

Design and Efficient Synthesis of Amino Acid Derived 2-Substituted Imidazoles by Palladium-Catalyzed Cross-Coupling Reactions

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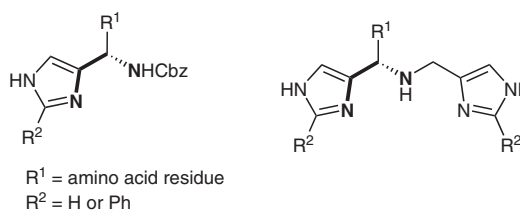
Abstract: Optically active imidazole derivatives featuring an α -amino acid motif substituted at the 2-position can be prepared in moderate to good yields by Negishi as well as Suzuki–Miyaura cross-couplings as the key synthetic steps. The reaction sequence involves N-protection (ethoxymethylation), whereby both generated regioisomers could be separated by column chromatography, and selective 2-lithiation. Subsequent transmetalation to zinc or an iodine quench affords reactants suitable for Pd-catalyzed Negishi and Suzuki–Miyaura reactions with (hetero)aromatics.

Key words: heterocycles, cross-coupling, amino acids, chiral pool, ligands

Since the first parent imidazole (glyoxaline) synthesis was reported by Debus,¹ heterocyclic compounds incorporating an imidazole nucleus and diverse imidazole-based systems have attracted the attention of organic chemists. Such heteroaromatic compounds are mainly designed, prepared and further investigated because of their prospective applicability as biologically² or pharmacologically³ active compounds, transition-metal-coordinating nitrogen ligands,⁴ ionic liquids⁵ and activating agents.⁶ However, the most widely known naturally occurring 4-substituted derivative of an imidazole is certainly the essential amino acid histidine, with its product of decarboxylation – histamine. Thus, the histamine-related molecules are worthwhile synthesizing because of their acid/base character, thermal and chemical robustness, tautomerism, easy synthesis and possible functionalization either on the imidazole ring or on the side chain. Moreover, the imidazole nitrogen(s) are able to bind transition metals and, due to the presence of a stereogenic center adjacent to the imidazole ring, their use as optically active nitrogen ligands with prospective applications in a wide range of fields, such as asymmetric synthesis or catalysis and chiral recognition or induction, has been encouraged.

In general terms, the application of the α -amino acids as enantiopure synthetic precursors for such systems seems to be advantageous because of their ready availability and low cost.⁷ Recently, we have reported the synthesis of bi- and tridentate enantiopure imidazole-based nitrogen ligands featuring an amino acid motif varying mainly in the nature of the substituent R (amino acid residue).⁸

known imidazoles



new imidazoles

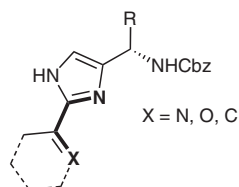
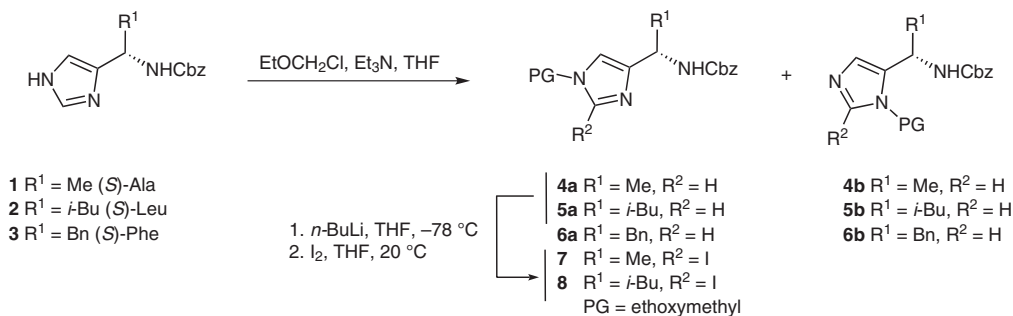


Figure 1 Known and newly proposed α -amino acid derived imidazoles

These compounds bind transition metals predominantly through the N=C–C–N coordination site where one carbon and one nitrogen come from the side chain bearing the stereogenic center (α to the imidazole at C-4) and the remaining two from the imidazole. We focus in this paper on the introduction of various (hetero)aromatic substituents at position C-2 in order to design imidazoles having a N=C–C=N coordinating pocket similar to those known for 2,2'-bipyridine (bipy) or 1,10-phenanthroline (phen) and related ligands (Figure 1).⁹ The side chain containing an asymmetric center (amino acid residue) at position C-4 is then involved only as a chiral auxiliary.

