Design and Synthesis of Optically Active 2-Phenylimidazolecarboxamides Featuring Amino Acid Motive

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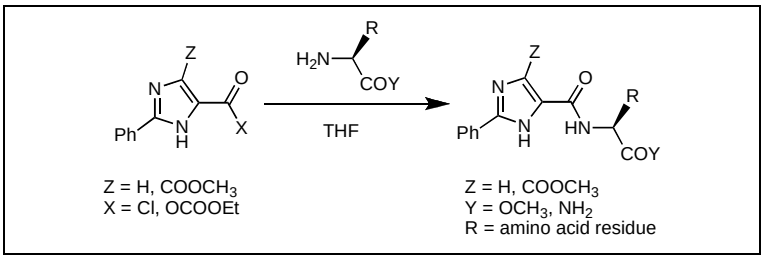

Overall sixteen new, optically active carboxamides **1**-**3** have been synthesized. These compounds based on the 2-phenylimidazole and featuring amino acid residues are linked on the 4-position by an amidic bond. Two general methods were used for their construction. Whereas the first method employs acylchlorides as a reactive species, the second one involves a condensation of mixed anhydrides with the amino acid counterparts. Actually, the second method proved to be more efficient than the first one. Carboxamides **1**-**3** were preliminarily tested as *N*-chelating ligands with an application in the Henry or Aldol reactions affording either poor yields or enantiomeric excesses.

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INTRODUCTION

Heterocyclic compounds incorporating the imidazole nucleus and their functionalization steadily attract considerable interest from organic chemists [1-2]. These compounds possess many attractive properties, in particular diverse biological and pharmacological [3-6] or antibacterial, antifungal and antiviral activities [3,7]. Miscellaneous naturally occurring alkaloids, *e.g.* the alkaloids isolated from marine sponge, soft corals, microorganisms and plants [8-10] or diverse ionic liquids [11], bear an imidazole ring as well. However, the most widely known imidazole structural motif comes from an essential amino acid – histidine and its analogs or derivatives such as a neurotransmitter histamine and ligands selective to the histamine receptors [3,12-13]. A report on the imidazole based receptors for the chiral recognition is known as well [14].

In the past several decades, the chemistry of transition metals and their coordination on diverse *N*-chelating ligands became an exponentially growing area of organic chemistry. Prospective applications of complexes such as organometallic catalysts [15] is considerably stimulating efforts of chemists to design and synthesize novel nitrogen ligands. The complexing ability of the imidazole ring to bind transition metals [16-19] as well as the application in some asymmetric reactions [20] has already been proven. Considering these findings, here we report on the synthesis, characterization and preliminary catalytic activity of the imidazole carboxamides having general formulas **1**-**3** (Figure 1). Whereas the imidazole ring should perform as a coordinating auxiliary, the amino acid chain (ester or amide) linked by an amidic bond bears the chiral center. Considering the practical applicability and ability to scale up the entire synthesis, our retro-synthetic strategy involves only the reasonable synthetic steps that particularly employ the commercially available amino acids (according to R). Several approaches to synthesizing such compounds already exist. Veronese *et al.* condense the 2-oximinoacetoacetamides and various benzyl amines to afford 4-carboxamido-5-methyl-2-phenylimidazoles [21]. Starting from the

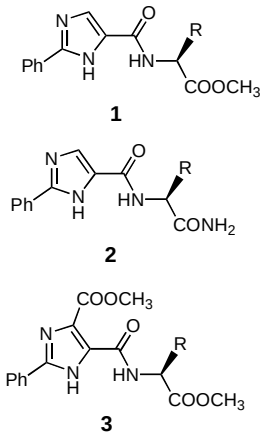


Figure 1

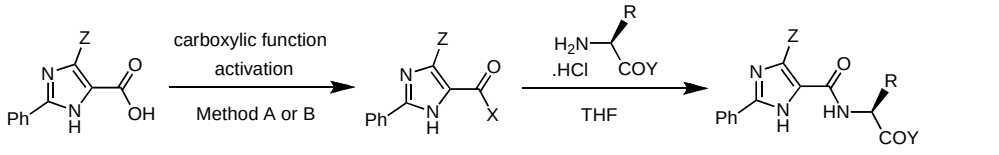
Meldrum's and amino acids, Gopalsamy and Shi have synthesized similar carboxamides in a four step transformation [22]. Rather than adopt these two strategies, and in view of a recent report by Baures and co-workers [23], we turned our attention to a direct condensation of the amino acids with the appropriate imidazole-4(5)-(di)carboxylic acid derivatives [24-25].

RESULTS AND DISCUSSION

The synthetic aspect of our work comprises of the synthesis of three ligands series (**1**-**3**). The first two series were generated from a 2-phenylimidazole-4-carboxylic acid (**4**) and its derivatization by amino acid esters (**1a**-**f**) and amides (**2a**-**d**), respectively. The starting carboxylic acid **4** was prepared *via* the HNO_3 oxidation of the 2-phenyl-4-hydroxymethylimidazole, generated from dihydroxyacetone [26]. Since this methodology of oxidation was mainly developed for the synthesis of 2-phenylimidazole-4-carbaldehyde, particular attention should be paid to the conditions of this reaction step. Whereas an oxidation using either fuming or concentrated nitric acid led only to the nitration of the phenyl ring at the 2-position or the formation of the undesired 2-phenylimidazole-4-carbaldehyde, a catalytic amount of $FeCl_3$ directed the oxidation to the 2-phenylimidazole-4-carboxylic acid **4** in an 85% yield. A third series of carboxamides was gained by the condensation of the activated monomethyl ester of the 2-phenylimidazole-4,5-dicarboxylic acid (**5**) with amino acid esters. The starting 2-phenylimidazole-4,5-dicarboxylic acid was synthesized in a two step reaction sequence from tartaric acid involving its transformation into the appropriate dinitrate and, subsequently, a condensation with benzaldehyde in the presence of ammonia afforded the desired acid [27]. A directed acid-catalyzed esterification of the 2-phenylimidazole-4,5-dicarboxylic acid with methanol furnished the desired mono- and diesters **5** and **9** in 36% and 81% yields, respectively. The condensation counterparts (Scheme I), amino acid esters and amides, were prepared by known methods [28-29].

