, 41.34, 61.30, 65.06, 105.83, 110.33, 141.60, 153.56, 173.46. HRMS: Calculated for molecular formula $C_9H_{12}O_4$: 184.1898 found 184.1901.

2.13 *(R)-ethyl-3-hydroxyhexanoate*

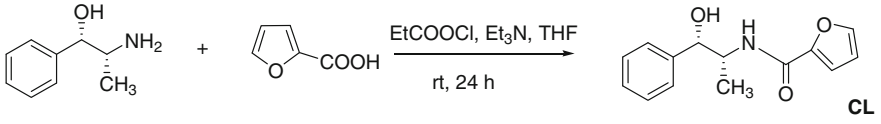
$[\alpha]_{21}^{589}$ −4.6° (c = 1, CH_2Cl_2), 30% *ee*. HPLC conditions: Chiralcel OD-H, 12.97 (Major), 16.67 (Minor), 98:2 Hexane/*i*-PrOH, flow rate: 0.5 ml/min, UV detector λ = 254 nm. ^{1}H NMR: 0.96 (t, 3H, ^3J = 6.6 Hz, CH_3), 1.28 (t, 3H, ^3J = 6.2 Hz, CH_3), 1.33 (m, 2H, ^3J = 6.2 z, CH_2), 1.42 (m, 2H, ^3J = 6.2 Hz, CH_2), 2.53 (m, 2H, ^3J = 6.2 Hz, CH_2), 3.88 (m, 1H, ^3J = 4.6 Hz, CH), 3.99 (q, 2H, ^3J = 6.2 Hz, CH_2), 4.84 (s, 1H, OH). ^{13}C NMR: 14.11, 14.44, 16.24, 39.62, 41.84, 61.37, 67.56, 173.36. HRMS: Calculated for molecular formula $C_8H_{16}O_3$: 160.2114 found 160.2118.

3. Results and discussion

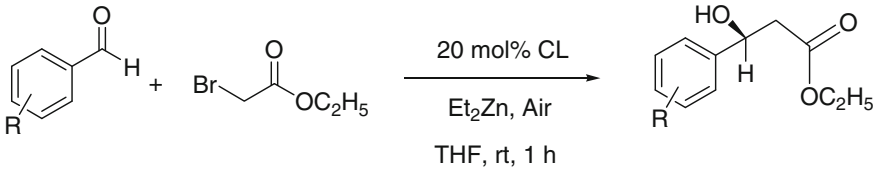
The chiral amide was synthesised from (1*S*, 2*R*)-(+)-norephedrine and 2-furoic acid (scheme 1) as per the reported procedure with ethylchloroformate as the activating reagent.[24] Treatment of 2-furoic acid with ethyl chloroformate in the presence of triethylamine in THF gave a mixed anhydride, which was subsequently reacted with (1*S*, 2*R*)-(+)-norephedrine to give the CL in 80% yield.

The Reformatsky reaction involves formation of an organozinc halide as an intermediate which then adds to the carbonyl compound to form an addition complex analogous to those involving in the Grignard reaction between Grignard reagent and carbonyl compounds. The intermediate complex is then decomposed in the presence of dilute acid to yield the final product. Activation of zinc by treatment with iodine or dibromomethane, or washing with dilute hydrochloric acid prior to use, are only moderately successful in the most known procedures. There are numerous reports on asymmetric Reformatsky reaction using dialkylzinc as zinc source.[8,17,26,27]

Cozzi and Revalta found that the complexating ability of the ligand in the transition state and the amount of the ligand are important factors for the enantioselectivity.[6] According to Fernandez-Ibanez *et al*., the presence of oxygen in the form of air is found to be essential to achieve an effective C-C bond formation.[8] It is known that dialkylzinc in the presence of oxygen forms the more reactive alkyl peroxides (RZnOOR),[29–31] which are able to initiate radical reactions.[31–35] The reaction temperature of most of the reported Reformatsky reactions with various ligands was room temperature.[25,36–38]



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



Scheme 2. Asymmetric Reformatsky reaction catalysed by chiral ligand.

Considering the above mentioned facts, initially asymmetric Reformatsky reaction (scheme 2) was carried out using 5 mol% of CL as catalyst for the reaction between α-bromo ethylacetate and benzaldehyde in tetrahydrofuran as solvent at room temperature with 2 equivalents of diethylzinc as zinc source in the presence of air. There was no product formation. The optimisation of reaction conditions is given in table 1. Even under reflux condition, no progress in the reaction was observed. As mentioned above, the amount of ligand plays an important role on yield and enantiomeric excess of the product. Hence, amount of catalyst was increased to 10 mol%. The reaction was carried out at room temperature and at the refluxing temperature of THF. With 10 mol% of the catalyst at different temperatures also, there was no product conversion.

