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Enantiocatalytic activity of substituted 5-benzyl-2-(pyridine-2-yl)imidazolidine-4-one ligands

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ABSTRACT

Currently, asymmetric synthesis represents one of the main streams of organic synthesis. Although an extensive research has been carried out in this area, the synthesis of chiral compounds with the required enantiomeric purity is still a challenging issue. Herein, we focus on the preparation of new enantioselective catalysts based on pyridine-imidazolidinones. The substituted 5-benzyl-2-(pyridine-2-yl)imidazolidine-4-ones **5–8** were prepared by condensation of chiral amino acid amides (α-methylDOPA and α-methylphenylalanine) with 2-acetylpyridine and pyridine-2-carbaldehyde. The individual isomers of the described ligands **5–8** were separated chromatographically. The copper(II) complexes of these chiral ligands were studied as enantioselective catalysts for the asymmetric Henry reaction of substituted aldehydes with nitromethane or nitroethane. The ligands containing a methyl group at the 2-position of the imidazolidinone ring **6a** and **8a** exhibit a high degree of enantioselectivity (up to 91% ee). The nitroaldols derived from nitroethane (2-nitropropan-1-ols) were obtained with a comparable enantiomeric purity to derivatives of 2-nitroethanol. This group of ligands represents a new and promising class of enantioselective catalysts, which deserve further attention.

1. Introduction

At present, the preparation and investigation of the enantiocatalytic properties of new chiral ligands and their metal complexes represent one of the main streams of organic synthesis.[1] Research has focused on the development of increasingly more efficient and versatile catalytic systems, which could be used as acceptable alternatives of already known enantioselective catalysts.[2] Although every year, new and in many respects better and more efficient enantioselective catalysts are reported,[3] the problem of synthesis of chiral compounds possessing the required enantiomeric purity, that is, their asymmetric synthesis, has not been fully solved. A key limitation is the degree of asymmetric induction that can be provided by a particular catalyst.[4a] Moreover, there are certain limits of the versatility of a catalyst, which restrict the set of starting compounds suitable for a given asymmetric reaction. From this point of view, it can be stated that an ideal chiral catalyst does not exist. Therefore, new catalytic systems[4b] should be developed with the aim of lowering the amount of catalyst used in order to make the catalytic process as economically profitable as possible.[4c]

Recently, we have published a study dealing with the preparation and enantioselective properties of copper(II) complexes of substituted 5-isopropyl-2-(pyridine-2-yl)imidazolidine-4-ones. We found that these complexes are very efficient enantioselective catalysts of asymmetric Henry reactions.[5] This significant reaction, in which a new C–C bond is formed, has been chosen as a standard for the evaluation of the enantioselective efficiency of newly prepared ligands. The reason for this, is the fact that the Henry reaction is among the most intensively studied asymmetric reactions that uses a metal complex as an enantioselective catalyst. This fact enables a relevant evaluation of the enantiocatalytic efficiency of a chiral complex.[6]

Herein our aim is to modify the structure of 2-(pyridine-2-yl) imidazolidine-4-ones by attaching a benzyl group to the stereogenic centre at the 5-position, which could lead to a new series of pyridine-imidazolidinone ligands. Predominantly, we focused on their enantiocatalytic properties in asymmetric Henry reactions and compared them with 5-isopropyl derivatives.[5] The replacement of the isopropyl group with a benzyl group was predominantly motivated by the similarity of our ligands with MacMillan's catalysts.[7] Their structure also contains the imidazolidinone ring with an aromatic substituent at the 5-position. We presumed that our ligands could exhibit a π–π interaction between the reactant (aromatic aldehyde) and the substituent, as this is known during the catalytic cycle of analogical MacMillan's catalysts.[8] This interaction could positively affect the stereoselectivity of the Henry reaction. In addition to the ligands containing only a benzyl group, we also attempted to prepare ligands derived from α-methylDOPA. Such compounds, thanks to the presence of two electron donor groups, should exhibit a higher electron density in the benzene nucleus, which is necessary for the creation of a significant π–π interaction.

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2. Results and discussion

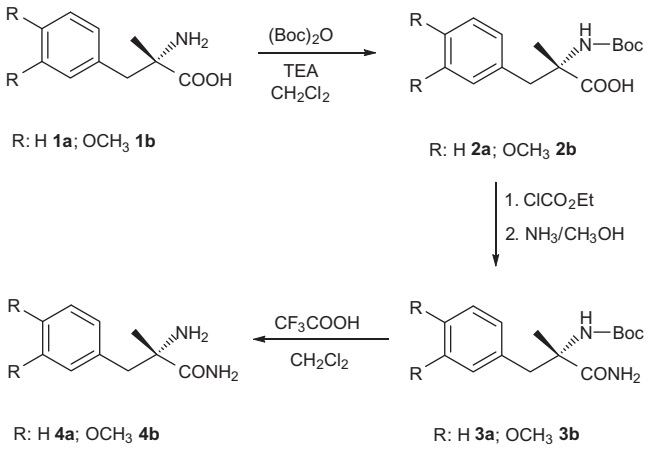
The key intermediates for the synthesis of imidazolidinone ligands **5**–**8** were the corresponding enantiomerically pure (*S*)-forms of 2-amino-3-phenyl-2-methylpropanamide (α-methylphenylalaninamide) **4a** and 2-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanamide **4b**.