With C-2 unsubstituted imidazoles ($R^1 = H$) already in hand,^{8c} our retrosynthetic strategy leading to the target imidazoles involved the formation of the imidazole–(hetero)aromatic C(sp^2)–C(sp^2) bond. According to the literature, cross-coupling reactions seemed to be optimal for such C-2 substitutions.¹⁰ Organozinc reagents (Negishi reaction),¹¹ boronic acids (Suzuki–Miyaura reaction),¹² organotin compounds (Stille reaction)¹³ or direct arylation¹⁴ are amongst the most frequently used reactions in such imidazole functionalizations. The desired C–C bond can be established through either an imidazole as a C-2 metalated heterocycle and a (hetero)aromatic halide as an electrophile or vice versa.

Three C-2 unsubstituted imidazoles **1–3**, derived from (*S*)-alanine, (*S*)-leucine and (*S*)-phenylalanine, obtained



Scheme 1 N-Protection and iodination of imidazoles **1–3**

from the condensation of the corresponding α -bromo ketones and formamidine in liquid ammonia,^{8c} were used as starting compounds. In order to perform the desired reactions with organometallic compounds, imidazoles **1–3** needed to be N-protected.

Treatment of **1–3** with chloromethylethyl ether in the presence of triethylamine afforded the protected imidazoles **4–6** in good yields (PG = ethoxymethyl, Scheme 1),¹⁵ however, since the starting 4(5)-substituted imidazoles **1–3** are unsymmetrical, the formation of two regioisomers was possible (**a** and **b** series). We observed formation of both regioisomers in a roughly 1:1 ratio which, importantly, could be separated by two consecutive chromatographic separations. In view of the proposed structures in Figure 1, since the regioisomers in series **b** have the side chain and the PG group on the same side (*cis*-arrangement), which would lead to a stereogenic center at a greater distance from the binding site, imidazoles **4b–6b** were not used for further cross-coupling reactions. The correct molecular structures of **4–6** were determined mainly on the basis of ^1H – ^{13}C NMR spectroscopy employing HMQC and HMBC methods, which showed interactions between the CH group of the side chain, the imidazole carbons and the CH_2 group of the protecting group.

Since it is well known that N-substituted imidazole may be selectively lithiated at the C-2 position,¹⁰ imidazoles **4a–6a** could therefore readily serve as the starting compounds for such lithiations and the subsequent Negishi cross-coupling reaction. However, in order to generate electrophilic counterparts suitable for reaction with boronic acids (Suzuki–Miyaura cross-coupling), we also attempted the C-2 lithiation of **4a** and **5b** followed by an iodine quench,^{11a,16} which afforded the desired imidazole iodides **7** and **8**, respectively, in moderate yields.

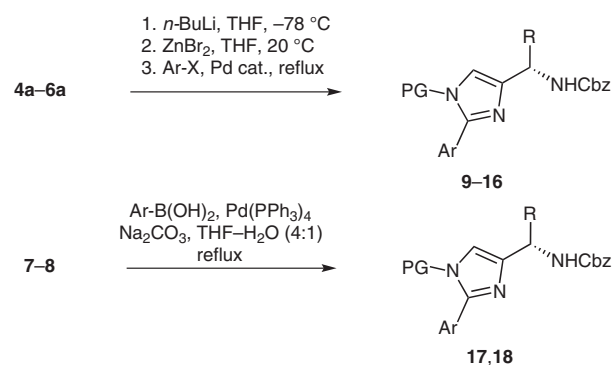
Thus, with both the organometallic as well as electrophilic reactants already in hand, we proceeded to the cross-coupling reactions (Scheme 2, Table 1). As an initial investigation, a standard Negishi reaction^{11b} involving lithiation of imidazoles **6a** and **4a** with $n\text{-BuLi}$ at -78°C was conducted; transmetalation with zinc bromide and subsequent $\text{Pd}(\text{PPh}_3)_4$ -catalyzed coupling with readily available bromobenzene and 4-iodo-*N,N*-dimethylaniline afforded compounds **9** and **10** in 48 and 66% yields, respectively. Delighted with such a smooth reaction, we followed this

protocol using 2-bromopyridine as an electrophile, which likewise led to the desired compound **11** in good yield. We did not observe any remarkable changes in the yields depending on the catalyst and zinc halide used [yields for **11**: $\text{Pd}(\text{PPh}_3)_4/\text{ZnBr}_2$: 68% and $\text{PdCl}_2(\text{PPh}_3)_2/\text{ZnCl}_2$: 69%]. In addition, 2-iodopyrazine, 3-bromopyridazine,¹⁷ 2-iodopyrimidine and 8-iodoquinoline also smoothly underwent the Negishi cross-coupling to afford the C-2 functionalized imidazoles **12–15** in yields of 54–64%. A similar procedure applied to C-2 unsubstituted imidazole **4a** and 2-iodoimidazoles **7** afforded bisimidazole derivative **16** in moderate yield (34%). It should be noted here that all of our synthetic attempts to prepare a similar bisimidazole derivative using known procedures such as copper-catalyzed Ullmann coupling¹⁶ or palladium-catalyzed oxidative homocoupling,¹⁸ failed.