With 10 mol% of chiral ligand, the amount of diethylzinc was increased from 2 to 3 equivalents and the reaction was carried out at room temperature. The product chiral β-hydroxy ester was formed in 50% yield with 45% *ee* at room temperature (table 1, entry 5). However, raising the reaction temperature to reflux condition did not improve the enantiomeric excess. Hence, room temperature was finalized as the optimised reaction temperature for the reaction. In order to increase the enantiomeric excess of the product β-hydroxy ester, the amount of diethylzinc and the amount of the catalyst were further increased. With 4 equivalents of diethylzinc, the asymmetric Reformatsky reaction was carried out with 20 mol% of the catalyst at room temperature. Under these conditions, we obtained almost the same enantioselectivity (46% *ee*) and similar conversion (50%) (table 1, entry 7). Then, the reaction was carried out with 20 mol% of the catalyst with 8 equivalents of diethylzinc at room temperature which resulted in the product chiral β-hydroxy ester in 60% yield with 67% *ee* (table 1, entry 8). Further increase in the amount of the catalyst also resulted in the same enantiomeric excess and yield.

In order to avoid the total oxidation of diethylzinc in the presence of air, diethylzinc was added in two portions. Four equivalents of diethylzinc was added at the beginning with chiral ligand. Another 4 equivalents of diethylzinc and aldehyde were added simultaneously. In order to determine the effect of air on the reaction, the reaction was carried in the absence of air under inert gas atmosphere. In the absence of air, the product was not formed (table 1, entry 9).

Based on the coordination mode of the catalyst CL with diethylzinc[24] and also on the radical pathway proposed by Fernandez-Ibanez *et al.*[7,8] for asymmetric Reformatsky reaction of ketones in the presence of air,

Table 1. Optimization of reaction conditions for asymmetric Reformatsky reaction between benzaldehyde and α-bromoethylacetate using CL.

S. No.	Catalytic amount (mol%)	Solvent	Temperature (°C)	Et_2Zn (equivalents)	Yield (%)[a]	*ee* (%)[b]	Absolute configuration[c]
1	5	THF	rt	2	0	0	–
2	5	THF	65	2	0	0	–
3	10	THF	rt	2	0	0	–
4	10	THF	65	2	0	0	–
5	10	THF	rt	3	50	45	*(R)*
6	10	THF	65	3	50	0	–
7	20	THF	rt	4	50	46	*(R)*
8	30	THF	rt	8	60	67	*(R)*
9[d]	30	THF	rt	8	0	0	–

[a]Isolated yield after column chromatography
[b]Determined by HPLC analysis using chiralcel OD-H column
[c]Absolute configuration was assigned by comparison with the sign of specific rotation in literature data[25]
[d]Reaction carried out in the absence of air

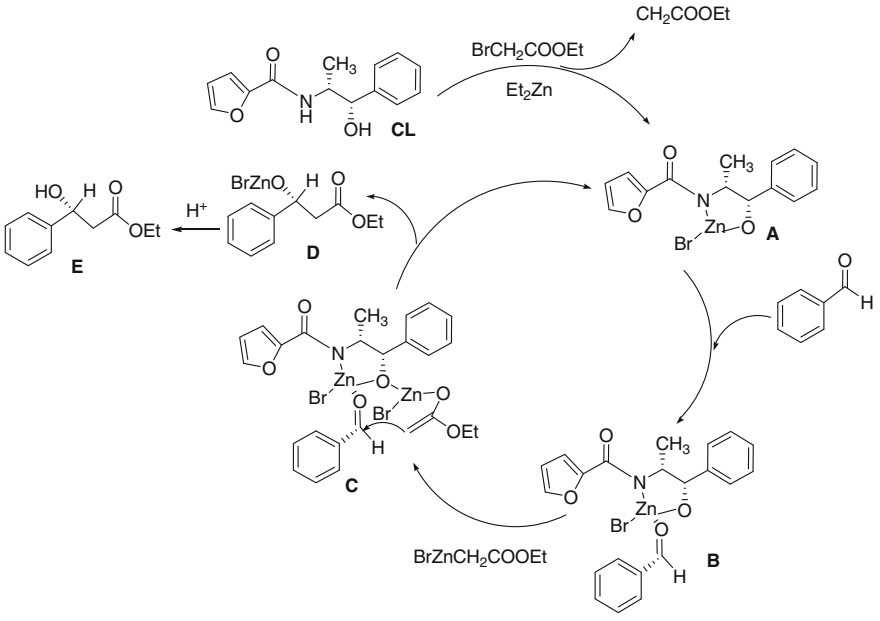


Figure 1. Proposed catalytic cycle for the asymmetric Reformatsky reaction catalysed by CL with diethylzinc in the presence of air.

we suggest a possible mechanism for the catalytic reaction (figure 1). The presence of air was found to be crucial for effective C-C bond formation.