The starting compound for the synthesis of amide **4b** was the commercially available medical drug L-α-methylDOPA (Aldomet®, Dopegyt®), which is used in human medicine regarding antihypertensivum.[9] According to the literature,[10] we carried out the *O*-methylation of L-α-methylDOPA to give (*S*)-2-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid **1b** in an overall yield of 67%. (*S*)-2-Amino-3-phenyl-2-methylpropanoic acid was prepared from phenylacetone, which was then transformed by a Strecker synthesis into 2-amino-3-phenyl-2-methylpropanenitrile. Hydrolysis of this compound in a medium of 6 M hydrochloric acid gave the racemic form of acid **1a**. The resolution of this racemate by means of cinchonidine[11] gave the enantiomerically pure (*S*)-form with the overall yield of 18% (Scheme 1).

Acid amides **4a**–**b** were prepared by a three-step synthesis. First, the amino group was protected by the introduction of a Boc group. The *N*-protected forms of amino acids **2a**–**b** were obtained with yields of 91–93%. The carboxylic group was then activated by ethyl chloroformate and transformed into an amide group by treatment with ammonia in methanol (89–94%). Deprotection of the amino group with trifluoroacetic acid in dichloromethane gave amides **4a**–**b** (Scheme 2) with yields of 93–95%. The conventional method of preparing the amino acid amide via esterification with methanol and subsequent aminolysis failed in this case, because the aminolysis of the methyl esters of these amino acids is very slow. This is caused by the steric hindrance at the ester group by the bulky substituents present on the α-carbon atom. For example, the aminolysis of the methyl ester of (*S*)-2-amino-3-(3,4-dimethoxyphenyl)-2-methylpropanoic acid with 7 M ammonia solution in methanol proceeded over a period of 7 days at the reaction temperature of 100 °C (pressure of 5 atm) with only a 55% conversion.

The condensation reaction of amide **4a** or **4b** with pyridine-2-carbaldehyde or 2-acetylpyridine was used to prepare imidazolidinones **5**–**8** (Scheme 3). The condensation reaction of commercially available phenylalanine amide with acetylpyridine gave the corresponding 5-benzyl-2-methyl-2-(pyridine-2-yl)imidazolidine-4-one. However, it was found that the reaction was accompanied by racemization of the stereogenic centre C-5 in the imidazolidinone cycle. Therefore, this type of ligand was not studied any further as an enantioselective catalyst. The reaction conditions of this condensation were identical with those used in the preparation of pyridine-imidazolidinones.[5] All four diastereoisomeric mixtures were successfully separated into individual configuration isomers by column chromatography. The overall yields of the condensation reaction (the sum of both epimers) were in the range of 51–65%. The absolute configuration at the stereogenic centre of the 2-imidazolidinone ring was determined by means of ^{1}H NMR 1D NOESY pulse sequence.[12]

The enantiocatalytic properties of the individual ligands **5**–**8** were studied in the asymmetric Henry reaction. The corresponding copper(II) complexes of these ligands were prepared in situ by



R: H **1a**; OCH_3 **1b**

R: H **2a**; OCH_3 **2b**

R: H **4a**; OCH_3 **4b**

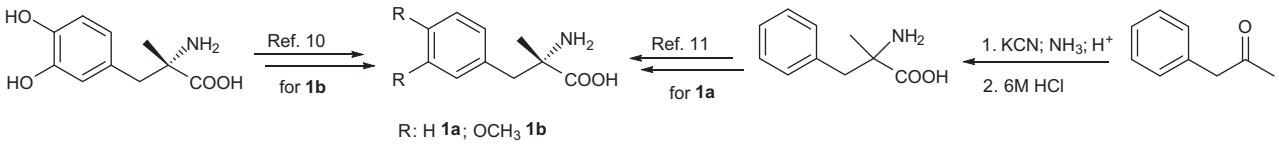
R: H **3a**; OCH_3 **3b**

Scheme 2. Preparation of amides **4a**–**b** from the corresponding amino acids **1a**–**b**.

treating the ligand with copper(II) acetate. First, we compared the catalytic efficiency of the individual ligands; the efficiency of the *anti*- and *syn*-forms was verified. The asymmetric Henry reaction was tested with four aldehydes, 2,2-dimethylpropanal, benzaldehyde, 4-nitrobenzaldehyde and 2-methoxybenzaldehyde; these aldehydes were reacted with nitromethane to give the corresponding 2-nitroethanols. In order to be able to compare the efficiency of these compounds with the pyridine-imidazolidinones studied earlier,[5] we performed the reactions under identical conditions, that is, the molar amount of catalyst, temperature and time. The results obtained are summarized in Table 1.