The prepared carboxylic acids themselves are not capable of condensing with the amino acid esters or amides to afford the desired carboxamides. Hence, an activation of the carboxylic function was necessary. The carboxylic acid function reactivity towards nucleophiles may be basically enhanced by several known methods [30]. In general, we can divide these methods into two main groups: i) derivatization of the carboxylic acid into the intermediates capable of isolation *e.g.* esters or acylhalogenides and ii) carboxylic function *in situ* activation into reactive intermediates used directly in the next reaction step *e.g.* DCC/CDI activation or activation *via* (mixed) anhydrides. Considering this elemental knowledge, we examined first the simplest and best known method of activation *via* DCC. To our great surprise, both carboxylic acids **4** and **5** remained unattached and no traces of the desired products **1**-**3** could be isolated either. For a second attempt, we tried a condensation between the methyl esters **7** and **9** and the amino acid counterparts achieving, unfortunately, the same result. On the other hand, the transformation of the acid **4** in the appropriate acylhalogenide **6** using convenient $SOCl_2$ and followed by condensation with the amino acid counterparts, afforded the target carboxamides in moderate to good yields (see Table I, Method A). Unfortunately, we found a similar transformation of **5** into the corresponding acylhalogenide infeasible. Acylhalogenides are overall a reactive species, however, in our case the main insufficiency of this activating method lies in difficult purification, physicochemical characterization and moisture sensitivity (possible hydrolysis). Hence, we turned our attention to the *in situ* activation using mixed anhydrides as reactive intermediates (see Table I, Method B). This known method [31] involves the reaction of free carboxylic acid with chloroformates at low temperature in the presence of triethylamine as a base, followed by the addition of amino acid counterparts. To our great delight, this method was synthetically simpler than method A affording comparable results and in some cases even higher yields. The optical purities of carboxamides **1**-**3** synthesized this way resemble those from starting amino acids. The yields of the activating steps are solely lowered due to the undesired formation of a carbamic function on the imidazole nitrogen. The formed side products were isolated and characterized. However, an attempted basic hydrolysis of such side products to the desired carboxamides **1**-**3** proceeded with partial racemization.

Scheme 1



4 - Z = H
5 - Z = $COOCH_3$

6 - Z = H, X = Cl
7 - Z = H, X = OCH_3
8 - Z = H, X = $OCOOCH_2Ph$
9 - Z = $COOCH_3$, X = OCH_3
10 - Z = $COOCH_3$, X = $OCOOCH_2Ph$

1a-f - Z = H, Y = OCH_3
2a-d - Z = H, Y = NH_2
3a-f - Z = $COOCH_3$, Y = OCH_3

Table 1

Synthetic Methods, Yields and Basic Physical Data for Target Carboxamides **1**-**3** (Scheme I).

Compound	R [starting amino acid]	Z	Y	Method	Yield [%]	Mp [°C]	$[\alpha]_D^{20}$ (*c* 0.05, CH_3OH)
1a	CH_3- [(*S*)-Ala]	H	OCH_3	A B	38 38	187-188	+35.2
1b	$(CH_3)_2CH$- [(*S*)-Val]	H	OCH_3	A B	49 53	75-77	+39.0
1c	$(CH_3)_2CHCH_2$- [(*S*)-Leu]	H	OCH_3	A B	64 40	146-147	+17.9
1d	$CH_3CH_2CH(CH_3)$- [(*S*)-Ile]	H	OCH_3	A B	51 24	125-127	+29.6
1e	Ph- [(*R*)-PheGly]	H	OCH_3	A B	73 23	177-179	+57.1
1f	$PhCH_2$- [(*S*)-Phe]	H	OCH_3	A B	76 33	130-132	+38.1
2a	CH_3- [(*S*)-Ala]	H	NH_2	A B	4 41	211-215	+80.8
2b	$(CH_3)_2CHCH_2$- [(*S*)-Leu]	H	NH_2	A B	35 42	135-137	+23.6
2c	Ph- [(*R*)-PheGly]	H	NH_2	A B	17 24	144-146	-35.1
2d	$PhCH_2$- [(*S*)-Phe]	H	NH_2	A B	25 75	165-167	-37.7
3a	CH_3- [(*S*)-Ala]	$COOCH_3$	OCH_3	B	41	186-187	+20.9
3b	$(CH_3)_2CH$- [(*S*)-Val]	$COOCH_3$	OCH_3	B	56	139-141	+16.8
3c	$(CH_3)_2CHCH_2$- [(*S*)-Leu]	$COOCH_3$	OCH_3	B	25	112-113	+10.8
3d	$CH_3CH_2CH(CH_3)$- [(*S*)-Ile]	$COOCH_3$	OCH_3	B	32	oil	+30.3
3e	Ph- [(*R*)-PheGly]	$COOCH_3$	OCH_3	B	18	103-104	+99.8
3f	$PhCH_2$- [(*S*)-Phe]	$COOCH_3$	OCH_3	B	28	137-139	+15.6

Thus the hydrolysis did not lead to the optically pure compounds.