Prepared iodo-derivatives **7** and **8** could also be coupled with commercially available boronic acids (phenylboronic acid and furan-2-ylboronic acid) under the conditions of $\text{Pd}(\text{PPh}_3)_4$ -catalyzed Suzuki–Miyaura reaction, whereby imidazoles **17** and **18** were isolated in good yields of 74 and 88%, respectively.

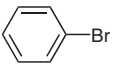
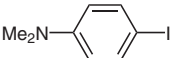
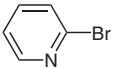
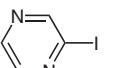
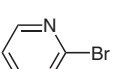
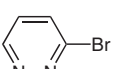
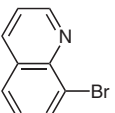
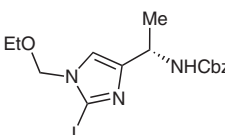
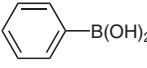
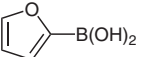
The optical purities of the final products **9–18** resemble those of the starting imidazoles **1–3**. The carbamic acid functionality (Cbz) was tolerated in the presence of organolithium as well as organozinc species.

In conclusion, we report in this paper the synthesis of ten new histamine-related, optically pure imidazole derivatives featuring an α -amino acid motif. Either Negishi or Suzuki–Miyaura cross-couplings proved to be feasible on



Scheme 2 Cross-coupling reactions leading to imidazoles **9–18**

Table 1 Synthesis of Target Imidazoles **9–18** (Scheme 2)

| Imidazole | Starting compd | R/ α -amino acid | ArX/ArB(OH) ₂ | Time (h) | Yield (%) | [α] _D ²⁰ (<i>c</i> 0.1, MeOH) |
|-----------------------|----------------|-------------------------------|---|----------|-----------|---|
| 9^a | 6a | Bn/(<i>S</i>)-Phe |  | 8 | 66 | −8.0 |
| 10^a | 4a | Me/(<i>S</i>)-Ala |  | 6 | 48 | −7.0 |
| 11^a | 4a | Me/(<i>S</i>)-Ala |  | 20 | 68 | −10.0 |
| 12^a | 4a | Me/(<i>S</i>)-Ala |  | 20 | 64 | −12.0 |
| 13^a | 4a | Me/(<i>S</i>)-Ala |  | 20 | 64 | −11.0 |
| 14^a | 4a | Me/(<i>S</i>)-Ala |  | 72 | 56 | −14.0 |
| 15^a | 5a | <i>i</i> -Bu/(<i>S</i>)-Leu |  | 20 | 54 | −27.0 |
| 16^a | 4a | Me/(<i>S</i>)-Ala |  | 72 | 34 | −8.0 |
| 17^b | 7 | Me/(<i>S</i>)-Ala |  | 20 | 74 | −11.0 |
| 18^b | 8 | <i>i</i> -Bu/(<i>S</i>)-Leu |  | 6 | 88 | −39.0 |

^a Negishi reaction.^b Suzuki–Miyaura reaction.

our systems, affording the target compounds in moderate to good yields.

Reagents and solvents were reagent-grade and were purchased from Penta and used as received. THF was freshly distilled from Na/benzophenone under N₂. The starting imidazoles **1–3** were synthesized according to literature procedures.^{8c} Column chromatography was carried out with SiO₂ 60 (particle size 0.040–0.063 mm, 230–400 mesh; Merck) and commercially available solvents. Thin-layer chromatography (TLC) was conducted on aluminum sheets coated with SiO₂ 60 F₂₅₄ 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. ¹H and ¹³C NMR spectra were recorded in CDCl₃ at 360/500 MHz and 90/125 MHz, respectively, with Bruker AMX 360 or Bruker Avance 500 instruments at 25 °C. Chemical shifts are reported in ppm relative to TMS. Residual solvent signal in the ¹H and ¹³C NMR spectra was used as an internal reference (CDCl₃: δ = 7.25 and 77.23 ppm). Coupling constants (*J*) are given in Hz. Cbz phenyl protons and carbons are marked as Ph. The pyridine, pyrazine, pyridazine, pyrimidine, quinoline and furane protons are marked as Py, Prz, PdZ, Pym, Qun and Fur, respectively. ¹H–¹H COSY, HMBC and HMQC NMR techniques were also used. Optical rota-

tion values were measured on a Perkin–Elmer 341 instrument, concentration *c* is given in g/100 mL MeOH.

The mass spectra were measured either on a GC/MS system comprised of an Agilent Technologies 6890N gas chromatograph (HP-5MS column, length 30 m, I.D. 0.25 mm, film 0.25 μ m) equipped with a 5973 Network MS detector (EI 70 eV, mass range 33–550 Da) or on a LC-MS Micromass Quattro Micro API (Waters) instrument with a direct input (ESI+, 0.5 mL/min stream of MeOH, mass range 200–800 Da and MassLynx software were used).