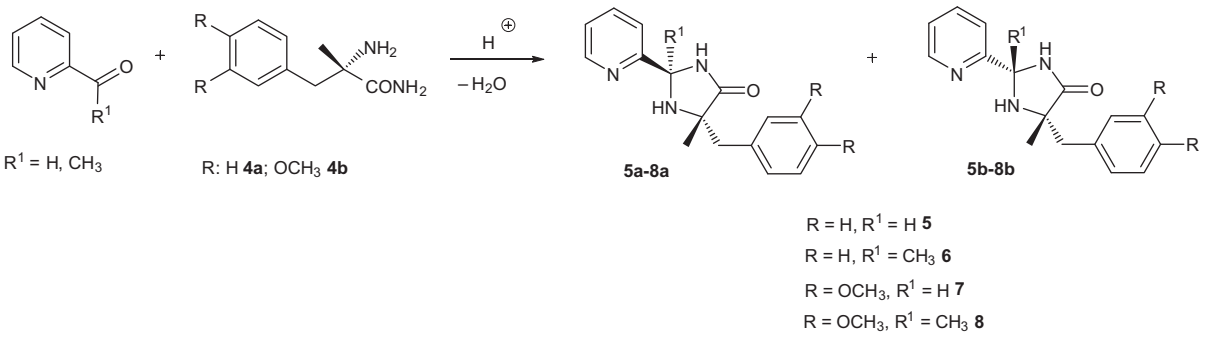
In comparison with the imidazolidinone ligands containing an isopropyl group at the 5-position,[5] the enantiocatalytic efficiency of the ligands with a *syn*-arrangement **5b**–**7b** is distinctly higher. The enantiomeric excesses are comparable for both ligands with a *syn*- or *anti*-arrangement **5a**–**7a**, however, the latter gives the nitroaldol with the opposite enantiomer. A significant difference between the enantiocatalytic activities of the *anti*- and *syn*-forms was found only in the case of derivative **8**. Hence, in the case of ligands **5**–**7**, there is only a minor difference between the efficiencies of the individual diastereoisomeric forms a and b; the ligands with an *anti*-arrangement were only slightly more selective. This is in complete contrast to the results obtained earlier with the imidazolidinones containing an isopropyl group, whose *anti*-forms exhibited much higher enantioselectivities than the *syn*-forms. Ligands **5**–**8** exhibit the highest degree of enantioselectivity in the reaction of 2,2-dimethylpropanal. This can be presumed to be a result of the steric effect of the bulky substituent (*t*-Bu), which dictates the stereospecific arrangement of the reactants in the activated complex.

A significant finding is the fact that the ligands with an *anti*-arrangement **5a**–**8a** exhibit higher enantiocatalytic efficiency in the case of derivatives containing a methyl group at the 2-position of the imidazolidinone cycle **6a** and **8a**. This finding can be considered as a positive feature, because, from the standpoint of application, ligands **6a** and **8a** are more versatile due to their higher stability. Thanks to the substituent at the C-2 carbon atom of the imidazolidinone cycle, ligands **6** and **8** cannot undergo a base-catalysed



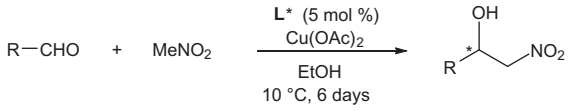
R: H **1a**; OCH_3 **1b**

Scheme 1. Synthesis of enantiomerically pure forms of 2-amino-3-phenyl-2-methylpropanoic acids **1a**–**b**.



Scheme 3. Preparation of imidazolidinone derivatives **5**–**8**.

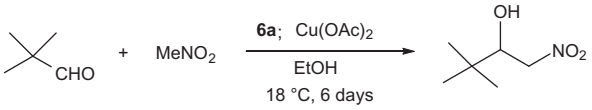
Table 1
Survey of experiments of the asymmetric Henry reaction catalysed by ligands **5–8**



R	*t*-Bu		4-$NO_2C_6H_4$		C_6H_5		2-$CH_3OC_6H_4$	
Ligand	Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)	Yield[a] (%)	ee[b] (%)
5a	95	81	71	66	87	68	93	68
5b	54	−70	74	−66	78	−66	88	−67
6a	94	91	54	74	80	76	73	79
6b	55	−63	61	−52	74	−43	72	−54
7a	97	80	92	50	81	51	94	60
7b	60	−54	85	−61	73	−40	75	−46
8a	95	89	87	61	85	68	90	67
8b	75	<2	88	<2	83	−12	88	−7

[a] The yield determined by ^{1}H NMR of the crude product.
[b] The enantiomeric excess determined by chiral HPLC.

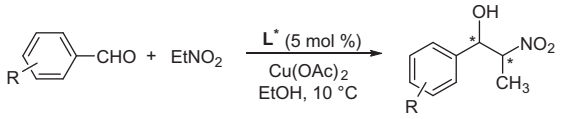
Table 2
Effect of the amount of catalyst **6a**/$Cu(OAc)_2$ on the course of the Henry reaction



Entry	Mol % of cat.	Yield[a] (%)	ee[b] (%)
1	5	94	91
2	3	73	91
3	2	72	91
4	1	52	89

[a] Isolated yield.
[b] Enantiomeric excess determined by chiral HPLC.

