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Conformationally rigid chiral ferrocene derivative: Synthesis, resolution and stereochemical assignment

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ABSTRACT

A conformationally rigid chiral molecule **LB-I** with Lewis basic site has been designed and synthesized in racemic form from ferrocene via Lewis acid mediated diastereoselective cyclization of hydroxy lactam. Both isomers were successfully obtained in enantiomerically pure form through classical resolution using dibenzoyl-D-tartaric acid as the chiral resolving agent in acetone. The nature of the diastereomeric salt formed in the resolution process was investigated by single crystal X-ray crystallographic studies. The absolute configuration of (+)-**LB-I** was unambiguously assigned as (S,R_p) by single crystal analysis of the salt **I** obtained from precipitate fraction containing (+)-**LB-I** and dibenzoyl-D-tartaric acid.

1. Introduction

Ferrocene derivatives with one or more heteroatoms are important in organic synthesis as they are suitable ligands capable of coordinating transition metal ions to provide complexes displaying potential applications as catalysts in different synthetic transformations.[1] Due to their availability, steric and electronic properties, unique stereochemical aspects and wide variety of coordination modes, these ligands have been successfully employed in a wide variety of stereoselective transformations.[2] Ferrocene derivatives containing nitrogen heterocycles, tertiary phosphines and amines (Lewis bases) are known to catalyze a variety of chemical reactions through their nucleophilic reactivity. Hence, the development of new ferrocene based chiral molecules for asymmetric catalysis has attracted much attention in recent years. Very few chiral catalysts have been reported in this field, amongst which the planar chiral ferrocene DMAP developed by Fu et al. has proven to be a very effective catalyst in variety of asymmetric transformations, such as additions of alcohols or amines to ketenes, rearrangements of *O*-acylated enolates, asymmetric [2+2] cycloadditions of aldehydes and ketenes and acylations of alcohols and silylated enolates by anhydrides.[3] The combination of both planar and central chirality usually display good enantioselectivity.[4]

Hence, a conformationally rigid skeleton, (±)-**L**, a hybrid unit visualized from isoindoloisoquinolinone and ferrocene, has been designed with both central and planar chirality (Fig. 1). Further modification of this molecule may lead to the Lewis base, (±)-**LB**. Due to the rigidity and presence of steric hindrance, the chiral molecule **LB** may display good stereoselectivity in asymmetric organic transformations. The planar chirality on ferrocene nucleus is usually introduced by either ortholithiation of Ugi's amine[5] or using *ortho*-directing units such as acetals,[6] oxazolines[7] or sulphoxides.[8] The direct introduction of both central and planar chirality on ferrocene skeleton in a single reaction sequence has not been reported so far.

2. Results and discussion

Isoindoloisoquinolinones can be efficiently synthesized through *6-exo-trig* cyclization of phenethylphthalimides in presence of either Lewis acid or Brønsted acid.[9] Based on our experience, retro synthetically, the target molecule (±)-**L** can be obtained from imide **5**. Imide **5** could be realized from ferrocenecarboxaldehyde **1** by nitroaldol condensation, and reduction of the double bond as well as nitro group followed by condensation of the amine with phthalic anhydride.

As illustrated in Scheme 1, condensation of ferrocenecarboxaldehyde **1**, which was prepared from ferrocene,[10] with nitromethane in presence of ammonium acetate and a catalytic amount of acetic acid under sonication afforded **2** in 82% yield.[11] The reduction of the double bond in **2** was achieved using $NaBH_4$ and silica gel combination in an isopropanol and chloroform solvent mixture to furnish **3** in 83% yield.[9] Catalytic hydrogenation of nitro alkane **3** with 10% Pd/C in methanol provided amine **4**.[12] Refluxing the toluene solution of **4** and phthalic anhydride produced water molecules, which were removed azeotropically using a Dean-Stark set up to afford 2-ferrocenylethylisoindoline-1,3-dione **5**

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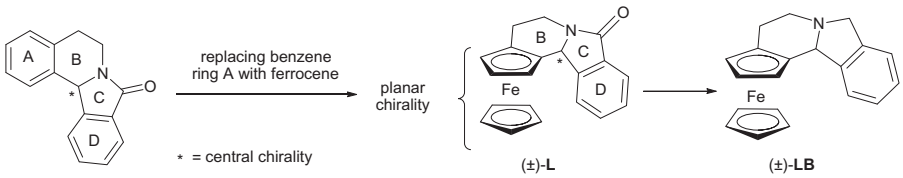
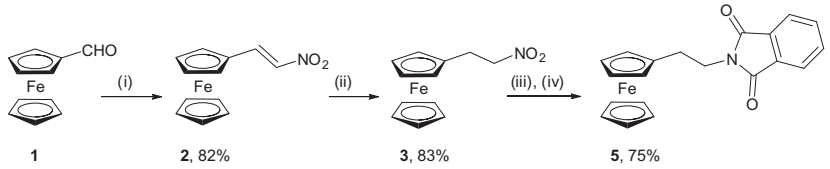


Figure 1. Novel chimeric molecule (±)-**L** hypothesized from isoindoloisoquinolinone.



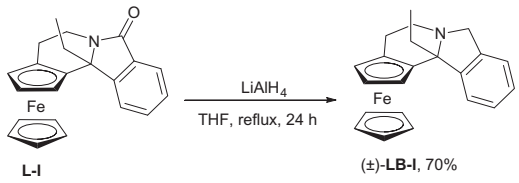
Scheme 1. Synthesis of imide **5**. Reagents and conditions: (i) CH_3NO_2, $AcONH_4$/AcOH, sonication, 3.5 h; (ii) $NaBH_4/SiO_2$, $CHCl_3$/*i*PrOH, rt, 5 h; (iii) 10% Pd/C, H_2 gas, MeOH, 24 h; (iv) phthalic anhydride, toluene, reflux, 5 h.

in 75% yield.[13] Partial reduction of imide **5** using $NaBH_4$ and a methanol system followed by cyclization using $BF_3{\cdot}OEt_2$ generated the cyclized lactam **L** in 79% yield (Scheme 2).[14] Unfortunately, lactam **L** underwent aerial oxidation while purifying through either column chromatography or through recrystallization (see Supporting information). The aerial oxidation problem may be alleviated by introducing an alkyl group. Accordingly, the ethyl group was introduced by treating imide **5** with ethylmagnesium bromide followed by cyclization of the resulting hydroxy lactam **6b** using Lewis acid (Scheme 2).[15]

The reduction of lactam **L-I** was accomplished with lithium aluminium hydride ($LiAlH_4$) to provide the target Lewis base **LB-I** in racemic form with 70% yield (Scheme 3).[16] The structure of (±)-**LB-I** was characterized and confirmed by using spectroscopic techniques such as IR, ^{1}H NMR, ^{13}C NMR, HRMS along with single crystal X-ray crystallography (Fig. 2).