The condensation of the activated carboxylic acids with amino acids esters and amides hydrochlorides required careful pH maintenance. Triethylamine as a base liberates the free amino acids and eventually scavenges the hydrogen chloride produced during the reaction. The optimal pH value revealed to be about 9.

When comparing both methods of activation, method A, utilizing acylchloride **6**, afforded moderate to good yields, almost no side products were observed but the method is limited by the synthesis of acylchlorides. On the contrary, the method B is operationally simple, applicable on both carboxylic acids **4** and **5**, affords yields comparable to method A and there is no need to isolate and purify the intermediates. Nevertheless we observed the formation of a side product. The optical purities of the carboxamides **1**-**3** synthesized by both methods correspond to each other and also ^{1}H NMR measurements using Mosher acid do not reveal a racemization. The molecular structures of the final compounds have been determined by the ^{1}H-, ^{13}C-NMR spectroscopy and elemental analysis while the optical rotations have been measured as well. Additional NMR techniques such as ^{1}H-^{1}H COSY, HMBC and HMQC spectra were further used for regular signal assignment. The prepared chiral carboxamides were examined as ligands in the asymmetric versions of the Henry reaction [20] and Aldol condensation [32-33]. Whereas the Henry reaction involves the reaction of an aldehyde with a nitroalkane (Scheme II), the asymmetric Aldol condensation employs an additional ketone as a nucleophile (Scheme III). These two reactions are widely applied as a basic screening of the enantioselectivity giving the first insight into the catalytical behaviour of the studied ligands. The attained yields and enantiomeric excesses (ee) of the Henry reaction and Aldol condensation are summarized in Table 2 and 3, respectively. From the measured values we can only suggest that, in general, the prepared carboxamides **1**-**3** revealed to be poor catalysts for these two selected reactions. Whereas they are able to catalyze the Henry reactions as bases, the enantiomeric excesses are poor varying from 1.1 to 13.3 %. The attained yields and ee's of the Aldol condensation are even worse than those for the Henry reaction.

However, an application of the synthesized carboxamides **1**-**3** as small molecules inhibiting protein-protein interactions, as has been shown by Baures [23], remains a challenge.

EXPERIMENTAL

Reagents and solvents were reagent-grade and were purchased from Aldrich and used as received. THF was freshly distilled from Na/benzophenone under N_2. The starting 2-phenyl-4-

Scheme 2

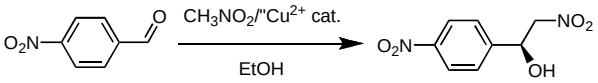


Table 2

Henry reaction [a]

Compound	Yield [%]	ee [%]
1a	79	1.1
1b	84	3.1
1c	85	8.4
1d	91	4.3
1e	70	3.6
1f	90	3.2
2a	82	13.3
2b	93	6.2
2c	88	1.9
2d	91	8.4
3a	88	2.6
3b	95	5.4
3c	91	6.4
3d	93	4.8
3e	90	3.9
3f	91	4.1

[a] For the reaction condition see Ref. [20]

Scheme 3

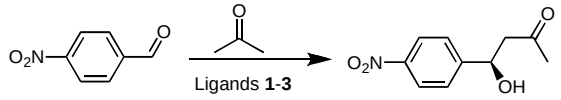


Table 3

Aldol condensation [a]

Compound	Yield [%]	ee [%]
1a	8	3.7
1b	5	2.1
1c	10	5.2
1d	13	3.9
1e	7	1.9
1f	4	1.8
2a	8	5.5
2b	15	4.9
2c	13	3.7
3a	7	3.7
3b	9	2.9
3c	7	4.9
3f	5	3.7

[a] For the reaction condition see Experimental

hydroxymethylimidazole [26] and 2-phenylimdiazole-4,5-dicarboxylic acid [27] were synthesized according to literature procedures. Evaporation and concentration *in vacuo* were performed at water aspirator pressure. Column chromatography (CC) was carried out with SiO_2 60 (particle size 0.040-0.063 mm, 230-400 mesh; Merck) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminium sheets coated with SiO_2 60 F_{254} obtained from Merck, with visualization by UV lamp (254 or 360 nm). Melting points (mp) were measured on a Büchi B-540 melting-point apparatus in open capillaries and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$, DMSO-d_6 or CD_3OD at 360/500 MHz and 90/125 MHz, respectively, with Bruker AMX 360 or Bruker AVANCE 500 instrument at 25°. Chemical shifts are reported in ppm relative to the signal of Me_4Si. Residual solvent signals in the ^{1}H- and ^{13}C-NMR spectra were used as an internal reference ($CDCl_3$ – 7.25 and 77.23, DMSO-d_6 – 2.55 and 39.51 and CD_3OD – 3.31 and 49.51 ppm for ^{1}H- and ^{13}C-NMR, respectively). Coupling constants (*J*) are given in Hz. The apparent resonance multiplicity is described as s (singlet), br s (broad singlet), d (doublet), dd (doublet of doublet), t (triplet), q (quartet) and m (multiplet). 2-Phenyl protons are marked as ArH. ^{1}H-^{1}H COSY, HMBC and HMQC NMR techniques were also used. Some of the imidazole carbons were not observed in ^{13}C-NMR spectra, most likely due to the hindered imidazole tautomerism or amide rotation(s). Optical rotation values were measured on a Perkin Elmer 341 instrument, concentration *c* is given in g/100 mL CH_3OH. The enantiomeric excesses were determined by chiral HPLC analysis on a Daicel Chiracel OB column and simultaneously deduced from [α] values [20, 33].