Table 3
Survey of experiments of the Henry reaction of substituted benzaldehydes with nitroethane



Aldehyde R	Ligand	Time (days)	Yield[a] (%)	dr[a] (%) *anti*/*syn*	ee[b] (%) *anti*	ee[b] (%) *syn*
H	**6a**	6	40	56/44	60	78
2-OCH_3	**6a**	6	26	68/32	67	82
4-NO_2	**6a**	6	18	59/41	—	65
H	**6a**	12	63	54/46	57	72
2-OCH_3	**6a**	12	68	60/40	67	83
4-NO_2	**6a**	12	45	59/41	—	70
H	**8a**	6	41	51/49	64	81
2-OCH_3	**8a**	6	44	65/35	56	79
4-NO_2	**8a**	6	20	56/44	—	73
H	**8a**	12	97	50/50	54	78
2-OCH_3	**8a**	12	57	67/33	64	76
4-NO_2	**8a**	12	48	57/43	—	67

[a] Yield and diastereoisomeric ratio determined by ^{1}H NMR of the crude product.
[b] Enantiomeric excess determined by chiral HPLC.

racemization of this stereogenic centre. Their oxidation to imidazolinone derivatives is also impossible (otherwise this is very easy and proceeds under mild conditions).[13] In the case of ligand, which formed with a *syn*-arrangement **5b**–**8b**, the more efficient derivatives were those without a methyl group at the 2-position **5b** and **7b**.

Table 1 shows that the highest value of enantioselectivity was attained with ligand **6a**. Therefore, this ligand was selected for further experiments to study the effect of the molar amount of the catalyst on the chemical yield of the Henry reaction and its enantioselectivity. In all preceding experiments, the amount used was 5 mol %. Therefore, further experiments were carried out with lower amounts of catalyst (1–3 mol %). The found enantioselectivity (Table 2) obtained was virtually the same in all cases (~90% ee). On the other hand, the chemical yield was dependent on the amount of catalyst: it decreased with a decreasing amount of catalyst, as expected. The optimum economical amount of catalyst for a successful Henry reaction, reaction time versus attained conversion, was considered to be 2 mol % (Table 2, entry 3).

In a subsequent study of the Henry reaction, nitromethane was replaced by nitroethane. In this case, the product is 2-nitroalcohol with two stereogenic centres, that is, four isomers are obtained. This variant of the asymmetric Henry reaction has been described

in the literature and studied less frequently,[14] although it gives chiral products that can be used as intermediates in the synthesis of a number of important compounds[14b,15] in enantiomerically pure form.

The reaction was studied only with aromatic aldehydes, which are more reactive than the aliphatic 2,2-dimethylpropanal. With regard to the lower reactivity of nitroethane, a slower course of the Henry reaction was expected. Only two ligands with the highest enantiocatalytic efficiency **6a** and **8a** were selected for these experiments. The results presented in Table 3 show that the chemical yields were somewhat lower than those in the reactions with nitromethane, even in cases in which the reaction time was prolonged. The representation of the individual diastereoisomers (dr) of the obtained 1-phenyl-2-nitropropan-1-ols was determined by ^{1}H NMR spectroscopy. In all cases, the diastereoselectivity of the Henry reaction was low (max. dr 68/32). The enantiomeric excesses were determined by chiral HPLC for both diastereoisomers. The only exception was the product formed from 4-nitrobenzaldehyde, in which case suitable chromatographic conditions enabling the determination of enantiomeric excess for the nitroaldol with an *anti*-arrangement were not found. The individual ee values (54–83%) show that the enantioselectivity attained is comparable to those obtained in other Henry reactions performed with nitromethane
(61–79% ee). Extending the reaction time had no effect on the enantioselectivity, and only the degree of conversion was increased (Table 3).

3. Conclusion

A new series of pyridine-imidazolidinone derivatives **5**–**8** containing a benzyl group at the 5-position of a ring cycle was prepared. The copper(II) complexes of these bidentate ligands were studied as enantioselective catalysts for the asymmetric Henry reactions of selected aldehydes with nitromethane or nitroethane. The ligands investigated exhibited good enantiocatalytic efficiency with the maximum attained value of ee 91%. In comparison with the copper(II) complexes of pyridine-imidazolinones,[16] these derivatives are significantly more enantioselective catalysts of the Henry reaction. In comparison with the pyridine-imidazolidinones[5] containing an isopropyl group at the 5-position of the imidazolidinone cycle, they were slightly less stereoselective. Only small differences in enantioselectivity were observed between the *anti*- and *syn*-forms of ligands **5**–**7**, with the enantiocatalytic efficiency even comparable in several cases. Moreover, the optimum amount of catalyst for the successful course of the catalytic process was determined. On the basis of the obtained results, it is possible to consider ligands **5**–**8** and their respective complexes with transition metals to be very promising enantioselective catalysts. Further research on their enantiocatalytic properties in other asymmetric reactions would be desirable.

4. Experimental

4.1. General

The starting substances were purchased from Sigma–Aldrich. Column chromatography was performed using 60–200 μm 60A silica gel. Ethanol was dried over 4 Å molecular sieves before use. The melting point temperatures are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 instrument (400.13 MHz for ^{1}H, and 100.61 MHz for ^{13}C). Chemical shifts δ were referenced to the solvent residual peak (2.50 ppm ^{1}H, 39.51 ppm ^{13}C for DMSO-d_6, and 7.26 ppm ^{1}H, 77.23 ppm ^{13}C for $CDCl_3$). The mass spectra were measured with a set of Agilent Technologies (gas chromatograph 6890N with mass detector 5973 Network; the samples were dissolved in CH_2Cl_2 or acetone). The elemental microanalysis was carried out using a FISONS Instruments EA 1108 CHN apparatus. The optical rotation was measured on a Perkin–Elmer 341 instrument; the concentration *c* was given in g/100 mL. High-resolution mass spectra were performed on Thermo Scientific MALDI LTQ Orbitrap instrument.