N-Protection (Ethoxymethylation) of Imidazoles **1–3**; General Procedure

Et₃N (0.9 mL, 6.5 mmol) and ethoxymethylchloride (0.3 mL, 3.27 mmol) were added to a solution of imidazole **1–3** (3.27 mmol) in THF (30 mL) and the reaction mixture was stirred for 2 h at 25 °C. The solvent was evaporated, H₂O (30 mL) was added and the reaction mixture was extracted with CH₂Cl₂ (3 \times 10 mL). The combined organic layers were dried (Na₂SO₄) and the solvent evaporated. The crude product was purified by two consecutive column chromatographic separations [SiO₂; hexane–EtOAc–MeOH–NH₃(aq), 3:5:1:0.1] to afford a pure mixture of both regioisomers, which could be further separated using a second column (SiO₂; EtOAc–hexane, 3:1).

(S)-Benzyl 1-[1-(Ethoxymethyl)-1H-imidazol-4-yl]ethylcarbamate (4a)

Yield: 466 mg (47%); oil; ee >95%; R_f = 0.75 [hexane–EtOAc–MeOH–NH₃(aq), 3:5:1:0.1], R_f = 0.14 (EtOAc–hexane, 3:1); $[\alpha]_D^{20}$ –8.0 (c 0.1, MeOH).

¹H NMR (360 MHz, CDCl₃): δ = 1.13 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 1.46 (d, J = 6.8 Hz, 3 H, CH₃CH), 3.38 (q, J = 7.0 Hz, 2 H, CH₂CH₃), 4.78–4.85 (m, 1 H, CHNH), 5.02–5.08 (m, 2 H, CH₂Ph), 5.13 (s, 2 H, OCH₂N), 5.62–5.64 (m, 1 H, NH), 6.86 (s, 1 H, 5-*H*_{im}), 7.25–7.31 (m, 5 H, Ph), 7.46 (s, 1 H, 2-*H*_{im}).

¹³C NMR (90 MHz, CDCl₃): δ = 14.8 (CH₃CH₂), 21.5 (CH₃CH), 45.2 (CH), 64.5 (CH₃CH₂), 66.6 (PhCH₂), 76.9 (OCH₂N), 114.8 (5-*C*_{im}), 128.0 (Ph), 128.1 (Ph), 128.5 (Ph), 136.8 (Ph), 137.2 (2-*C*_{im}), 144.8 (4-*C*_{im}), 155.8 (CO).

EI-MS (70 eV): m/z (%) = 303 [M⁺] (1), 195 (15), 180 (40), 168 (30), 151 (70), 122 (15), 108 (100), 91 (50), 79 (95), 59 (100), 51 (20).

Anal. Calcd for C₁₆H₂₁N₃O₃: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.25; H, 7.07; N, 13.93.

(S)-Benzyl 1-[1-(Ethoxymethyl)-1H-imidazol-4-yl]-3-methylbutylcarbamate (5a)

Yield: 406 mg (36%); oil; ee >95%; R_f = 0.71 [hexane–EtOAc–MeOH–NH₃(aq), 3:5:1:0.1], R_f = 0.18 (EtOAc–hexane, 3:1); $[\alpha]_D^{20}$ –32.0 (c 0.1, MeOH).

¹H NMR (360 MHz, CDCl₃): δ = 0.88 [d, J = 6.6 Hz, 6 H, (CH₃)₂CH], 1.11 (t, J = 6.9 Hz, 3 H, CH₃CH₂), 1.47–1.57 [m, 1 H, CH(CH₃)₂], 1.69 (t, J = 7.2 Hz, 2 H, CHCH₂), 3.34 (q, J = 6.3 Hz, 2 H, CH₂CH₃), 4.74–4.79 (m, 1 H, CHNH), 4.98–5.12 (m, 4 H, CH₂Ph and OCH₂N), 5.86 (d, J = 8.8 Hz, 1 H, NH), 6.85 (s, 1 H, 5-*H*_{im}), 7.25–7.30 (m, 5 H, Ph), 7.46 (s, 1 H, 2-*H*_{im}).

¹³C NMR (90 MHz, CDCl₃): δ = 14.8 (CH₃CH₂), 22.6 and 22.7 [(CH₃)₂CH], 24.9 [(CH₃)₂CH], 44.6 (CH₂CH), 47.6 (CHNH), 64.5 (CH₃CH₂), 66.6 (PhCH₂), 76.3 (OCH₂N), 115.4 (5-*C*_{im}), 128.0 (Ph), 128.1 (Ph), 128.5 (Ph), 136.8 (Ph), 137.4 (2-*C*_{im}), 143.8 (4-*C*_{im}), 156.0 (CO).