The hydroxy lactam **6a** or **6b** upon cyclization is supposed to furnish a pair of diastereomers due to the creation of both central and planar chiral components in the resulting molecule. This reaction furnished only an enantiomeric pair in a highly diastereoselective fashion. This may be due to the *exo*-selective S_EAr reaction of the ferrocene ring with electrophilic iminium ion as depicted in the Figure 3. The advantage of this method is the capability of introducing both planar and central chirality on **L** or **L-I** in a single reaction.

During the development of new chiral molecules for asymmetric transformations,[17] we have successfully employed the classical resolution technique involving diastereomeric salt formation between a racemic base with a chiral acid as well as a racemic acid with a chiral base.[18] Therefore, the resolution of (±)-**LB-I** was carried out with L-tartaric acid (1.0 equiv.) in different solvents such as methanol, chloroform, acetonitrile and acetone. Although the diastereomeric salt formation was observed in acetonitrile as well



Scheme 3. Synthesis of (±)-**LB-I**.

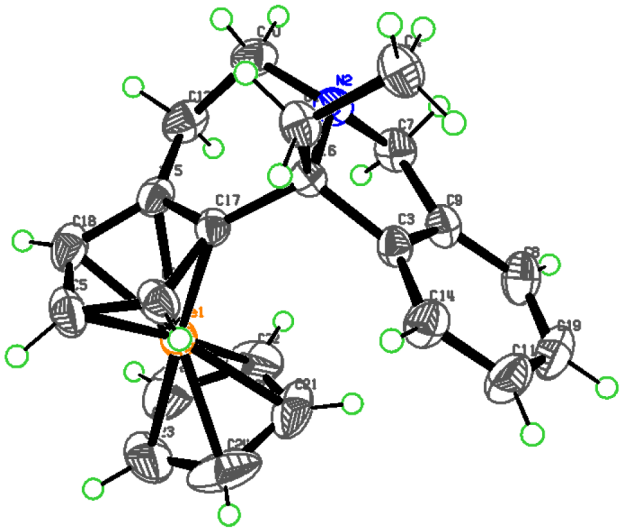
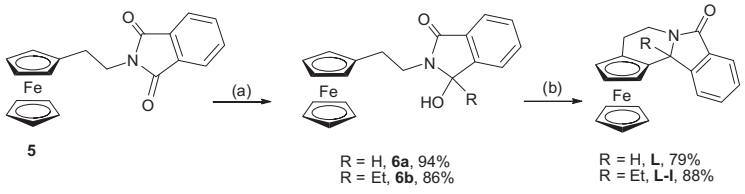


Figure 2. ORTEP representation of the X-ray crystal structure of (±)-**LB-I** with 50% probability ellipsoids.



Scheme 2. Synthesis of (±)-**L** and (±)-**L-I**. Reagents and conditions: For **6a** (a) $NaBH_4$/MeOH, −40 °C, 1 h, −20 °C, 5 h; for **6b** (a) EtMgBr, THF, −70 °C, 0.5 h, rt, 3 h; for **L** (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C – rt, 48 h; for **L-I** (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C – rt, 4 h.

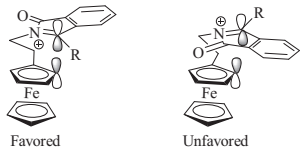


Figure 3. The *exo*-selective cyclization of ferrocene with iminium ion.

as in acetone solvents at room temperature, the compound **LB-I** liberated from the precipitate fractions failed to show a specific rotation. This observation prompted us to resolve (±)-**LB-I** using (+)-*O*,*O*′-dibenzoyl tartaric acid (D-DBTA), which is a stronger acid (pK_a = 1.85) than L-tartaric acid (pKa1 = 2.98, pKa2 = 4.34).

Hence, the resolution of (±)-**LB-I** was carried out with a 1:1 mixture of (±)-**LB-I** and D-DBTA in solvents such as methanol, acetone or acetonitrile at room temperature. Except in methanol, both in acetone and in acetonitrile, the precipitation was realized (Table 1, entries 1–3). For example, (±)-**LB-I** and D-DBTA were dissolved in acetone and allowed to stir at room temperature for 15 min, followed by standing at room temperature for 1 h (Table 1, entry 2) to furnish the precipitate, which was filtered and washed with cold acetone. After digestion of the precipitate fraction with a 1:1 mixture of CH_2Cl_2/aq K_2CO_3, (+)-**LB-I** was obtained in 43% yield with 99% ee. The filtrate, upon evaporation and digestion with a CH_2Cl_2/aq K_2CO_3 mixture, afforded (−)-**LB-I** isomer in 48% yield and with 93% ee (Scheme 4). When using acetonitrile as the solvent, (+)-**LB-I** was obtained in 41% yield and with 97% ee from the precipitate, and (−)-**LB-I** in 43% yield and with 90% ee from the filtrate (Table 1, entry 3). Based on these observations, acetone was considered as a good solvent for the resolution of (±)-**LB-I** using 1.0 equiv of D-DBTA. To improve the enantiomeric purity and yields of the isomers of **LB-I**, the experiments were carried out with (±)-**LB-I** using 1.0 equiv of D-DBTA in acetone by varying the precipitation time and the results are shown in Table 1 (entries 2, 4). The yields and enantiomeric purity of the product from both the precipitate and the filtrate fractions did not change with precipitation time. Therefore, the optimum time for the resolution of (±)-**LB-I** was found to be stirring of (±)-**LB-I** with D-DBTA (1.0 equiv) for 15 min followed by standing at room temperature for 1 h. Decreasing the number of equivalents of chiral resolving agent from 1.0 equiv to 0.5 equiv with respect to (±)-**LB-I** decreased the yield of (+)-**LB-I** from 43% to 31% with no change in the enantiomeric excess and a decrease in the enantiomeric excess of (−)-**LB-I** from 93% to 85% with an increase in the yield from 48% to 55% (Table 1, entry 5).