2-Phenyl-1*H*-imidazole-4-carboxylic acid (4). A mixture of 2.0 g (0.0115 mole) of the 2-phenyl-4-hydroxymethylimidazole in 7 mL of fuming nitric acid and 0.02 g (0.12 mmole) of $FeCl_3$ were heated for 2 h at 140°. After being stand overnight at 5°, the yellowish crystals were collected by filtration, rinsed with water and crystallized form ethanol-water (1:1) to yield 1.84 g (85%), mp 238-240° (lit.[34] mp 239°); ^{1}H nmr (360 MHz, DMSO-d_6): δ 7.45 (t, 1H, ArH, *J* =7.2 Hz), 7.52 (t, 2H, ArH, *J* = 7.6 Hz), 7.91 (s, 1H, CH_{im}), 8.07 (d, 2H, ArH, *J* = 7.2 Hz); ^{13}C nmr (90 MHz, DMSO-d_6): δ 126.5, 127.3, 128.9, 129.5, 131.3, 144.7, 174.5 (1C missing); *Anal.* Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.92; H, 4.21; N, 14.82.

5-(Methoxycarbonyl)-2-phenyl-1*H*-imidazole-4-carboxylic acid (**5**). To a solution of 5.0 g (0.0215 mole) of 2-phenyl-imidazole-4,5-dicarboxylic acid in 150 mL (3.70 mole) of dry methanol one drop of sulphuric acids was added. The reaction mixture was refluxed for 6 h, concentrated *in vacuo* and the residue crystallized from ethyl acetate to yield the title compound as off-white solid, 1.9 g (36%), mp 155-156°; ^{1}H nmr (360 MHz, DMSO-d_6): δ 3.92 (s, 3H, -OCH_3), 7.50-7.56 (m, 3H, ArH), 8.17 (d, 2H, ArH, *J* = 7.6 Hz), 13.64 (br s, 1H, -COOH); ^{13}C nmr (90 MHz, DMSO-d_6): δ 51.3, 127.3, 128.4, 129.9, 134.7, 136.5, 137.8, 147.7, 167.4, 172.9; *Anal.* Calcd. for $C_{12}H_{10}N_2O_4$: C, 58.54; H, 4.09; N, 11.38. Found: C, 58.53; H, 4.12; N, 11.36.

Methyl 2-Phenyl-1*H*-imidazole-4-carboxylate (**7**). The title compound was synthesized from 5.0 g (0.0266 mole) of **4** following the procedure as described for **5** and refluxing the reaction mixture for 10 h. Yield 3.6 g (67%), mp 144-145° (lit.[35] mp 219-221°); ^{1}H nmr (500 MHz, $CDCl_3$): δ 3.89 (s, 3H, -OCH_3), 7.38-7.42 (m, 3H, ArH), 7.78 (s, 1H, CH_{im}), 7.90 (d, 2H, ArH, *J* = 7.5 Hz); ^{13}C nmr (125 MHz, $CDCl_3$): δ 52.2, 126.1, 129.1, 129.2, 130.1, 149.2, 162.2 (2C missing); *Anal.* Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.34; H, 4.98; N, 13.85. Found: C, 65.30; H, 5.02; N, 13.82.

Dimethyl 2-Phenyl-1*H*-imidazole-4,5-dicarboxylate (**9**). The title compound was synthesized following the same procedure as described for **5** refluxing the reaction mixture for

50 h. Yield 4.5 g (81%), mp 134-135º (lit.[27] mp 157-158º); ^{1}H nmr (360 MHz, DMSO-d_6): δ 3.90 (s, 6H, -OCH_3), 7.47-7.56 (m, 3H, ArH), 8.15-8.20 (m, 2H, ArH), 13.85 (br s, 1H, NH_{im}).

General Procedure for Method A. Into a stirred and ice-cooled suspension of 1.0 g (0.0053 mole) of **4** in 200 mL of dry THF 5 mL (0.069 mole) of thionylchloride was added dropwise. The reaction mixture was refluxed for 6 h and all of the volatiles evaporated *in vacuo*. The crude acylchloride **6** was used in the next step without further purification. Into a stirred and ice-cooled solution of 1 g (0.0048 mole) of **6** in dry THF a suspension of the amino acid ester or amide hydrochloride (0.0047 mole) in 30 mL of THF containing 0.74 mL (0.0053 mole) of triethylamine was added. Another portion of 1.49 mL (0.0107 mole) of triethylamine was added gradually at 0º maintaining the pH value about 9. The reaction mixture was stirred for 12 h at 25º, precipitated triethylamine hydrochloride filtered off, filtrate concentrated *in vacuo* and the residue purified on CC (SiO_2; ethyl acetate).

General Procedure for Method B. Into a solution of **4** or **5** (0.0053 mole) in 200 mL of dry THF and 1.5 mL (0.0108 mole) of triethylamine 0.97 mL (0.0068 mole) of the benzylchloroformate was added dropwise under N_2 at -10º. The reaction mixture was stirred for additional 30 min whereupon a suspension of the amino acid ester or amide hydrochloride (0.0052 mole) in 30 mL of dry THF containing 0.74 mL (0.0053 mole) of triethylamine was added. The reaction was stirred for 12 h at 25º, precipitated triethylamine hydrochloride filtered off, filtrate concentrated *in vacuo* and the residue purified on CC (SiO_2; ethyl acetate).