EI-MS (70 eV): m/z (%) = 345 [M⁺] (1), 288 (30), 244 (20), 194 (20), 180 (90), 153 (30), 135 (30), 122 (20), 108 (70), 91 (70), 79 (70), 59 (100), 41 (15).

Anal. Calcd for C₁₉H₂₇N₃O₃: C, 66.06; H, 7.88; N, 12.16. Found: C, 66.01; H, 8.01; N, 12.24.

(S)-Benzyl 1-[1-(Ethoxymethyl)-1H-imidazol-4-yl]-2-phenylethylcarbamate (6a)

Yield: 446 mg (36%); oil; ee >95%; R_f = 0.58 [hexane–EtOAc–MeOH–NH₃(aq), 3:5:1:0.1], R_f = 0.25 (EtOAc–hexane, 3:1); $[\alpha]_D^{20}$ –30.0 (c 0.1, MeOH).

¹H NMR (360 MHz, CDCl₃): δ = 1.10 (t, J = 6.9 Hz, 3 H, CH₃CH₂), 3.09–3.13 (dd, J = 9.2, 5.8 Hz, 1 H, CHCH₂Ph), 3.22–3.25 (m, 3 H, CHCH₂Ph and CH₃CH₂), 4.94–4.99 (m, 1 H, CHNH), 5.02–5.09 (m, 4 H, CH₂Ph and OCH₂N), 6.17–6.21 (m, 1 H, NH), 6.58 (s, 1 H, 5-*H*_{im}), 7.04 (d, J = 6.1 Hz, 2 H, ArH), 7.12–7.17 (m, 3 H, ArH), 7.29–7.32 (m, 5 H, Ph), 7.47 (s, 1 H, 2-*H*_{im}).

¹³C NMR (90 MHz, CDCl₃): δ = 14.8 (CH₃CH₂), 41.9 (CHCH₂Ph), 50.9 (CH), 64.2 (CH₃CH₂), 66.6 (PhCH₂O), 76.2 (OCH₂N), 115.9 (5-*C*_{im}), 126.3 (Ar), 128.0 (Ph), 128.1 (Ph), 128.1 (Ar), 128.5 (Ph), 129.5 (Ar), 136.8 (Ph), 137.4 (2-*C*_{im}), 138.1 (Ar), 142.1 (4-*C*_{im}), 155.9 (CO).

Anal. Calcd for C₂₂H₂₅N₃O₃: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.59; H, 6.81; N, 11.15.

(S)-Benzyl 1-[1-(Ethoxymethyl)-1H-imidazol-5-yl]ethylcarbamate (4b)

Yield: 416 mg (42%); oil; ee >95%; R_f = 0.66 [hexane–EtOAc–MeOH–NH₃(aq), 3:5:1:0.1], R_f = 0.05 (EtOAc–hexane, 3:1); $[\alpha]_D^{20}$ –4.0 (c 0.1, MeOH).

¹H NMR (360 MHz, CDCl₃): δ = 1.13 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 1.54 (d, J = 6.7 Hz, 3 H, CH₃CH), 3.39 (q, J = 6.7 Hz, 2 H, CH₂CH₃), 5.01–5.09 (m, 3 H, CHNH and CH₂Ph), 5.14 and 5.36 (dd, J = 11.5, 10.5 Hz, 2 H, OCH₂N), 5.19 (s, 1 H, NH), 6.96 (s, 1 H, 4-*H*_{im}), 7.28–7.34 (m, 5 H, Ph), 7.50 (s, 1 H, 2-*H*_{im}).

¹³C NMR (90 MHz, CDCl₃): δ = 14.8 (CH₃CH₂), 21.5 (CH₃CH), 45.2 (CH), 64.5 (CH₃CH₂), 66.6 (PhCH₂), 76.9 (OCH₂N), 127.4 (4-*C*_{im}), 128.3 (Ph), 128.4 (Ph), 128.7 (Ph), 133.4 (5-*C*_{im}), 136.5 (Ph), 138.9 (2-*C*_{im}), 155.6 (CO).

EI-MS (70 eV): m/z (%) = 244 (10), 166 (35), 122 (20), 108 (100), 91 (50), 79 (95), 59 (100), 51 (20), 41 (20).

Anal. Calcd for C₁₆H₂₁N₃O₃: C, 63.35; H, 6.98; N, 13.85. Found: C, 63.36; H, 7.17; N, 14.03.

(S)-Benzyl 1-[1-(Ethoxymethyl)-1H-imidazol-5-yl]-3-methylbutylcarbamate (5b)

Yield: 395 mg (35%); oil; ee >95%; R_f = 0.63 [hexane–EtOAc–MeOH–NH₃(aq), 3:5:1:0.1], R_f = 0.10 (EtOAc–hexane, 3:1); $[\alpha]_D^{20}$ –16.0 (c 0.1, MeOH).