4.2. General procedure for the synthesis of *N*-protected aminoacids 2a,b

A mixture of amino acid hydrochloride **1** (16.5 mmol) TEA (7 mL, 50 mmol) and Boc_2O (3.96 g, 18.1 mmol) in CH_2Cl_2 (50 mL) was stirred at room temperature for 3 days. The solvent was distilled off under reduced pressure, and the residue was treated with a solution of citric acid (23.5 g, 112 mmol) in water (75 mL). The emulsion formed was extracted with AcOEt (3 × 50 mL). The solvent was evaporated in vacuo until dry.

4.2.1. (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-methyl-3-phenylpropanoic acid 2a

Yield: 91%; mp: viscous oil; $[\alpha]_D^{20} = -28.0$ (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.44 (br s, 1H, COOH), 7.29–7.08 (m, 5H, C_6H_5), 6.70 (br s, 1H, CONH), 2.93–2.63 (m, 2H, CH_2), 1.41 (s, 9H, $(CH_3)_3$), 1.19 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.7, 154.5, 137.0, 130.6, 127.9, 126.5, 78.0, 58.4, 42.8, 28.4, 22.7. Anal. Calcd for $C_{15}H_{21}NO_4$ (279.3): C, 64.50; H, 7.58; N, 5.01. Found: C, 64.38; H, 7.66; N, 4.94.

4.2.2. (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-methyl-3-(3,4-dimethoxyphenyl)propanoic acid 2b

Yield: 93%; mp: 58–60 °C; $[\alpha]_D^{20} = -14.7$ (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.84 (d, ^3J = 8.0 Hz, 1H, C_6H_3), 6.64 (m, 3H, C_6H_3 + CONH), 3.71 (2 × s, 6H, 2 × OCH_3), 3.17 (d, ^2J = 13.4 Hz, 1H, CH_2), 2.86 (d, ^2J = 13.4 Hz, 1H, CH_2), 1.40 (s, 9H, $(CH_3)_3$), 1.17 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ 175.7, 154.4, 148.1, 147.6, 129.2, 122.6, 114.3, 111.4, 78.0, 58.5, 55.5, 55.4, 41.2, 28.4, 22.7. Anal. Calcd for $C_{17}H_{25}NO_6$ (339.3): C, 60.11; H, 7.37; N, 4.12. Found: C, 59.98; H, 7.62; N, 4.23.

4.3. General procedure for the synthesis of *N*-protected amino amides 3a,b

Ethyl chloroformate (3.85 mL, 40 mmol) was added to a stirred solution of *N*-protected amino acid **2a** or **2b** (16 mmol) and TEA (5.6 mL, 40 mmol) in CH_2Cl_2 (50 mL) cooled at 0 °C. After ca. 15 min, a 7 M methanolic solution of ammonia (14 mL, 100 mmol) was added, and the suspension formed was stirred at room temperature for 4 days. The reaction mixture was washed with water (4 × 40 mL) and the organic layer was dried over sodium sulfate. After evaporation of the solvent under reduced pressure, the residue was dissolved in AcOEt (100 mL) and passed through a plug (1 cm) of silica. The solvent was evaporated, and the crude product was recrystallized from toluene.

4.3.1. (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-methyl-3-phenylpropanamide 3a

Yield: 94%; mp: 70–72 °C; $[\alpha]_D^{20} = -50.3$ (*c* 1, CH_3OH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.15 (m, 5H, C_6H_5), 6.33 (br s, 1H, $CONH_2$), 5.61 (br s, 1H, $CONH_2$), 4.86 (br s, 1H, CONH), 3.38 (d, ^2J = 13.6 Hz, 1H, CH_2), 3.12 (d, ^2J = 13.6 Hz, 1H, CH_2), 1.47 (s, 9H, $(CH_3)_3$), 1.44 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.9, 154.9, 136.3, 130.7, 128.5, 127.1, 80.6, 60.1, 41.6, 28.6, 24.2. Anal. Calcd for $C_{15}H_{22}N_2O_3$ (278.3): C, 64.73; H, 7.97; N, 10.06. Found: C, 64.61; H, 8.06; N, 9.79.

4.3.2. (2*S*)-2-[(*tert*-Butoxycarbonyl)amino]-2-methyl-3-(3,4-dimethoxyphenyl)propanamide 3b

Yield: 89%; mp: 102–103 °C; $[\alpha]_D^{20} = -44.1$ (*c* 0.9, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 6.80 (d, ^3J = 8.4 Hz, 1H, C_6H_3), 6.71 (m, 2H, C_6H_3), 6.28 (br s, 1H, $CONH_2$), 5.37 (br s, 1H, $CONH_2$), 4.87 (br s, 1H, CONH), 3.86 (2 × s, 6H, 2 × OCH_3), 3.32 (d, ^2J = 13,6 Hz, 1H, CH_2), 3.03 (d, ^2J = 13.6 Hz, 1H, CH_2), 1.47 (s, 9H, $(CH_3)_3$), 1.45 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.0, 154.9, 148.8, 148.2, 128.7, 122.8, 113.8, 111.1, 76.9, 60.2, 56.0, 41.5, 24.1. Anal. Calcd for $C_{17}H_{26}N_2O_5$ (338.4): C, 60.28; H, 7.68; N, 8.27. Found: C, 60.17; H, 7.85; N, 8.04.