(2*S*)-Methyl 2-{[(2-Phenyl-1*H*-imidazol-4-yl)carbonyl]-amino}propanoate (**1a**). This compound was obtained as off-white solid, mp 187-188º; $[\alpha]_D^{20}$ = +35.2 (*c* 0.05, CD_3OD); ^{1}H nmr (500 MHz, DMSO-d_6): δ 1.47 (d, 3H, -CH_3, *J* = 7.3 Hz), 3.70 (s, 3H, -OCH_3), 4.57 (m, 1H, -CH-), 7.45 (t, 1H, ArH, *J* = 7.5 Hz), 7.53 (t, 2H, ArH, *J* = 7.5 Hz), 7.84 (s, 1H, CH_{im}), 8.07 (d, 2H, ArH, *J* = 7.5 Hz), 8.26 (br s, 1H, NH), 13.08 (br s, 1H, NH_{im}); ^{13}C nmr (90 MHz, DMSO-d_6): δ 17.3, 47.4, 52.0, 122.9, 125.4, 128.8, 129.9, 136.4, 145.6, 162.5, 173.2, (1C missing); *Anal.* Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.58; H, 5.54; N, 15.38.

(2*S*)-Methyl 3-Methyl-2-{[(2-phenyl-1*H*-imidazol-4-yl)carbonyl]amino}butanoate (**1b**). This compound was obtained as off-white solid, mp 75-77°; $[\alpha]_D^{20}$ = +39.0 (*c* 0.05, CH_3OH); ^{1}H nmr (500 MHz, $CDCl_3$): δ 0.99 (d, 6H, -$(CH_3)_2$, *J* = 7.0 Hz), 2.24-2.30 (m, 1H, -C*H*$(CH_3)_2$), 3.70 (s, 3H, -OCH_3), 4.70 (dd, 1H, -CH-, *J* = 5.5, 9.5 Hz), 7.34 (t, 1H, ArH, *J* = 7.5 Hz), 7.40 (t, 2H, ArH, *J* = 7.5 Hz), 7.60 (s, 1H, CH_{im}), 7.83 (d, 1H, NH, *J* = 8.5 Hz), 8.02 (d, 2H, ArH, *J* = 8.0 Hz), 12.50 (br s, NH_{im}); ^{13}C nmr (125 MHz, $CDCl_3$): δ 18.1, 19.1, 31.4, 52.1, 57.3, 120.4, 125.8, 128.7, 129.1, 129.6, 135.9, 147.4, 163.9, 172.1; *Anal.* Calcd. for $C_{16}H_{19}N_3O_3$: C, 63.77; H, 6.36; N, 13.94. Found: C, 63.72; H, 6.34; N, 13.96.

(2*S*)-Methyl 4-Methyl-2-{[(2-phenyl-1*H*-imidazol-4-yl)carbonyl]amino}pentanoate (**1c**). This compound was obtained as off-white solid, mp 146-147°; $[\alpha]_D^{20}$ = +17.9 (*c* 0.05, CH_3OH); ^{1}H nmr (500 MHz, $CDCl_3$): δ 0.90-0.95 (m, 6H, -$(CH_3)_2$), 1.69-1.76 (m, 3H, -CH_2C*H*-), 3.69 (s, 3H, -OCH_3), 4.79-4.83 (m, 1H, -CH-), 7.35 (t, 1H, ArH, *J* = 7.5 Hz), 7.41 (t, 2H, ArH, *J* = 7.5 Hz), 7.59 (s, 1H, CH_{im}), 7.66 (d, 1H, NH, *J* = 8.0 Hz), 8.0 (d, 2H, ArH, *J* = 8.0 Hz), 12.28 (br s, 1H, NH_{im}); ^{13}C nmr (125 MHz, $CDCl_3$): δ 22.6, 23.8, 39.8, 50.1, 53.2, 126.8, 127.4, 127.9, 129.5, 129.9, 136.9, 147.8, 163.5, 173.5; *Anal.* Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.73; H, 6.74; N, 13.30.

(2*S*,3*S*)-Methyl 3-Methyl-2-{[(2-phenyl-1*H*-imidazol-4-yl)-carbonyl]amino}pentanoate (**1d**). This compound was obtained as off-white solid, mp 125-127°; $[\alpha]_D^{20}$ = +29.6 (*c* 0.05, CH_3OH); ^{1}H nmr (500 MHz, CD_3OD): δ 0.92 (t, 3H, -CH_2CH_3, *J* = 7.5 Hz), 0.96 (d, 3H, -CHCH_3, *J* = 7.0 Hz), 1.25-1.34 (m, 1H, -CH_2-), 1.50-1.58 (m, 1H, -CH_2-), 1.95-2.00 (m, 1H, -C*H*CH_2-), 3.72 (s, 3H, -OCH_3), 4.62 (d, 1H, -CH-, *J* = 6.0 Hz), 7.37 (t, 1H, ArH, *J* = 7.5 Hz), 7.43 (t, 2H, ArH, *J* = 7.5 Hz), 7.77 (s, 1H, CH_{im}), 7.9 (d, 2H, ArH, J = 7.5 Hz); ^{13}C nmr (125 MHz, CD_3OD): δ 11.9, 16.2, 26.5, 38.8, 52.7, 58.0, 126.8, 124.6, 130.1, 130.5, 130.9, 136.5, 148.8, 164.9, 173.6; *Anal.* Calcd. for $C_{17}H_{21}N_3O_3$: C, 64.74; H, 6.71; N, 13.32. Found: C, 64.72; H, 6.68; N, 13.35.