Based on these studies, the optimized conditions for the resolution of (±)-**LB-I** were found to be stirring (±)-**LB-I** with D-DBTA (1.0 equiv) in acetone at room temperature for 15 min, then standing at the same temperature for 1 h. The isomer (+)-**LB-I** from precipitate was obtained in 43% yield and with 99% ee, while the other isomer (−)-**LB-I** was obtained from filtrate in 48% yield and with 93% ee (Scheme 4). To enrich the enantiomeric purity of (+)-**LB-I**, the precipitate I formed in the reaction between (±)-**LB-I** and D-DBTA (1.0 equiv) in acetone was recrystallized from a mixture of methanol and acetonitrile (8:2) to afford the enantiomerically pure isomer (+)-**LB-I** in 36% yield (Scheme 4). The enrichment of enantiomeric purity of (−)-**LB-I** (93% ee) was carried out using two different methods. In method A, (−)-**LB-I** was stirred with L-DBTA (1.0 equiv) in acetone at room temperature for 15 min and then standing at room temperature for 1 h, which afforded (−)-**LB-I** in 41% yield and with >99% ee from the precipitate fraction (Scheme 4).

Periasamy et al. developed a methodology for the enrichment of the enantiomeric purity of partially resolved (non-racemic) amino alcohols and a diamine via the preparation of the corresponding hydrogen bonded homochiral or heterochiral aggregates (achiral acids).[19] This methodology prompted us to enrich the scalemic (−)-**LB-I** using available achiral acids. Following this methodology, (method B) the scalemic (−)-**LB-I** (93% ee) was treated with 1.0 equivalent of achiral acids, such as oxalic acid, malonic acid and phthalic acid. Among these achiral acids, oxalic acid afforded enantiomerically pure (−)-**LB-I** in 31% yield from the precipitate fraction; this may be because of the predominant formation of homochiral aggregates in the precipitate fraction (Scheme 4). The enantiomeric excess of enantiomerically pure (+)-**LB-I** and (−)-**LB-I** were further confirmed by NMR studies using chiral solvating agent (*R*)-(−)-BINOL-phosphoric acid[20] in $CDCl_3$ (see Supporting information).

After the successful resolution of (±)-**LB-I**, we focused our attention on assigning the configurations in chiral molecule (+)-**LB-I** using crystallographic analysis of a single crystal obtained from the precipitate **I**. Single crystal was obtained by recrystallization of the precipitate **I** in ethanol (dissolving the precipitate **I** by heating at 50 °C for 15 min and then allowed to stand at room temperature). The crystal structure (Figure 4)[21] reveals that the D-DBTA was crystallized with one molecule of (+)-**LB-I**. Furthermore, the C—O bond lengths (C33—O5 = 1.251 Å and C33—O6 = 1.250 Å) of one of the two carboxylic acid groups of D-DBTA were found to be nearly equal; this indicates that the substrate and D-DBTA formed a diastereomeric ammonium salt **I**. The configuration of the C13 stereogenic center and the planar chirality of (+)-**LB-I** were assigned relative to the (2*S*,3*S*)-(+)-dibenzoyl tartaric acid. Based on this relative configuration, it was found that the configurations of the stereogenic center C13 and the planar chirality in (+)-**LB-I** are (*S*) and (R_p) respectively. Hence, the stereogenic center C13 and planar chirality in (−)-**LB-I** are (*R*) and (S_p), respectively.

3. Conclusion

In conclusion, a new ferrocene based conformationally rigid chiral molecule with a Lewis base site has been designed and synthesized in racemic form. We have developed a simple and economical method for the resolution of (±)-**LB-I** using commercially available dibenzoyl-D-tartaric acid. Enrichment of scalemic (−)-**LB-I** was accomplished by using an achiral acid, i.e. oxalic acid. The absolute configurations in (+)-**LB-I** were determined by using single crystal X-ray crystallographic analysis. Further investigations into the structural modification and scope of those molecules as chiral catalysts in asymmetric transformations are currently in progress.