¹H NMR (360 MHz, CDCl₃): δ = 0.90–0.92 [m, 6 H, (CH₃)₂CH], 1.10 (t, J = 6.9 Hz, 3 H, CH₃CH₂), 1.59–1.70 [m, 3 H, CH₂CH(CH₃)₂], 3.36 (q, J = 6.7 Hz, 2 H, CH₂CH₃), 4.92–5.13 (m, 4 H, CHNH and CH₂Ph), 5.50 (dd, J = 10.9, 9.0 Hz, 2 H, OCH₂N), 6.89 (s, 1 H, 4-*H*_{im}), 7.25–7.28 (m, 5 H, Ph), 7.43 (s, 1 H, 2-*H*_{im}).

¹³C NMR (90 MHz, CDCl₃): δ = 14.7 (CH₃CH₂), 22.4 and 22.6 [(CH₃)₂CH], 25.0 [(CH₃)₂CH], 43.9 (CH), 43.9 (CH₂CH), 64.0 (CH₃CH₂), 66.8 (PhCH₂), 74.7 (OCH₂N), 127.4 (4-*C*_{im}), 128.1 (Ph), 128.2 (Ph), 128.6 (Ph), 133.2 (5-*C*_{im}), 136.5 (Ph), 138.5 (2-*C*_{im}), 155.8 (CO).

EI-MS (70 eV): m/z (%) = 288 (20), 244 (20), 180 (40), 108 (60), 91 (100), 79 (55), 59 (70), 44 (15).

Anal. Calcd for C₁₉H₂₇N₃O₃: C, 66.06; H, 7.88; N, 12.16. Found: C, 65.99; H, 8.08; N, 12.14.

(S)-Benzyl 1-[1-(Ethoxymethyl)-1H-imidazol-5-yl]-2-phenylethylcarbamate (6b)

Yield: 446 mg (36%); oil; ee >95%; R_f = 0.52 [hexane–EtOAc–MeOH–NH₃(aq), 3:5:1:0.1], R_f = 0.1 (EtOAc–hexane, 3:1); $[\alpha]_D^{20}$ –23.0 (c 0.1, MeOH).

¹H NMR (360 MHz, CDCl₃): δ = 1.07 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 3.15–3.30 (m, 4 H, CHCH₂Ph and CH₃CH₂), 5.97–5.07 (m, 3 H, CHNH and CH₂Ph), 5.12–5.20 (m, 2 H, NH and OCH₂N), 5.31 (d, J = 10.0 Hz, 1 H, OCH₂N), 7.00 (s, 1 H, 4-*H*_{im}), 7.13–7.32 (m, 10 H, Ph and ArH), 7.54 (s, 1 H, 2-*H*_{im}).

¹³C NMR (90 MHz, CDCl₃): δ = 14.8 (CH₃CH₂), 41.5 (CHCH₂Ph), 57.8 (CH), 64.2 (CH₃CH₂), 67.1 (PhCH₂O), 74.9 (OCH₂N), 127.0 (4-*C*_{im}), 127.0 (Ar), 128.3 (Ph), 128.4 (Ar), 128.7 (Ph), 128.8 (Ph), 129.5 (Ar), 132.3 (5-*C*_{im}), 136.5 (Ph), 137.0 (Ar), 138.6 (2-*C*_{im}), 155.6 (CO).

Anal. Calcd for C₂₂H₂₅N₃O₃: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.63; H, 6.65; N, 11.12.

Iodination; General Procedure

A solution of imidazole **4a** or **5a** (3.30 mmol) in anhydrous THF (15 mL) was treated with *n*-BuLi (2 equiv, 1.6 M in hexane) under N₂ at –78 °C until a red-brown color was established. A solution of I₂ (2.5 g, 9.90 mmol) in THF (5 mL) was added and the mixture was stirred for 2 h at –78 °C and for an additional 12 h at 25 °C. The re-

action was quenched with $\text{Na}_2\text{S}_2\text{O}_3$ (sat., 20 mL) and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried (Na_2SO_4), the solvent evaporated and the crude product was purified by column chromatography (SiO_2 ; EtOAc–hexane, 1:2).

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-iodo-1*H*-imidazol-4-yl]ethylcarbamate (7)

Yield: 524 mg (37%); oil; ee >95%; R_f = 0.27 (SiO_2 ; EtOAc–hexane, 1:2); $[\alpha]_{\text{D}}^{20}$ –8.0 (c 0.1, MeOH).