Initially, the chiral ligand CL reacts with diethylzinc and α-bromo ethyl acetate to form complex **A.** Addition of benzaldehyde to complex **A** results in complex **B**. Addition of another molecule of $BrZnCH_2COOEt$ to complex **B**, results in complex **C**. In complex **C**, the double bond of the α-bromo ethyl acetate attacks the carbonyl group of benzaldehyde resulting in compound **D** which on acid work-up gave the product chiral β-hydroxy ester. The chiral ligand provides the necessary asymmetric environment for the substrates which results in the enantiopure β-hydroxy ester. Formation of complex **A** is evident from IR spectroscopy. In the IR spectrum of complex **A**, the stretching frequency of NH and OH group is shifted to higher frequency than that of pure chiral ligand **CL**. Frequency of carbonyl group

Table 2. Asymmetric Reformatsky reaction between various substituted benzaldehydes with α-bromo ethylacetate catalysed by 20 mol% of CL.

S. No	Aldehyde	Yield (%)[a]	*ee* (%)[b]	Absolute configuration[c]
1	Benzaldehyde	60	67	*(R)*
2	*p*-Methyl benzaldehyde	90	77	*(R)*
3	*p*-Methoxy benzaldehyde	95	47	*(R)*
4	*o*-Nitro benzaldehyde	95	87	*(R)*
5	*m*-Nitro benzaldehyde	95	90	*(R)*
6	*p*-Nitro benzaldehyde	80	76	*(R)*
7	Salicylaldehyde	95	64	*(R)*
8	Pyrrole-2-carboxaldehyde	57	48	*(R)*
9	Thiophene-2-carboxaldehyde	60	53	*(R)*
10	Furan-2-carboxaldehyde	50	45	*(R)*
11	Butyraldehyde	35	30	*(S)*

[a]Isolated yield after column chromatography
[b]Determined by HPLC analysis using chiralcel OD-H column
[c]Absolute configuration was assigned by comparison with the sign of the specific rotation in literature data[25]

is same as that of chiral ligand **CL**. Hence, it is evident that chiral ligand **CL** coordinates to zinc metal through OH and NH groups.

In order to explore the synthetic utility of the catalyst CL in the asymmetric Reformatsky reaction, various substituted aldehydes with both electron donating and withdrawing groups, aliphatic aldehyde and heteroyclic aldehydes were reacted with α-brmoethylacetate. The results are presented in table 2.

Aromatic aldehydes produce the corresponding chiral β-hydroxy esters in good yield and enantioselectivity compared to aliphatic aldehyde. Heterocyclic aldehydes gave the corresponding products in less enantioselectivity (table 2, entries 8, 9 and 10). This may be due to the extra coordination of hetero atoms present in the aldehydes with diethylzinc. Benzaldehydes with electron withdrawing groups gave the corresponding β-hydroxy esters with good yield and enantioselectivity (table 2, entries 4, 5 and 6). Reformatsky reaction of *m*-nitro benzaldehyde gave the corresponding β-hydroxy ester in 95% yield with 90% *ee* (entry 5). Aromatic aldehydes substituted with electron donating groups gave the corresponding chiral product in less *ee* (entries 2 and 3) and good yield compared to electron withdrawing groups substituted benzaldehydes. Aliphatic aldehyde butyraldehyde gave the chiral ester in 35% yield with 30% *ee*. All the β-hydroxy esters formed are in *R*-configuration except the β-hydroxy ester formed from butyraldehyde.

4. Conclusion

To conclude, the (1*S*, 2*R*)-(+)-norephedrine and 2-furoic acid derived amide was found to catalyse the asymmetric Reformatsky reaction of aldehydes with α-bromo ethylacetate. The product chiral β-hydroxy esters were formed in good yield and enantiomeric excess. All the hydroxy esters were formed in *R*-configuration. The presence of air was found to be essential leading to the chiral products through a radical mechanism. Hence, the reaction can be carried out without the need for air exclusion which makes the catalyst more attractive. Finally, this catalyst is advantageous in such a way that the synthesis is very easy.