4. Experimental

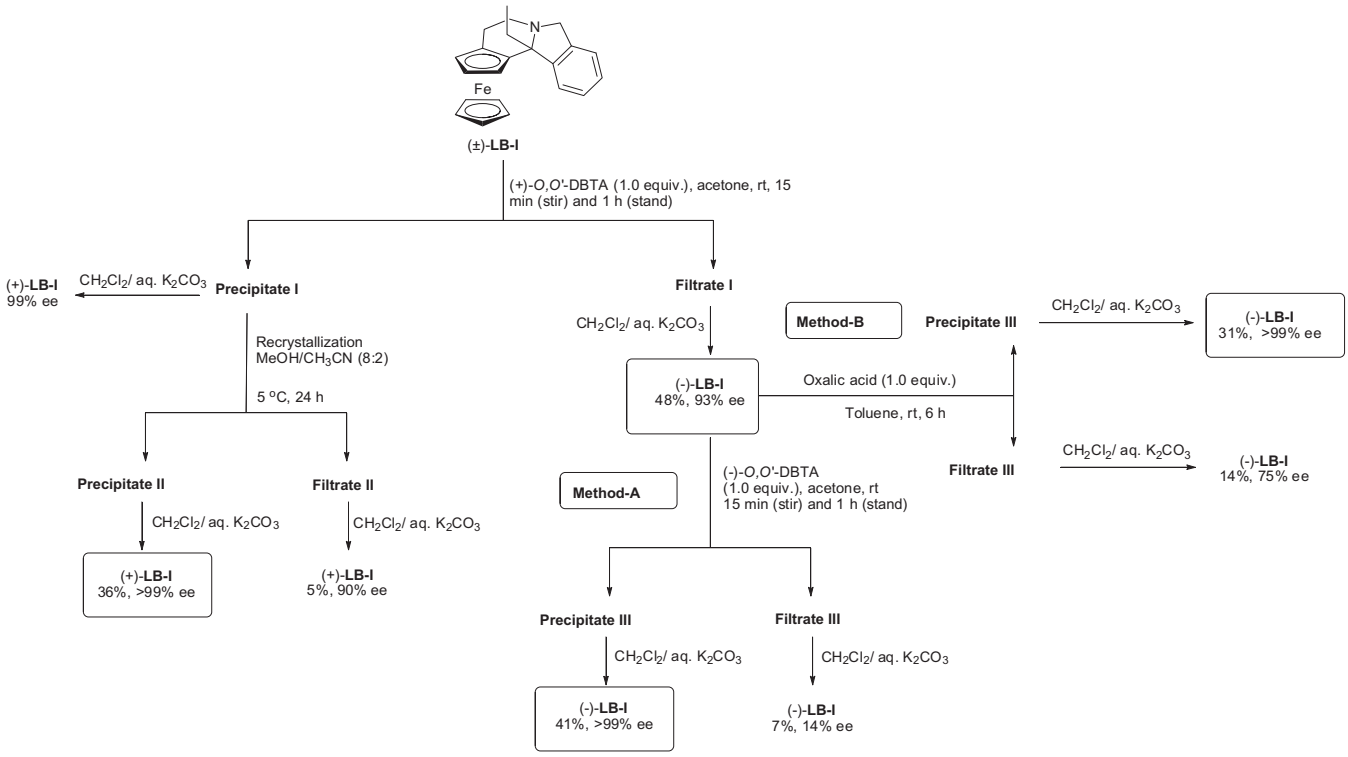
4.1. General

All reactions were performed in an oven-dried round bottom flasks. Stainless steel syringes or cannulae were used to transfer air and moisture sensitive liquids. Melting points are uncorrected and were determined using a Buchi Melting Point M-560, Switzerland. Infrared spectra were recorded on Thermo Nicolet iS10 FT-IR Spectrophotometer and are reported in frequency of absorption (cm^{-1}). Mass spectra were measured with Agilent-6530 B Q-TOF (ESI-HRMS), ^1H and ^{13}C NMR were recorded on Brucker AVANCE 400 spectrometer. NMR spectra for all the samples were measured in $CDCl_3$ using TMS as an internal standard. The chemical shifts are expressed in δ ppm downfield from the signal of internal TMS. Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, ddd = doublet of doublet of doublet, td = triplet of doublet, m = multiplet), coupling constants in Hertz (Hz) and integration. Solvents used for the reactions were dried using standard

Table 1
Optimization conditions for resolution of (±)-**LB-I**[a]

Entry	D-DBTA (equiv.)	Solvent	Reaction time (t)	Precipitation time (t)	Precipitate		Filtrate	
					%Yield[b]	%ee[c]	%Yield[b]	%ee[c]
1	1.0	MeOH	15 min	1 h	–	–	–	–
2	**1.0**	**Acetone**	**15 min**	**1** h	**43**	(+)-**99**	**48**	(−)-**93**
3	1.0	CH_3CN	15 min	1 h	41	(+)-97	43	(−)-90
4	1.0	Acetone	15 min	2 h	41	(+)-99	46	(−)-90
5	0.5	Acetone	15 min	1 h	31	>99 (+)	55	(−)-85

[a] In all experiments, (±)-**LB-I** (178 mg, 0.5 mmol) and D-DBTA were dissolved in solvent (8 mL).
[b] Yields are of isolated scalemic **LB-I** [(+)-**LB-I** from precipitate and (−)-**LB-I** from filtrate fractions].
[c] Enantiomeric excess of the regenerated samples were determined by chiral HPLC analysis (Chiral stationary phase: Diacel-Chiralcel OD, Mobile phase: hexane and isopropyl alcohol (99.5:0.5), 0.5 mL/min, t_R = 15.02 min [(+)-**LB-I**], t_R = 16.69 min [(−)-**LB-I**]).



Scheme 4. Optimization conditions for the resolution of (±)-**LB-I**.

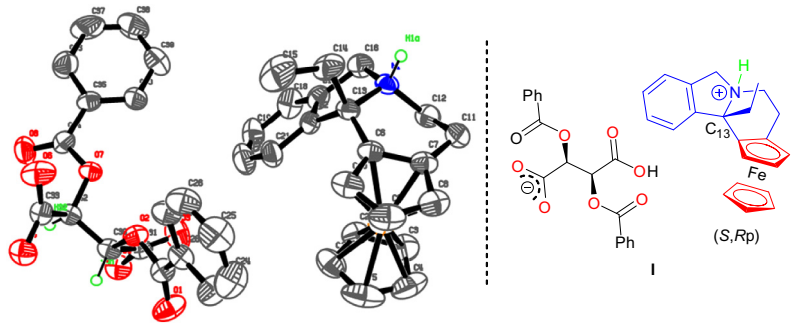


Figure 4. ORTEP diagram of diastereomeric salt **I** with 50% probability (hydrogen atoms are omitted for clarity except on nitrogen atom N1, C30 and C32 in D-DBTA).

procedures.[22] For syntheses, the chemicals such as ferrocene, sodium borohydride, boron trifluoride etherate and lithium aluminium hydride were supplied by Aldrich, USA. The remaining reagents were from Avra, RANKEM and Sd Fine Chemicals were used. Column chromatography was performed on Merck silica gel 100–200 mesh, and TLC analyses were facilitated using phosphomolybdic acid stain in addition to UV light with Merck 60 GF_{254} pre-coated silica plates. X-ray crystal data were collected on Oxford Diffraction Xcalibur diffractometer with Mo-Kα radiation (λ = 0.71073 Å). Empirical absorption correction using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm, were applied. Structure solution and refinement were

performed with SHELX-97.[23] Optical rotations were measured in an AUTOPOL-IV automatic polarimeter. Enantiomeric excess of the samples were determined on a Shimadzu HPLC systems using the Daicel-Chiralcel OD column.

4.2. Preparation of ferrocenecarboxaldehyde 1

Ferrocenecarboxaldehyde was prepared from ferrocene according to the literature.[10] Phosphorus oxychloride (50 mL, 536 mmol) was added dropwise to the dimethylformamide (39.0 g, 536 mmol) at 0 °C and the resulting mixture was stirred for 30 min at this temperature under a nitrogen atmosphere. Next ferrocene (50.0 g, 268 mmol) in dry chloroform (250 mL) was added dropwise to the mixture for 30 min at 0 °C. After completion of the addition, the reaction mixture was kept stirring for 28 h with heating at 55–60 °C on an oil bath, taking care that the temperature did not exceed 60 °C. The reaction mixture was then cooled to room temperature and neutralized carefully with an aqueous saturated Na_2CO_3 solution and then extracted repeatedly with the dichloromethane. The combined organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified through silica gel column chromatography using hexane/ethyl acetate mixture (95:05) as eluent to give ferrocenecarboxaldehyde **1** in 55% yield (31.7 g) as a reddish brown solid. (mp: 122 °C, *lit.*[10] 123 °C); IR (KBr, cm^{-1}): 3093, 2837, 2760, 1683, 1447; ^1H NMR (400 MHz, $CDCl_3$): δ_H 9.95 (s, 1H); 4.80–4.60 (m, 4H), 4.27 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 193.63, 79.49, 73.33, 69.78; HRMS-ESI (*m*/*z*): $[M+H]^+$ Found 215.0157 and calculated 215.0159 for $C_{11}H_{11}FeO$.