(2*R*)-Methyl 2-Phenyl-2-{[(2-phenyl-1*H*-imidazol-4-yl)carbonyl]amino}ethanoate (**1e**). This compound was obtained as off-white solid, mp 177-179°; $[\alpha]_D^{20}$ = +57.1 (*c* 0.05, CH_3OH); ^{1}H nmr (500 MHz, $CDCl_3$): δ 3.71 (s, 3H, -OCH_3), 5.72 (d, 1H, -CH-, *J* = 7.2 Hz), 7.28-7.39 (m, 6H, ArH+Ph), 7.43 (d, 2H, Ph, *J* = 8.0 Hz), 7.54 (s, 1H, CH_{im}), 7.93 (d, 2H, ArH, *J* = 7.0 Hz), 8.22 (d, 1H, NH, *J* = 7.2 Hz), 11.80 (br s, 1H, NH_{im}); ^{13}C nmr (90 MHz, $CDCl_3$): δ 52.7, 56.5, 120.8, 125.6, 127.3, 128.5, 128.7, 128.9, 129.1, 129.4, 135.5, 136.0, 147.2, 163.1, 171.0; *Anal.* Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.10; H, 5.09; N, 12.52.

(2*S*)-Methyl 3-Phenyl-2-{[(2-phenyl-1*H*-imidazol-4-yl)carbonyl]amino}propanoate (**1f**). This compound was obtained as off-white solid, mp 129-133°; $[\alpha]_D^{20}$ = +38.1 (*c* 0.05, CH_3OH); ^{1}H nmr (500 MHz, $CDCl_3$): δ 3.18 (m, 2H, -CH_2-), 3.63 (s, 3H, -OCH_3), 5.01 (q, 1H, CH, *J* = 8.0 Hz), 7.14-7.22 (m, 5H, Ph), 7.32 (t, 1H, ArH, *J* = 7.5 Hz), 7.37 (t, 2H, ArH, *J* = 8.0 Hz), 7.50 (s, 1H, CH_{im}), 7.84 (d, 1H, NH, *J* = 7.5 Hz), 7.96 (d, 2H, ArH, *J* = 7.5 Hz), 12.33 (br s, 1H, NH_{im}); ^{13}C nmr (125 MHz, $CDCl_3$): δ 38.4, 52.3, 53.4, 120.3, 125.7, 127.1, 128.6, 128.7, 129.0, 129.2, 129.6, 135.9, 147.3, 163.6, 171.8, (1C missing); *Anal.* Calcd. for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03. Found: C, 68.77; H, 5.44; N, 12.02.

(1*S*)-*N*-[1-Carbamoylethyl]-2-phenyl-1*H*-imidazole-4-carboxamide (**2a**). This compound was obtained as off-white solid, mp 211-215°; $[\alpha]_D^{20}$ = +80.8 (*c* 0.05, CH_3OH); ^{1}H nmr (360 MHz, DMSO-d_6): δ 1.39 (d, 3H, -CH_3, *J* = 6.8 Hz), 4.50 (m, 1H, -CH-), 7.23 (s, 1H, -NH_2), 7.45 (t, 1H, ArH, *J* = 7.2 Hz), 7.53 (t, 2H, ArH, *J* = 7.4 Hz), 7.62 (s, 1H, -NH_2), 7.84 (s, 1H, CH_{im}), 7.89 (d, 1H, NH, *J* = 7.9 Hz), 8.04 (d, 2H, ArH, *J* = 7.2 Hz), 13.06 (br s, 1H, NH_{im}); ^{13}C nmr (90 MHz, DMSO-d_6): δ 17.5, 54.4, 126.7; 127.8, 128.9, 129.9, 130.3, 136.9, 145.7, 162.4, 174.4; *Anal.* Calcd. for $C_{13}H_{14}N_4O_2$: C, 60.45; H, 5.46; N, 21.69. Found: C, 60.45; H, 5.46; N, 21.66.

(1*S*)-*N*-[1-Carbamoyl-3-methylbutyl]-2-phenyl-1*H*-imidazole-4-carboxamide (**2b**). This compound was obtained as off-white solid, mp 135-137°; $[\alpha]_D^{20}$ = +23.6 (*c* 0.05, CH_3OH); ^{1}H nmr (500 MHz, CD_3OD): δ 0.97 (d, 3H, -$(CH_3)_2$, *J* = 3.0 Hz), 0.98 (d, 3H, -$(CH_3)_2$, *J* = 3.0 Hz), 1.67-1.79 (m, 3H, -CH_2C*H*-), 4.64-4.67 (m, 1H, -CH-), 4.90 (br s, 4H, NH+NH_{im}+NH_2), 7.40 (t, 1H, ArH, *J* = 7.5 Hz), 7.46 (t, 2H, ArH, *J* = 7.5 Hz), 7.75 (s, 1H, CH_{im}), 7.92 (d, 2H, ArH, *J* = 7.05 Hz); ^{13}C nmr (125 MHz, CD_3OD): δ 22.2, 23.7, 26.2, 42.7, 52.8, 123.1, 126.9, 130.2, 130.6, 131.2, 134.5, 148.9, 165.1, 177.9; *Anal.* Calcd. for $C_{16}H_{20}N_4O_2$: C, 63.98; H, 6.71; N, 18.65. Found: C, 63.98; H, 6.68; N, 18.64.

(1*R*)-*N*-[1-Carbamoyl-1-phenylmethyl]-2-phenyl-1*H*-imidazole-4-carboxamide (**2c**). This compound was obtained as off-

white solid, mp 144-146°; $[\alpha]_D^{20}$ = -35.1 (*c* 0.05, CH_3OH); ^1H nmr (500 MHz, CD_3OD): δ 5.65 (s, 1H, -CH-), 7.31-7.47 (m, 6H, ArH+Ph), 7.55 (d, 2H, Ph, *J* = 7.5 Hz), 7.74 (s, 1H, CH_{im}), 7.91 (d, 2H, ArH, *J* = 7.5 Hz); ^{13}C nmr (125 MHz, CD_3OD): δ 58.2, 123.2, 126.9, 128.7, 129.5, 130.0, 130.2, 130.6, 131.0, 136.3, 139.5, 149.0, 164.5, 175.0; *Anal.* Calcd. for $C_{18}H_{16}N_4O_2$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.47; H, 5.01; N, 17.49.