^1H NMR (500 MHz, CDCl_3): δ = 1.17 (t, J = 6.8 Hz, 3 H, CH_3CH_2), 1.47 (d, J = 6.8 Hz, 3 H, CH_3CH), 3.48 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.78–4.81 (m, 1 H, CHNH), 5.04–5.11 (m, 2 H, CH_2Ph), 5.16 (s, 2 H, OCH_2N), 5.30 (d, J = 6.7 Hz, 1 H, NH), 7.01 (s, 1 H, 5- H_{im}), 7.27–7.35 (m, 5 H, Ph).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.0 (CH_3CH_2), 21.6 (CH_3CH), 45.4 (CH), 64.8 (CH_3CH_2), 66.8 (PhCH_2), 68.3 (OCH_2N), 89.8 (2- C_{im}), 119.5 (5- C_{im}), 128.2 (Ph), 128.3 (Ph), 128.7 (Ph), 136.8 (Ph), 147.9 (4- C_{im}), 155.8 (CO).

EI-MS (70 eV): m/z (%) = 429 (5), 294 (60), 277 (50), 248 (15), 221 (15), 108 (35), 91 (100), 79 (40), 59 (90).

Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{IN}_3\text{O}_3$: C, 44.77; H, 4.70; I, 29.56; N, 9.79. Found: C, 44.49; H, 4.79; I, 29.49; N, 9.95.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-iodo-1*H*-imidazol-4-yl]-3-methylbutylcarbamate (8)

Yield: 762 mg (49%); oil; ee >95%; R_f = 0.18 (SiO_2 ; EtOAc–hexane, 1:2); $[\alpha]_{\text{D}}^{20}$ –30.0 (c 0.1, MeOH).

^1H NMR (500 MHz, CDCl_3): δ = 0.90 (d, J = 6.4 Hz, 6 H, $(\text{CH}_3)_2\text{CH}$), 1.18 (t, J = 6.9 Hz, 3 H, CH_3CH_2), 1.51–1.58 [m, 1 H, $\text{CH}(\text{CH}_3)_2$], 1.68 [t, J = 7.1 Hz, 2 H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$], 3.46 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.69–4.73 (m, 1 H, CHNH), 5.02–5.08 (m, 2 H, CH_2Ph), 5.16 (s, 2 H, OCH_2N), 5.30 (d, J = 8.64 Hz, 1 H, NH), 7.02 (s, 1 H, 5- H_{im}), 7.22–7.34 (m, 5 H, Ph).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.0 (CH_3CH_2), 22.5 and 22.7 [$(\text{CH}_3)_2\text{CH}$], 25.0 [$(\text{CH}_3)_2\text{CH}$], 44.5 (CH_2CH), 47.7 (CHNH), 64.8 (CH_3CH_2), 66.7 (PhCH_2), 78.3 (OCH_2N), 90.0 (2- C_{im}), 120.0 (5- C_{im}), 128.1 (Ph), 128.2 (Ph), 128.5 (Ph), 136.8 (Ph), 147.0 (4- C_{im}), 156.0 (CO).

Anal. Calcd for $\text{C}_{19}\text{H}_{26}\text{IN}_3\text{O}_3$: C, 48.42; H, 5.56; I, 26.92; N, 8.92. Found: C, 48.46; H, 5.82; I, 26.67; N, 9.01.

Negishi Cross-Coupling to Generate Target Imidazoles 9–16; General Procedure

A solution of imidazole **4a–6a** (1.0 mmol) in anhydrous THF (25 mL) was treated with $n\text{-BuLi}$ (2 equiv, 1.6 M in hexane) under N_2 at -78°C until the reaction mixture turned dark red. The reaction was stirred for 20 min at -78°C then a freshly prepared solution of ZnBr_2 (225 mg, 1.0 mmol) in anhydrous THF (5 mL) was added. The reaction mixture was allowed to reach 25°C and stirred for 30 min. A solution of ArX (1.3 mmol) in anhydrous THF (5 mL) and $\text{Pd}(\text{PPh}_3)_4$ (50 mg, 0.043 mmol) were added, and the reaction was refluxed for 1 h whereupon ZnBr_2 (450 mg, 2.0 mmol) was added and the suspension was refluxed until TLC showed that the reaction was complete (see Table 1 for the reaction times). The reaction was quenched by adding an aqueous solution of Chelaton III (0.6 M, 10 mL) and the pH was adjusted to 8 using 10% solution of Na_2CO_3 . The product was extracted with CH_2Cl_2 (3×50 mL), the solvent was evaporated and the crude product was purified by column chromatography.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-phenyl-1*H*-imidazol-4-yl]-2-phenylethylcarbamate (9)

Yield: 300 mg (66%); oil; ee >95%; R_f = 0.25 (SiO_2 ; acetone–hexane, 1:2); $[\alpha]_{\text{D}}^{20}$ –8.0 (c 0.1, MeOH).