4.4. General procedure for the synthesis of amides 4a,b

A solution of *N*-protected amide **3a** or **3b** (5 mmol) in CH_2Cl_2 (10 mL) and TFA (1.2 mL, 16 mmol) was refluxed for 8 h. The solvents were then distilled off under reduced pressure, and the residue was treated with saturated aqueous solution of sodium carbonate (20 mL). The emulsion formed was extracted with CH_2Cl_2 (3 × 25 mL), the organic layer was dried over sodium sulfate and evaporated to dryness.

4.4.1. (2*S*)-2-Amino-2-methyl-3-phenylpropanamide 4a

Yield: 93%; mp: 114–116 °C; $[\alpha]_D^{20} = -33.0$ (*c* 1.1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 7.35–7.25 (m, 6H, C_6H_5 + $CONH_2$), 5.75 (br s, 1H, $CONH_2$), 3.42 (d, ^2J = 13.2 Hz, 1H, CH_2), 2.70 (d, ^2J = 13.2 Hz, 1H, CH_2), 1.45 (s, 3H, CH_3), 1.38 (br s, 2H, NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.9, 137.0, 130.5, 128.5, 127.0, 58.6, 46.7, 28.0. Anal. Calcd for $C_{10}H_{14}N_2O$ (178.2): C, 67.39; H, 7.92; N, 15.72. Found: C, 67.31; H, 7.91; N, 15.67.

4.4.2. (2*S*)-2-Amino-2-methyl-3-(3,4-dimethoxyphenyl)propanamide 4b

Yield: 95%; yellow oil; $[\alpha]_D^{20} = -22.7$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 7.29 (br s, 1H, $CONH_2$), 6.74 (m, 3H, C_6H_3), 5.63 (br s, 1H, $CONH_2$), 3.84 (2 × s, 6H, 2 × OCH_3), 3.35 (d, ^2J = 13.2 Hz, 1H, CH_2), 2.51 (d, ^2J = 13.2 Hz, 1H, CH_2), 1.38 (m, 5H, CH_3 + NH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.1, 149.0, 148.2, 129.6, 122.6, 113.6, 111.2, 58.7, 56.1, 56.0, 46.5, 28.2. Anal. Calcd for $C_{12}H_{18}N_2O_3$ (238.3): C, 60.43; H, 7.55; N, 11.75. Found: C, 60.18; H, 7.68; N, 11.63.

4.5. General procedure for the synthesis of ligands 5a,b and 7a,b

A solution of the corresponding 2-aminoamide (3 mmol), pyridine-2-carbaldehyde (4 mmol) and one drop of acetic acid in dry methanol (5 mL) was refluxed for 12 h. The solvent was distilled off under reduced pressure, and the residue was treated with CH_2Cl_2 (10 mL) and extracted with a saturated aqueous solution of sodium carbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was submitted to chromatography on silica gel with the appropriate solvent.

4.5.1. (2*R*,5*S*)-5-Benzyl-5-methyl-2-(pyridine-2-yl) imidazolidine-4-one 5a

Yield: 35%; yellow oil; R_f 0.53 (SiO_2; acetone/CH_2Cl_2 (2/1; v/v); $[\alpha]_D^{20} = -38.5$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.53 (m, 1H, Py), 7.68 (m, 1H, Py), 7.38–7.21 (m, 7H, Py + Ph), 6.59 (br s, 1H, CONH), 4.87 (s, 1H, CH), 3.16 (d, ^2J = 13.2 Hz, 1H, CH_2), 2.85 (br s, 1H, NH), 2.76 (d, 1H, ^2J = 13.2 Hz, CH_2), 1.39 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 158.2, 149.6, 137.3, 136.8, 130.5, 128.5, 127.1, 123.9, 121.3, 70.3, 63.5, 44.4, 25.7. Anal. Calcd for $C_{16}H_{17}N_3O$ (267.3): C, 71.89; H, 6.41; N, 15.72. Found: C, 71.65; H, 6.33; N, 15.74. HRMS: *m*/*z* Calcd for $C_{16}H_{27}N_3O$: 268.14444 $[M+H]^+$. Found: 268.14394.

4.5.2. (2*S*,5*S*)-5-Benzyl-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one 5b

Yield: 29%; yellow oil; R_f 0.40 (SiO_2; acetone/CH_2Cl_2 (2/1; v/v); $[\alpha]_D^{20} = +30.5$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.39 (m, 1H, py), 7.99 (br s, 1H, CONH), 7.50 (m, 1H, py), 7.19–7.11 (m, 6H, Py + Ph), 6.80 (m, 1H, C_6H_5), 5.51 (s, 1H, CH), 3.15 (d, ^2J = 13.6 Hz, 1H, CH_2), 2.69 (d, ^2J = 13.6 Hz, 1H, CH_2), 2.61 (br s, 1H, NH), 1.38 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.2, 158.8, 149.1, 137.1, 136.7, 130.6, 130.5, 128.4, 126.7, 123.6, 123.0, 120.6, 70.5, 63.4, 43.4, 24.3. Anal. Calcd for $C_{16}H_{17}N_3O$ (267.3): C, 71.89; H, 6.41; N, 15.72. Found: C, 71.59; H, 6.35; N, 15.76. HRMS: *m*/*z* Calcd for $C_{16}H_{27}N_3O$: 268.14444 $[M+H]^+$. Found: 268.14432.