4.3. Preparation of 2-nitro-1-ferrocenylethylene 2

To a solution of ferrocenecarboxaldehyde **1** (10.0 g, 46.6 mmol) in nitromethane (30 mL, 560 mmol) were added acetic acid (2.7 mL, 46.6 mmol) and ammonium acetate (9.0 g, 116 mmol). The reaction mixture was then subjected to ultrasound (sonication) for 3.5 h. The crude mixture was extracted with dichloromethane. The combined organic layer was washed with brine solution, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The residue was purified through silica gel column chromatography using hexane/ethyl acetate mixture (97:03) as eluent to give 2-nitro-1-ferrocenylethylene **2** in 82% yield (9.85 g) as a purple solid. (mp: 138 °C, *lit.*[24] 139–140 °C); IR (KBr, cm^{-1}): 3102, 3084, 3043, 2919, 1627, 1495; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.98 (d, J = 13.2 Hz, 1H), 7.26 (d, J = 13.2 Hz, 1H), 4.61 (t, J = 2.0 Hz, 2H), 4.55 (t, J = 2.0 Hz, 2H) 4.23 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 142.17, 133.34, 73.70, 72.94, 70.33, 69.86; HRMS-ESI (*m*/*z*): [M] Found 257.0143 and calculated 257.0217 for $C_{12}H_{11}FeNO_2$.

4.4. Preparation of 2-nitro-1-ferrocenylethane 3

To an efficiently stirred mixture of 2-nitro-1-ferrocenylethylene **2** (20.0 g, 77.5 mmol), silica gel (193.0 g, 2.5 g/mmol), isopropanol (290 mL, 1.5 mL/g of SiO_2) and chloroform (1.55 L, 8 mL/g of SiO_2) was added $NaBH_4$ (11.73 g, 310 mmol) in 1 g portion over a period of 1 h and the reaction mixture was stirred for 5 h at room temperature. The disappearance of the pink color of 2-nitrovinylferrocene indicates the completion of the reaction and the excess $NaBH_4$ was decomposed using dil. HCl after which the mixture was filtered. The silica gel was washed with chloroform. The combined filtrate was washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated under reduced pressure. The crude material was purified through silica gel chromatography using hexane as eluent to give 2-nitro-1-ferrocenylethane **3** in 83% yield (16.72 g) as a yellow solid. (mp: 99 °C); IR (KBr, cm^{-1}): 3096, 2916, 1645, 1559, 1447, 1380; ^1H NMR (400 MHz, $CDCl_3$): δ_H 4.50 (t, J = 7.2 Hz, 2H), 4.14 (s, 5H), 4.12–4.09 (m, 4H), 3.06 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 82.63, 76.38, 68.86, 68.25, 68.18, 27.95; HRMS-ESI (*m*/*z*): [M] Found 259.0296 and calculated 259.0296 for $C_{12}H_{13}FeNO_2$.

4.5. Preparation of 2-amino-1-ferrocenylethane 4

A mixture of 2-nitro-1-ferrocenylethane **3** (20.0 g, 77 mmol) and 10% Pd/C (0.82 g, 7.7 mmol) in methanol was stirred under 1 atm. H_2 gas for 24 h. The reaction mixture was then filtered through a pad of Celite and washed with methanol. The solvent was removed under reduced pressure to give 2-amino-1-ferrocenylethane **4** in 92% yield (16.27 g) as a dark red viscous oil. Compound **4** was used for next step without further purification. IR (KBr, cm^{-1}): 3428, 3087, 2922, 2849, 1642, 1574, 1468; ^1H NMR (400 MHz, $CDCl_3$): δ_H 4.09 (s, 5H), 4.06–4.05 (m, 4H), 2.79 (t, J = 6.8 Hz, 2H), 2.47 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 86.22, 68.62, 68.46, 67.50, 43.47, 33.91; HRMS-ESI (*m*/*z*): [M] Found 229.0554 and calculated 229.0554 for $C_{12}H_{15}FeN$.

4.6. Preparation of 2-ferrocenylethylisoindoline-1,3-dione 5

2-Amino-1-ferrocenylethane **4** (18.0 g, 78.2 mmol) and phthalic anhydride (15.06 g, 101.7 mmol) were refluxed in toluene (200 mL) at 130 °C. The water formed in this reaction was removed from the mixture using Dean-Stark apparatus and the reaction was continued for 5 h. The reaction mixture was cooled to room temperature and toluene was evaporated under vacuum. This reaction mixture was dissolved in dichloromethane and washed with 2 M NaOH. The organic layer was separated, dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude material was purified through silica gel column chromatography using hexane/ethyl acetate (95:05) as eluent to give 2-ferrocenylethylisoindoline-1,3-dione **5** in 75% yield (21.13 g) as a yellow solid. (mp: 156–157 °C); IR (KBr, cm^{-1}): 3084, 2977, 2939, 1771, 1716, 1610, 1517; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.84 (dd, J = 5.2, 3.2 Hz, 2H), 7.71 (dd, J = 5.2, 3.2 Hz, 2H), 4.14 (s, 5H), 4.11–4.09 (m, 2H), 4.07–4.06 (m, 2H), 3.87–3.83 (m, 2H), 2.72–2.68 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 168.35, 134.04, 132.28, 123.34, 84.69, 68.72, 68.29, 67.75, 38.99, 28.64; HRMS-ESI (*m*/*z*): [M] Found 359.0609 and calculated 359.0609 for $C_{20}H_{17}FeNO_2$.