(1*S*)-*N*-[1-Carbamoyl-2-phenylethyl]-2-phenyl-1*H*-imidazole-4-carboxamide (**2d**). This compound was obtained as off-white solid, mp 165-167°; $[\alpha]_D^{20}$ = -37.7 (*c* 0.05, CH_3OH); ^1H nmr (500 MHz, DMSO-d_6): δ 3.07-3.20 (m, 2H, -CH_2-), 4.75-4.79 (m, 1H, -CH-), 7.21-7.33 (m, 6H, Ph+NH), 7.44 (t, 1H, ArH, *J* = 7.5 Hz), 7.53 (t, 2H, ArH, *J* = 7.5 Hz), 7.70 (s, 1H, NH_2), 7.80 (s, 1H, CH_{im}), 7.83 (d, 1H, NH_2, *J* = 8.5 Hz), 8.02 (d, 2H, ArH, *J* = 7.5 Hz), 13.06 (br s, 1H, NH_{im}); ^{13}C nmr (125 MHz, DMSO-d_6): δ 38.1, 53.0, 120.7, 125.3, 126.4, 128.1, 128.8, 128.9, 129.3, 129.9, 136.6, 137.6, 145.6, 161.6, 172.9; *Anal.* Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76. Found: C, 68.26; H, 5.43; N, 16.72.

(1*S*)-Methyl 5-{[1-(Methoxycarbonyl)ethyl]carbamoyl}-2-phenyl-1*H*-imidazole-4-carboxylate (**3a**). This compound was obtained as off-white solid, mp 186-187°; $[\alpha]_D^{20}$ = +20.9 (*c* 0.05, CH_3OH); ^1H nmr (360 MHz, DMSO-d_6): δ 1.49 (d, 3H, CH_3, *J* = 6.6 Hz), 3.74 (s, 3H, -OCH_3), 3.96 (s, 3H, -OCH_3), 4.60-4.62 (m, 1H, -CH-), 7.49-7.51 (m, 3H, ArH), 8.21 (d, 2H, ArH, *J* = 7.5 Hz), 10.20 (br s, 1H, NH), 13.73 (br s, 1H, NH_{im}); ^{13}C nmr (90 MHz, DMSO-d_6): δ 17.5, 49.5, 52.4, 57.6, 127.4, 128.1, 129.6, 129.9, 147.4, 150.4, 167.1, 169.5, 177.2 (1C missing); *Anal.* Calcd. for $C_{16}H_{17}N_3O_5$: C, 58.0; H, 5.17; N, 12.68. Found: C, 57.98; H, 5.15; N, 12.75.

(1*S*)-Methyl 5-{[1-(Methoxycarbonyl)-2-methylpropyl]carbamoyl}-2-phenyl-1*H*-imidazole-4-carboxylate (**3b**). This compound was obtained as off-white solid, mp 139-141°; $[\alpha]_D^{20}$ = +16.8 (*c* 0.05, CH_3OH); ^1H nmr (500 MHz, $CDCl_3$): δ 0.84 (d, 3H, -$(CH_3)_2$, *J* = 6.5 Hz), 0.90 (d, 3H, -$(CH_3)_2$, *J* = 6.5 Hz), 2.13-2.20 (m, 1H, -C*H*$(CH_3)_2$), 3.64 (s, 3H, -OCH_3), 3.95 (s, 3H, -OCH_3), 4.52-4.55 (dd, 1H, -CH-, *J* = 5.0, 8.5 Hz), 7.36-7.38 (m, 3H, ArH), 7.98-8.00 (m, 2H, ArH), 10.66 (d, 1H, NH, J = 8.5 Hz), 12.49 (br s, 1H, NH_{im}); ^{13}C nmr (125 MHz, $CDCl_3$): δ 21.6, 22.9, 41.7, 51.5, 52.1, 127.1, 128.7, 129.4, 136.6, 144.4, 150.7, 167.9, 171.6, 176.9 (1C missing); *Anal.* Calcd. for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.12; H, 5.92; N, 11.65.

(1*S*)-Methyl 5-{[1-(Methoxycarbonyl)-3-methylbutyl]carbamoyl}-2-phenyl-1*H*-imidazole-4-carboxylate (**3c**). This compound was obtained as off-white solid, mp 112-113°; $[\alpha]_D^{20}$ = +10.8 (*c* 0.05, CH_3OH); ^1H nmr (360 MHz, $CDCl_3$): δ 0.93 (d, 3H, -$(CH_3)_2$, *J* = 6.5 Hz), 0.96 (d, 3H, -$(CH_3)_2$, *J* = 6.5 Hz), 1.72 (s, 1H, -C*H*$(CH_3)_2$), 1.73-1.75 (m, 2H, -CH_2-), 3.74 (s, 3H, -OCH_3), 4.04 (s, 3H, -OCH_3), 4.71 (q, 1H, -CH-, *J* = 7.6 Hz), 7.44-7.46 (m, 3H, ArH), 7.93-7.96 (m, 2H, ArH), 10.48 (d, 1H, NH, *J* = 7.2 Hz), 11.15 (br s, 1H, NH_{im}); ^{13}C nmr (90 MHz, $CDCl_3$): δ 22.3, 23.5, 40.5, 50.8, 52.8, 54.7, 127.8, 128.6, 129.9, 130.5, 136.9, 147.9, 166.9, 176.9 (2C missing); *Anal.* Calcd. for $C_{19}H_{23}N_3O_5$: C, 61.11; H, 6.21; N, 11.25. Found: C, 61.10; H, 6.18; N, 11.33.