4.5.3. (2*R*,5*S*)-5-(3,4-Dimethoxybenzyl)-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one 7a

Yield: 37%; yellow oil; R_f 0.45 (SiO_2; acetone/CH_2Cl_2 (1/1; v/v); $[\alpha]_D^{20} = +79.9$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.52 (m, 1H, Py), 7.68 (m, 1H, Py), 7.38 (m, 1H, Py), 7.22 (m, 1H, Py), 6.91–6.78 (m, 3H, C_6H_3), 6.59 (br s, 1H, CONH), 4.92 (s, 1H, CH), 3.86 (s, 6H, 2 × CH_3O), 3.12 (d, ^2J = 13.6 Hz, 1H, CH_2), 2.83 (br s, 1H, NH), 2.67 (d, ^2J = 13.6 Hz, 1H, CH_2), 1.36 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 158.9, 149.6, 148.5, 148.1, 137.2, 129.3, 123.7, 122.5, 121.2, 113.4, 111.1, 70.3, 63.5, 56.1, 56.0, 44.1, 25.9. Anal. Calcd for $C_{18}H_{21}N_3O_3$ (327.4): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.97; H, 6.42; N, 12.83. HRMS: *m*/*z* Calcd for $C_{18}H_{21}N_3O_3$: 328.16557 $[M+H]^+$. Found: 328.16523.

4.5.4. (2*S*,5*S*)-5-(3,4-Dimethoxybenzyl)-5-methyl-2-(pyridine-2-yl)imidazolidine-4-one 7b

Yield: 28%; yellow oil; R_f 0.29 (SiO_2; acetone/CH_2Cl_2 (1/1; v/v); $[\alpha]_D^{20} = -111.4$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.43 (m, 1H, Py), 7.54 (m, 1H, Py), 7.18 (m, 1H, Py), 6.91 (br s, 1H, CONH), 6.85 (m, 1H, Py), 6.74–6.71 (m, 3H, C_6H_3), 5.52 (s, 1H, CH), 3.83 (s, 3H, CH_3O), 3.72 (s, 3H, CH_3O), 3.18 (d, ^2J = 14.0 Hz, 1H, CH_2), 2.65 (d, ^2J = 14.0 Hz, 1H, CH_2), 2.61 (br s, 1H, NH), 1.42 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.1, 158.6, 149.3, 148.9, 148.1, 137.1, 129.1, 123.7, 122.6, 120.5, 113.6, 111.1, 70.3, 63.5, 56.0, 55.8, 43.0, 24.4. Anal. Calcd for $C_{18}H_{21}N_3O_3$ (327.4): C, 66.04; H, 6.47; N, 12.84. Found: C, 65.99; H, 6.45; N, 12.87. HRMS: *m*/*z* Calcd for $C_{18}H_{21}N_3O_3$: 328.16557 $[M+H]^+$. Found: 328.16512.

4.6. General procedure for the synthesis of ligands 6a,b and 8a,b

A solution of the corresponding 2-aminoamide (3 mmol), 2-acetylpyridine (4 mmol) and *p*-toluenesulfonic acid (0.3 mmol) in 1, 2-dichlorobenzene (5 mL) was heated at 140 °C for 2 h. The solvent was then distilled off under reduced pressure, and the residue was treated with CH_2Cl_2 (10 mL) and extracted with a saturated aqueous solution of sodium carbonate (10 mL). The organic layer was dried over sodium sulfate and concentrated in vacuo. The residue was submitted to chromatography on silica gel with the appropriate solvent.

4.6.1. (2*R*,5*S*)-5-Benzyl-2,5-dimethyl-2-(pyridine-2-yl) imidazolidine-4-one 6a

Yield: 24%; mp: 118–121 °C; R_f 0.47 (SiO_2; acetone/CH_2Cl_2 (2/1; v/v); $[\alpha]_D^{20} = -21.7$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (m, 1H, Py), 8.13 (br s, 1H, CONH), 7.66 (m, 1H, Py), 7.57 (m, 1H, Py), 7.26 (m, 5H, Ph), 7.08 (m, 1H, Py), 3.28 (d, ^2J = 13.6 Hz, 1H, CH_2), 2.64 (d, ^2J = 13.6 Hz, 1H, CH_2), 2.56 (br s, 1H, NH), 1.12 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.1, 164.4, 148.9, 136.8, 136.7, 131.1, 130.4, 128.7, 128.3, 127.1, 122.4, 119.0, 74.8, 64.2, 43.9, 30.4, 26.3. Anal. Calcd for $C_{17}H_{19}N_3O$ (281.4): C, 72.57; H, 6.81; N, 14.94. Found: C, 72.46; H, 6.80; N, 14.89. HRMS: *m*/*z* Calcd for $C_{17}H_{19}N_3O$: 282.16009 $[M+H]^+$. Found: 282.15981.