4.7. Preparation of 3-hydroxy-2-ferrocenethylisoindolin-1-one 6a

At first, $NaBH_4$ (1.42 g, 37.5 mmol) was added portionwise at −40 °C for 1 h to a solution of imide **5** (3.0 g, 8.3 mmol) in a mixture of MeOH (40 mL) and CH_2Cl_2 (60 mL) under a nitrogen atmosphere. The reaction mixture was warmed to −20 °C and stirred at this temperature for 5 h. The reaction was quenched by the addition of water. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. This crude material was purified through silica gel column chromatography using hexane/ethyl acetate (70:30) as eluent to give **6a** in 94% yield (2.84 g) as a yellow solid. (mp: 103–104 °C); IR (KBr, cm^{-1}): 3540, 3272, 3075, 2922, 2846, 1668, 1618, 1471; ^1H NMR (400 MHz, $CDCl_3$): δ_H 7.64–7.63 (m, 1H), 7.56 (dd, J = 5.2, 1.2 Hz, 2H), 7.49–7.42 (m, 1H), 5.57 (d, J = 12.0 Hz, 1H), 4.11 (s, 5H), 4.07 (s, 2H), 4.04–4.02 (m, 2H), 3.65–3.58 (m, 1H), 3.48–3.41 (m, 1H),

3.13 (d, J = 11.6 Hz, 1H), 2.68–2.64 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.45, 144.03, 132.31, 131.69, 129.90, 123.42, 123.30, 85.51, 82.33, 68.81, 68.54, 68.21, 67.85, 67.80, 40.81, 28.51; HRMS-ESI (m/z): [M] Found 361.0765 and calculated 361.0765 for $C_{20}H_{19}FeNO_2$.

4.8. Preparation of ferroceno[1,2-*a*]-3,10b-dihydropyrido[2,1-*a*] isoindol-6(4*H*)-one L

The hydroxy lactam **6a** (0.100 g, 0.276 mmol) was dissolved in dry dichloromethane under a nitrogen atmosphere. To this solution was added $BF_3{\cdot}Et_2O$ (0.42 mL, 3.314 mmol) at 0 °C and the reaction mixture was allowed to warm to room temperature with stirring. Stirring was continued for 48 h at room temperature. The reaction was quenched with aqueous saturated $NaHCO_3$ solution and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 x 15 mL). The organic layers were combined, washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure to give **L** in 79% yield (0.075 g) as a yellow solid. (mp: 175 °C); IR (KBr, cm^{-1}): 3040, 2939, 2913, 1684, 1463, 1415; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.00 (d, J = 7.6 Hz, 1H), 7.67–7.66 (m, 2H), 7.60–7.55 (m, 1H), 5.26 (s, 1H), 4.66–4.60 (m, 1H), 4.23–4.20 (m, 2H), 4.09 (t, J = 2.4 Hz, 1H), 3.46 (s, 5H), 3.14 (td, J = 12.0, 5.4 Hz, 1H), 3.06–2.97 (m, 1H), 2.52–2.46 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.35, 146.64, 132.80, 131.42, 128.56, 124.00, 122.62, 85.62, 81.72, 69.49, 66.48, 66.07, 63.18, 57.50, 37.01, 24.43; HRMS-ESI (m/z): [M−H] Found 342.0582 and calculated 342.0581 for $C_{20}H_{16}FeNO$. The crude sample of **L** (0.075 g) was purified through silica gel column chromatography using hexane/ethyl acetate (80:20) as eluent to give compound **7** in 0.072 g (91%) instead of **L**.

4.9. Purification of L

Compound **L** (0.100 g, 0.29 mmol) was dissolved in dry dichloromethane and the solution was left at room temperature for recrystallization. The formed yellow crystals were washed with cold hexane to give 10b-hydroxy-ferroceno[1,2-*a*]-3,10b-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one **7** in 0.096 g (92%) instead of **L**. (mp: 201–202 °C); IR (KBr, cm^{-1}): 3267, 2943, 2922, 1678, 1470, 1414; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.88–7.84 (m, 2H), 7.72 (t, J = 7.2 Hz, 1H), 7.56 (t, J = 7.2 Hz, 1H), 4.45 (s, 1H), 4.27–4.23 (m, 2H), 4.12 (s, 1H), 3.42 (s, 5H), 3.38 (d, J = 5.6 Hz, 1H), 3.29 (td, J = 12.8, 5.2 Hz, 1H), 3.04–2.95 (m, 1H), 2.49 (dd, J = 16.0, 5.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 166.36, 148.92, 132.33, 130.84, 129.70, 123.69, 122.09, 99.94, 87.63, 85.77, 70.20, 67.50, 66.73, 64.25, 33.55, 24.18; HRMS-ESI (m/z): [M] Found 359.0606 and calculated 359.0609 for $C_{20}H_{17}FeNO_2$.

4.10. Preparation of 3-ethyl-3-hydroxy-2-ferrocenethylisoindolin-1-one 6b

Ethylmagnesium bromide was prepared from bromoethane (12.0 g, 111.11 mmol) and magnesium turnings (2.70 g, 111.11 mmol) and small amount of iodine in THF (15 mL). This solution of Grignard reagent was added dropwise via syringe to a stirred solution of 2-phthalimido-1-ferrocenylethane **5** (20.0 g) in degassed THF (250 mL) at −70 °C under a nitrogen atmosphere. The solution was stirred at −70 °C for 0.5 h and then allowed to warm to room temperature and stirring was continued for 3 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 mL). The reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. This crude material was purified through silica gel column chromatography using hexane/ethyl acetate (70:30) as eluent to give **6b** in 86% yield (18.8 g) as a yellow solid. (mp: 146–147 °C); IR (KBr, cm^{-1}): 3261, 2975, 2942, 1674, 1616, 1471, 1443, 1418; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.75–7.72 (m, 1H), 7.57–7.53 (m, 1H), 7.48–7.44 (m, 2H), 4.14 (s, 6H), 4.08 (s, 1H), 4.04–4.02 (m, 2H), 3.76 (ddd, J = 13.8, 9.5, 4.4 Hz, 1H), 3.26 (ddd, J = 13.6, 9.2, 7.4 Hz, 1H), 2.93 (ddd, J = 14.0, 9.5, 7.4 Hz, 1H), 2.67 (ddd, J = 13.8, 9.3, 4.4 Hz, 1H), 2.33 (s, 1H) 2.17–1.98 (m, 2H), 0.49 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.55, 146.55, 132.36, 131.74, 129.67, 123.20, 121.78, 91.93, 86.05, 68.85, 68.49, 68.35, 67.90, 67.76, 40.26, 29.21, 28.53, 7.98; HRMS-ESI (m/z): [M] Found 389.1078 and calculated 389.1078 for $C_{22}H_{23}FeNO_2$.