Acknowledgements

The authors thank the Department of Science and Technology (DST) (SR/S1/OC-06/2011), New Delhi and Council of Scientific and Industrial Research (CSIR) (01(2282)/08/EMR-II), New Delhi for financial support in the form of sponsored projects.

References

1. Reformatsky S 1887 *Chem. Ber.* **20** 1210
2. Becker D, Brodsky N and Kalo I 1978 *J. Org. Chem.* **43** 2557
3. Barco A, Benett S and Pollini G P 1980 *J. Org. Chem.* **45** 4776
4. Henecka H 1952 In *Methoden der organischen chemie* (Stuttgart: T V Georg)
5. Rathke M W 1970 *J. Org. Chem.* **35** 3966
6. Cozzi P G and Rivalta E 2005 *Angew. Chem. Int. Ed.* **44** 3600
7. Fernandez-Ibanez M A, Macia B, Minnaard A J and Feringa B L 2008 *Chem. Commun.* **22** 2571
8. Fernandez-Ibanez M A, Macia B, Minnaard A J and Feringa B L 2008 *Org. Lett.* **10** 4041
9. Emmerson P G D, Hems W P and Davis B G 2005 *Tetrahedron: Asymmetry* **16** 213
10. Wang Z Y, Shen J, Jiang C S and You T P 2000 *Chin. Chem. Lett.* **11** 659
11. Mukaiyama T and Asami M 1985 *Top. Curr. Chem.* **127** 133
12. Soai K and Kawase Y 1991 *Tetrahedron: Asymmetry* **2** 781
13. Seebach D and Langer W 1979 *Helv. Chim. Acta.* **62** 1701
14. Andres J M, Pedrosa R and Perez-Encabo A 2000 *Tetrahedron* **56** 1217
15. Skarzewski J, Gupta A and Vogt A 1995 *J. Mol. Catal.* **A103** 63
16. Cozzi P G and Rivalta E 2006 *Pure Appl. Chem.* **78** 287
17. Cozzi P G 2006 *Angew. Chem. Int. Ed.* **45** 2951
18. Marioka K, Hashimoto S, Kitagawa Y, Yamamaoto H and Nozaki H 1977 *J. Am. Chem. Soc.* **99** 7705
19. Harada T and Mukaiyama T 1982 *Chem. Lett.* 161
20. Imamoto T, Kusumoto T, Tawarayama Y, Sugiura Y and Yokoyama M 1984 *J. Org. Chem.* **49** 3904
21. Soai K, Oshio A and Saito T 1993 *J. Chem. Soc. Chem. Commun.* 811
22. Andres J M, Maria M A, Rafael P and Alfonso P E 1996 *Synthesis* **9** 1070
23. Zhang Y and Wu W 1997 *Tetrahedron: Asymmetry* **8** 3575
24. Ananthi N, Balakrishnan U, Vinu A, Ariga K and Velmathi S 2009 *Tetrahedron: Asymmetry* **20** 1731
25. Boaz N W 1992 *J. Org. Chem.* **57** 4289
26. Fernandez-Ibanaz M A, Macia B, Minnard A J and Feringa B L 2008 *Angew. Chem. Int. Ed.* **47** 1317
27. Yang T K 2007 *Tetrahedron: Asymmetry* **18** 949
28. Lewinski J, Ochal Z, Bojarski E, Tratkiewicz E, Justyniak I and Lipkowski J 2003 *Angew. Chem. Int. Ed.* **42** 4643
29. Lewinski J, Sliwinski W S, Dranka M, Justyniak I and Lipkowski J 2006 *Angew. Chem. Int. Ed.* **45** 4826
30. Bertrand M, Feray L and Gastaldi S 2002 *Compt. Rend. Chim.* **5** 623
31. Yamada K I, Yamamoto Y and Tomioka K 2003 *Org. Lett.* **5** 1797
32. Yamada K I, Yamamoto Y, Maekawa M and Tomioka K 2004 *J. Org. Chem.* **69** 1531

33. Yamada K I, Yamamoto Y, Maekawa M, Akindele T, Umeki H and Tomioka K 2006 *Org. Lett.* **8** 87
34. Yamamoto Y, Yamada K I and Tomioka K 2004 *Tetrahedron Lett.* **45** 795
35. Yamamoto Y, Maekawa M, Akindele T, Yamada K I and Tomioka K 2005 *Tetrahedron* **61** 379
36. Ocampo R, Dolbier Jr W R, Abboud K A and Zuluaga F 2002 *J. Org. Chem.* **67** 72
37. Katritzky A R, Hong Q and Yang Z 1995 *J. Org. Chem.* **60** 3405
38. Adrian J C and Snapper M L 2003 *J. Org. Chem.* **68** 2143