4.6.2. (2*S*,5*S*)-5-Benzyl-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-one 6b

Yield: 27%; mp: 106–108 °C; R_f 0.39 (SiO_2; acetone/CH_2Cl_2 (2/1; v/v); $[\alpha]_D^{20} = -147.0$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.46 (m, 1H, Py), 7.56 (m, 1H, Py), 7.51 (br s, 1H, CONH), 7.34 (m, 1H, Py), 7.13–7.09 (m, 6H, Py + Ph), 2.83 (d, ^2J = 13.6 Hz, 1H, CH_2), 2.64 (d, ^2J = 13.6 Hz, 1H, CH_2), 2.55 (br s, 1H, NH), 1.70 (s, 3H, CH_3), 1.41 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.2, 163.9, 148.8, 137.0, 136.9, 130.5, 128.2, 126.6, 122.5, 118.8, 74.9, 63.9, 43.9, 32.4, 26.7. Anal. Calcd for $C_{17}H_{19}N_3O$ (281.4): C, 72.57; H, 6.81; N, 14.94. Found: C, 72.48; H, 6.78; N, 14.86. HRMS: *m*/*z* Calcd for $C_{17}H_{19}N_3O$: 282.16009 $[M+H]^+$. Found: 282.15964.

4.6.3. (2*R*,5*S*)-5-(3,4-Dimethoxybenzyl)-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-one 8a

Yield: 39%; yellow oil; R_f 0.45 (SiO_2; acetone/CH_2Cl_2 (1/1; v/v); $[\alpha]_D^{20} = -3.3$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.47 (m, 1H, Py), 7.73 (m, 1H, Py), 7.65 (m, 1H, Py), 7.15 (m, 1H, Py), 6.87–6.80 (m, 3H, C_6H_3), 6.74 (br s, 1H, CONH), 3.88 (s, 6H, 2 × CH_3O), 3.30 (d, ^2J = 13.6 Hz, 1H, ^2J = 14.0 Hz, 1H, CH_2), 2.60 (d, ^2J = 14.0 Hz, 1H, CH_2), 2.49 (br s, 1H, NH), 1.13 (s, 3H, CH_3), 1.11 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.0, 164.4, 149.2, 149.0, 148.3, 136.7, 129.2, 122.5, 122.4, 119.0, 113.2, 111.1, 74.6, 64.3, 56.0, 56.0, 43.4, 30.7, 26,3. Anal. Calcd for $C_{19}H_{23}N_3O_3$ (341.4): C, 66.84; H, 6.79; N, 12.31. Found: C, 66.83; H, 6.75; N, 12.29. HRMS: *m*/*z* Calcd for $C_{19}H_{23}N_3O_3$: 342.18122 $[M+H]^+$. Found: 342.18067.

4.6.4. (2*S*,5*S*)-5-(3,4-Dimethoxybenzyl)-2,5-dimethyl-2-(pyridine-2-yl)imidazolidine-4-one 8b

Yield: 24%; yellow oil; R_f 0.37 (SiO_2; acetone/CH_2Cl_2 (1/1; v/v); $[\alpha]_D^{20} = -42.9$ (*c* 1, CH_3OH); ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (m, 1H, Py), 7.52 (m, 1H, Py), 7.22 (m, 1H, Py), 7.11 (m, 1H, Py), 6.96 (br s, 1H, CONH), 6.65–6.57 (m, 3H, C_6H_3), 3.78 (s, 6H, CH_3O), 3.76 (s, 6H, CH_3O), 2.85 (d, ^2J = 14.0 Hz, 1H, CH_2), 2.61 (br s, 1H, NH), 2.53 (d, ^2J = 14.0 Hz, 1H, CH_2), 1.67 (s, 3H, CH_3), 1.43 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.4, 163.7, 148.5, 148.4, 147.6, 136.5, 129.4, 122.4, 122.2, 118.6, 113.4, 110.8, 74.9, 64.0, 55.8, 55.7, 43.5, 32.4, 27.0. Anal. Calcd for $C_{19}H_{23}N_3O_3$ (341.4): C, 66.84; H, 6.79; N, 12.31. Found: C, 66.62; H, 6.86; N, 12.38. HRMS: *m*/*z* Calcd for $C_{19}H_{23}N_3O_3$: 342.18122 $[M+H]^+$. Found: 342.18097.

4.7. General experimental procedure for the Henry reaction

A mixture of ligands **5–8** (30 μmol) and $Cu(OAc)_2$ (4.9 mg; 27 μmol) in absolute ethanol (1 mL) was stirred for 1 hour at room temperature. The resulting clear blue solution was cooled to the appropriate temperature, and then nitroalkane (0.5 mL) and aldehyde (0.5 mmol) were added. The mixture was stirred for the time period indicated in Tables 1–3. The crude product was isolated by column chromatography. Enantiomeric excess was determined by chiral HPLC (using Daicel columns Chiralcel OD-H or Chiralpak AS-H). Diastereomeric ratio was determined by ^1H NMR spectroscopy.

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