4.11. Preparation of 10b-ethyl-ferroceno[1,2-*a*]-3,10b-dihydropyrido[2,1-*a*]isoindol-6(4*H*)-one L-I

The hydroxy lactam **6b** (0.389 g, 1 mmol) was dissolved in dry dichloromethane. To this solution was added $BF_3{\cdot}Et_2O$ (1.5 mL, 12 mmol) at 0 °C and the reaction mixture was allowed to warm to room temperature with stirring. Stirring was continued for 4 h at room temperature. The reaction was quenched with an aqueous saturated $NaHCO_3$ solution and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). Organic layers were combined, washed with brine solution, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. This crude material was purified through silica gel column chromatography using hexane/ ethyl acetate (80:20) as eluent to give **L-I** in 88% yield (0.326 g) as a yellow solid. (mp: 172–173 °C); IR (KBr, cm^{-1}): 3101, 3046, 2963, 2929, 1685, 1465, 1403; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 8.00–7.98 (m, 1H), 7.67 (td, J = 7.5, 1.1 Hz, 1H), 7.61–7.59 (m, 1H), 7.54 (td, J = 7.4, 1.0 Hz, 1H), 4.62–4.52 (m, 1H), 4.15–4.14 (m, 2H), 4.04 (t, J = 2.4 Hz, 1H), 3.40 (s, 5H), 3.07–2.98 (m, 2H), 2.50–2.41 (m, 1H), 2.09–1.99 (m, 2H), 0.47 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 167.76, 150.20, 132.58, 131.35, 128.21, 123.73, 121.38, 91.12, 80.69, 69.52, 66.03, 65.68, 65.54, 62.88, 33.58, 32.84, 24.02, 8.19; HRMS-ESI (m/z): [M] Found 371.0977 and calculated 371.0973 for $C_{22}H_{21}FeNO$.

4.12. Preparation of 10b-ethyl-ferroceno[1,2-*a*]-3,4,6,10b-tetrahydropyrido[2,1-*a*]isoindole LB-I

Lithium aluminium hydride (0.51 g, 13.5 mmol) weighed into a pre-dried schlenk round bottom flask containing compound **L-I** (1.0 g, 2.7 mmol). Anhydrous THF was added to the reaction mixture at 0 °C and the reaction mixture was heated at reflux for 24 h. After complete conversion of starting material, monitored by TLC, *tert*-butyl methyl ether (25 mL) was added and the reaction mixture was quenched by the careful addition of saturated aqueous sodium potassium tartrate solution. The mixture was stirred for 1 h before the addition of anhydrous Na_2SO_4 and then filtered through a Celite pad. The filtrate was evaporated under reduced pressure. This crude material was purified through silica gel column chromatography using hexane/ethyl acetate (90:10) as eluent to give **LB-I** in 70% yield (0.672 g) as yellow solid. (mp: 133–134 °C); IR (KBr, cm^{-1}): 3102, 3078, 2971, 2932, 2911, 2876, 2785, 1462, 1437, 1353; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H 7.36–7.35 (m, 1H), 7.34–7.33 (m, 1H), 7.32–7.31 (m, 1H), 7.29–7.27 (m, 1H), 4.43 (d, J = 13.2 Hz, 1H), 4.35 (d, J = 13.2 Hz, 1H), 4.10 (dd, J = 2.0 Hz, 1.2 Hz, 1H), 3.99–3.97 (m, 2H), 3.46 (s, 5H), 3.20–3.15 (m, 1H), 2.99–2.87 (m, 2H), 2.22–2.18 (m, 1H), 1.87–1.69 (m, 2H), 0.67 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C 148.54, 141.67, 139.57, 126.84, 126.69, 122.58, 122.49, 91.30, 82.99, 69.41, 65.06, 64.96, 62.39, 55.99, 44.42, 34.74, 20.71, 9.64; HRMS-ESI (m/z): [M+H] Found 358.1257 and calculated 358.1258 for $C_{22}H_{23}FeN$.

4.13. Resolution of (±)-LB-I

(+)-Dibenzoyl-D-tartaric acid (358 mg, 1.0 mmol) and (±)-**LB-I** (357 mg, 1.0 mmol) were taken in acetone (16 mL) and the contents were stirred for 15 minutes and then left to stand for 1 h at room temperature. The obtained precipitate I was filtered and washed with cold acetone (10 mL). The precipitate I was recrystallized from a mixture of methanol and acetonitrile (8:2) (10 mL). The formed precipitate II fraction was suspended and stirred in a mixture of dichloromethane (20 mL) and 10% aqueous K_2CO_3 (20 mL) until complete dissolution occurred. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to obtain crude (+)-**LB-I**. The crude material was purified through silica gel column chromatography (hexanes/ethyl acetate = 90:10) to afford (+)-**LB-I** as a yellow solid (36%, >99% ee), $[\alpha]_D^{25}$ = +208.5 (*c* 1, $CHCl_3$); mp: 107–108 °C. Enantiomeric excesses of the optically active compounds were determined by chiral HPLC analysis (Chiral stationary phase: Diacel-Chiralcel OD, Mobile phase: hexane and isopropyl alcohol (99.5:0.5), 0.5 mL/min, t_R = 15.02 min [(+)-**LB-I**], t_R = 16.69 min [(−)-**LB-I**]).

The filtrate I was evaporated and the residue was suspended and stirred in a mixture of dichloromethane (20 mL) and 10% aqueous K_2CO_3 (20 mL) until complete dissolution occurred. The organic layer was separated and aqueous layer was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to obtain crude (−)-**LB-I**. The crude material was purified through silica gel column chromatography (hexanes/ethylacetate = 90:10) to afford (−)-**LB-I** as yellow solid (48%, 93% ee). Enantiomeric excesses of the optically active compounds were determined by chiral HPLC analysis (Chiral stationary phase: Diacel-Chiralcel OD, Mobile phase: hexane and isopropyl alcohol (99.5:0.5), 0.5 mL/min, t_R = 15.02 min [(+)-**LB-I**], t_R = 16.69 min [(−)-**LB-I**]).

4.14. Enrichment of scalemic (−)-LB-I using L-DBTA

(−)-Dibenzoyl-L-tartaric acid (179 mg, 0.5 mmol) and scalemic (−)-**LB-I** (93% ee, 178 mg, 0.5 mmol) were taken in acetone (8 mL) and the contents were stirred for 15 minutes and then left to stand for 1 h at room temperature. The formed precipitate III was suspended and stirred in a mixture of dichloromethane (20 mL) and 10% aqueous K_2CO_3 (20 mL) until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to obtain crude (−)-**LB-I**. The crude material was purified through silicagel column chromatography (hexanes/ethyl acetate = 90:10) to afford (−)-**LB-I** as a yellow solid (41%,>99% ee), $[\alpha]_D^{25}$ = −208.5 (*c* 1, $CHCl_3$); mp: 107–108 °C]. Enantiomeric excesses of the optically active compounds were determined by chiral HPLC analysis (Chiral stationary phase: Diacel-Chiralcel OD, Mobile phase: hexane and isopropyl alcohol (99.5:0.5), 0.5 mL/min, t_R = 15.02 min [(+)-**LB-I**], t_R = 16.69 min [(−)-**LB-I**]).