(1*S*,2*S*)-Methyl 5-{[1-(Methoxycarbonyl)-2-methylbutyl]carbamoyl}-2-phenyl-1*H*-imidazole-4-carboxylate (**3d**). This compound was obtained as oil. $[\alpha]_D^{20}$ = +30.3 (*c* 0.05, CH_3OH); ^1H nmr (500 MHz, $CDCl_3$): δ 0.89 (t, 3H, -CH_2CH_3, *J* = 7.0 Hz), 0.93 (d, 3H, -$CHCH_3$, *J* = 7.0 Hz), 1.23-1.32 (m, 1H, -CH_2-) 1.43-1.49 (m, 1H, -CH_2-), 1.96-2.00 (m, 1H, -C*H*CH_2-), 3.72 (s, 3H, -OCH_3), 4.03 (s, 3H, -OCH_3), 4.66 (dd, 1H, -CH-, *J* = 5.0, 8.5 Hz), 7.43-7.44 (m, 3H, ArH), 7.97-7.99 (m, 2H, ArH), 10.64 (d, 1H, NH, *J* = 8.0 Hz), 11.81 (br s, 1H, NH_{im}); ^{13}C nmr (125 MHz, $CDCl_3$): δ 13.8, 16.3, 24.7, 33.5, 51.2, 53.3, 64.6, 127.9, 129.3, 129.8, 130.9, 139.9, 147.6, 164.3, 176.9 (2C missing); *Anal.* Calcd. for $C_{19}H_{23}N_3O_5$: C, 61.11; H, 6.21; N, 11.25. Found: C, 61.08; H, 6.26; N, 11.24.

(1*R*)-Methyl 5-{[1-(Methoxycarbonyl)-1-phenylmethyl]carbamoyl}-2-phenyl-1*H*-imidazole-4-carboxylate (**3e**). This compound was obtained as off-white solid, mp 103-104°; $[\alpha]_D^{20}$ = +99.8 (*c* 0.05, CH_3OH); ^1H nmr (360 MHz, $CDCl_3$): δ 3.73 (s, 3H, -OCH_3), 4.06 (s, 3H, -OCH_3), 5.72 (q, 1H, -CH-, *J* = 7.2 Hz), 7.32-7.43 (m, 8H, Ar+Ph), 7.94-7.97 (m, 2H, ArH), 11.22 (d, 1H, NH, *J* = 7.3 Hz), 11.43 (br s, 1H, NH_{im}); ^{13}C nmr (90 MHz, $CDCl_3$): δ 50.9, 51.7, 52.9, 122.8, 125.6, 127.9, 128.1, 128.7, 128.9, 129.1, 130.4, 136.8, 147.9, 163.7, 176.3 (2C missing); *Anal.* Calcd. for $C_{21}H_{19}N_3O_5$: C, 64.12; H, 4.87; N, 10.68. Found: C, 64.10; H, 4.80; N, 10.73.

(1*S*)-Methyl 5-{[1-(Methoxycarbonyl)-2-phenyl-ethyl]carbamoyl}-2-phenyl-1*H*-imidazole-4-carboxylate (**3f**). This compound was obtained as off-white solid, mp 137-139°; $[\alpha]_D^{20}$ = +15.6 (*c* 0.05, CH_3OH); ^1H nmr (500 MHz, $CDCl_3$): δ 3.07-3.11 (dd, 1H, -CH_2-, *J* = 7.5, 14.0), 3.20-3.24 (dd, 1H, -CH_2-, *J* = 5.5, 13.5 Hz), 3.72 (s, 3H, -OCH_3), 4.01 (s, 3H, -OCH_3), 4.93 (q, 1H, -CH-, *J* = 7.0 Hz), 7.12-7.23 (m, 6H, ArH+Ph), 7.44-7.46 (m, 2H, Ph), 7.95-7.99 (m, 2H, ArH), 10.63 (d, 1H, NH, *J* = 8.0 Hz), 11.34 (br s, 1H, NH_{im}); ^{13}C nmr (125 MHz, $CDCl_3$): δ 39.4, 51.8, 51.9, 53.8, 120.8, 126.7, 127.3, 128.6, 128.9, 129.1, 129.3, 129.6, 134.7, 136.7, 140.9, 147.2, 163.9, 176.8; *Anal.* Calcd. for $C_{22}H_{21}N_3O_5$: C, 64.86; H, 5.20; N, 10.31. Found: C, 64.88; H, 5.17; N, 10.35.

General Procedure for the Aldol Condensation. A mixture of 0.6 g (4.0 mmole) of 4-nitrobenzaldehyde, 6 mL of acetone and 0.4 mmole of tested ligand were stirred 3 days at 25º. The solvent was evaporated *in vacuo* and the residue purified on CC (SiO_2; ethyl acetate/cyclohexane 2:3). ^1H nmr (500 MHz, $CDCl_3$): δ 2.19 (s, 3H, -CH_3), 2.82-2.84 (m, 2H, -CH_2-), 3.61 (d, 1H, *J*=2.8 Hz, O*H*), 5.23 (m, 1H, -CH-), 7.50 (d, 2H, ArH, *J* = 8.8 Hz), 8.17 (d, 2H, ArH *J* = 8.8 Hz).

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