4.15. Enrichment of scalemic (−)-LB-I using oxalic acid

The scalemic (−)-**LB-I** (93% ee, 178 mg, 0.5 mmol) and oxalic acid (45 mg, 0.5 mmol) were taken in toluene (3 mL) and the contents were stirred for 6 h at room temperature. The formed precipitate III was suspended and stirred in a mixture of dichloromethane (20 mL) and 10% aqueous K_2CO_3 (20 mL) until dissolution occurred. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined extracts were dried over anhydrous Na_2SO_4, filtered and evaporated to obtain crude (−)-**LB-I**. The crude material was purified through silica gel column chromatography (hexanes/ethyl acetate = 90:10) to afford (−)-**LB-I** as a yellow solid (31%, >99% ee), $[\alpha]_D^{25}$ = −208.5 (*c* 1, $CHCl_3$); mp: 107–108 °C. Enantiomeric excesses of the optically active compounds were determined by chiral HPLC analysis (Chiral stationary phase: Diacel-Chiralcel OD, Mobile phase: hexane and isopropyl alcohol (99.5:0.5), 0.5 mL/min, t_R = 15.02 min [(+)-**LB-I**], t_R = 16.69 min [(−)-**LB-I**]).

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.05.006.

References

1. Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857.
2. Dai, L. X.; Tu, T.; You, S. L.; Deng, W. P.; Hou, X. L. *Acc. Chem. Res.* **2003**, *36*, 659.
3. (a) Fu, G. C. *Acc. Chem. Res.* **2000**, *33*, 412; (b) Fu, G. C. *Acc. Chem. Res.* **2004**, *37*, 542; (c) Wilson, J. E.; Fu, G. C. *Angew. Chem., Int. Ed.* **2004**, *43*, 6358.
4. (a) Enders, D.; Runsink, J.; Bats, J. W. *Org. Lett.* **1999**, *1*, 1863; (b) Enders, D.; Peters, R.; Lochtman, R.; Raabe, G.; Bats, Runsink J.; J.W. *Eur. J. Org. Chem.* **2000**, 3399; (c) Drusan, M.; Šebesta, R. *Tetrahedron* **2014**, *70*, 759.
5. Marquarding, D.; Klusacek, H.; Gokel, G.; Hoffmann, P.; Ugi, I. *J. Am. Chem. Soc.* **1970**, *92*, 5389.
6. Riant, O.; Samuel, O.; Kagan, H. B. *J. Am. Chem. Soc.* **1993**, *115*, 5835.
7. Sammakia, T.; Latham, H. A.; Schaad, D. R. *J. Org. Chem.* **1995**, *60*, 10.
8. Ferber, B.; Kagan, H. B. *Adv. Synth. Catal.* **2007**, *349*, 493.
9. (a) Selvakumar, J.; Makriyannis, A.; Ramanathan, C. R. *Org. Biomol. Chem.* **2010**, *8*, 4056; (b) Selvakumar, J.; Ramanathan, C. R. *Org. Biomol. Chem.* **2011**, *9*, 7643; (c) Selvakumar, J.; Sreenivasa Rao, R.; Srinivasapriyan, V.; Marutheeswaran, S.; Ramanathan, C. R. *Eur. J. Org. Chem.* **2015**, 2175.
10. Masaru, S.; Hiromichi, K.; Mikio, S.; Izumi, M.; Kazuo, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 252.
11. Pettit, R. K.; Pettit, G. R.; Hamel, E.; Hogan, F.; Moser, B. R.; Wolf, S.; Pon, S.; Chapuis, J. C.; Schmidt, J. M. *Med. Chem.* **2009**, *17*, 6606.
12. Trost, B. M.; Yeh, V. S. C.; Ito, H.; Bremeyer, N. *Org. Lett.* **2002**, *4*, 2621.
13. Luo, S.; Zificsak, C. A.; Hsung, R. P. *Org. Lett.* **2003**, *5*, 4709.
14. Osante, I.; Collado, M. I.; Lete, E.; Sotomayor, N. *Eur. J. Org. Chem.* **2001**, 1267.
15. Gómez-Sanjuan, A.; Sotomayor, N.; Lete, E. *Tetrahedron Lett.* **2012**, *53*, 2157.
16. Allin, S. M.; Thomas, C. I.; Allard, J. E.; Doyle, K.; Elsegood, M. R. J. *Eur. J. Org. Chem.* **2005**, 4179.
17. (a) Gnanamani, E.; Someshwar, N.; Ramanathan, C. R. *Adv. Synth. Catal.* **2012**, *354*, 2101; (b) Gnanamani, E.; Someshwar, N.; Ramanathan, C. R. *Adv. Synth. Catal.* **2014**, *356*, 2219.
18. (a) Gnanamani, E.; Ramanathan, C. R. *Tetrahedron Asymmetry* **2009**, *20*, 2211; (b) Someshwar, N.; Ramanathan, C. R. *Tetrahedron Asymmetry* **2015**, *26*, 1209.
19. (a) Periasamy, M.; Sivakumar, S.; Reddy, M. N.; Padmaja, M. *Org. Lett.* **2004**, *6*, 265; (b) Vairaprakash, P.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 3636; (c) Vairaprakash, P.; Periasamy, M. *J. Chem. Sci.* **2008**, *120*, 175.
20. Parker, D. *Chem. Rev.* **1991**, *91*, 1441.
21. Detailed X-ray crystallographic data (CCDC No. 1518070) are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.
22. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 6th ed.; Elsevier Inc.: UK, 2009.
23. Sheldrick, G. M. *SHELXS-97 and SHELXL-97, Programs for the Solution and Refinement of Crystal Structures*; University of Göttingen: Germany, 1997.
24. Shiga, M.; Kono, H.; Motoyama, I.; Hata, K. *Bull. Chem. Soc. Jpn.* **1968**, *48*, 1897.