^1H NMR (360 MHz, CDCl_3): δ = 1.16 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 3.15 (dd, J = 8.5, 4.4 Hz, 1 H, CHCH_2Ph), 3.28–3.38 (m, 3 H, CHCH_2Ph and CH_3CH_2), 4.94–5.00 (m, 1 H, CHNH), 5.09 (s, 2 H, OCH_2N), 5.16–5.12 (m, 2 H, CH_2Ph), 5.70 (d, J = 7.5 Hz, 1 H, NH), 6.63 (s, 1 H, 5- H_{im}), 7.09 (d, J = 6.6 Hz, 2 H, ArH), 7.16–7.25 (m, 3 H, ArH), 7.28–7.33 (m, 5 H, Ph), 7.42–7.48 (m, 3 H, 2- ArH), 7.75 (d, J = 6.9 Hz, 2 H, 2- ArH).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.0 (CH_3CH_2), 42.1 (CHCH_2Ph), 50.1 (CH), 64.4 (CH_3CH_2), 66.7 (PhCH_2O), 75.8 (OCH_2N), 118.4, 126.4, 128.1, 128.3, 128.6, 128.9, 129.2, 129.3, 129.8, 130.3, 136.9, 138.3, 140.6, 148.6, 155.9 (1 C missing).

ESI-MS: m/z = 478 [M^+ + Na].

Anal. Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_3$: C, 73.82; H, 6.42; N, 9.22. Found: C, 73.63; H, 6.59; N, 9.38.

(S)-Benzyl 1-[2-[4-(Dimethylamino)phenyl]-1-(ethoxymethyl)-1*H*-imidazol-4-yl]ethylcarbamate (10)

Yield: 203 mg (48%); oil; ee >95%; R_f = 0.66 (SiO_2 ; EtOAc–hexane, 5:1); $[\alpha]_{\text{D}}^{20}$ –7.0 (c 0.1, MeOH).

^1H NMR (360 MHz, CDCl_3): δ = 1.21 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.53 (d, J = 6.6 Hz, 3 H, CH_3CH), 2.99 [s, 6H, $(\text{CH}_3)_2\text{N}$], 3.52 (q, J = 6.8 Hz, 2 H, CH_2CH_3), 4.83–4.87 (m, 1 H, CHNH), 4.96–5.12 (m, 2 H, CH_2Ph), 5.17 (s, 2 H, OCH_2N), 5.54 (d, J = 6.4 Hz, 1 H, NH), 6.74 (d, J = 8.9 Hz, 2 H, 2- ArH), 6.9 (s, 1 H, 5- H_{im}), 7.26–7.34 (m, 5 H, Ph), 7.58 (d, J = 8.9 Hz, 2 H, 2- ArH).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.1 (CH_3CH_2), 22.0 (CH_3CH), 40.5 [$(\text{CH}_3)_2\text{N}$], 45.5 (CH), 64.5 (CH_3CH_2), 66.6 (PhCH_2), 75.9 (OCH_2N), 112.1, 116.4, 117.9, 128.1, 128.2, 128.6, 130.1, 137.0, 142.8, 149.6, 151.0, 155.9.

ESI-MS: m/z = 445 [M^+ + Na].

Anal. Calcd for $\text{C}_{24}\text{H}_{30}\text{N}_4\text{O}_3$: C, 68.22; H, 7.16; N, 13.26. Found: C, 67.84; H, 7.49; N, 13.41.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-(pyridin-2-yl)-1*H*-imidazol-4-yl]ethylcarbamate (11)

Yield: 258 mg (68%); oil; ee >95%; R_f = 0.48 (SiO_2 ; EtOAc–hexane, 5:1); $[\alpha]_{\text{D}}^{20}$ –10.0 (c 0.1, MeOH).

^1H NMR (360 MHz, CDCl_3): δ = 1.13 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.53 (d, J = 6.7 Hz, 3 H, CH_3CH), 3.47 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 4.87–4.89 (m, 1 H, CHNH), 5.07–5.12 (m, 2 H, CH_2Ph), 5.57 (d, J = 6.3 Hz, 1 H, NH), 5.95 (s, 2 H, OCH_2N), 7.03 (s, 1 H, 5- H_{im}), 7.19 (t, J = 4.9 Hz, 1 H, Py), 7.27–7.37 (m, 5 H, Ph), 7.71 (t, J = 7.8 Hz, 1 H, Py), 8.11 (d, J = 8.0 Hz, 1 H, Py), 8.54 (d, J = 4.8 Hz, 1 H, Py).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.7 (CH_3CH_2), 21.6 (CH_3CH), 45.1 (CH), 64.1 (CH_3CH_2), 66.3 (PhCH_2), 76.6 (OCH_2N), 117.9, 122.6, 122.9, 127.8, 128.3, 128.3, 136.5, 143.2, 144.4, 148.1, 150.1, 155.5 (1 C missing).

ESI-MS: m/z = 403 [M^+ + Na].

Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_3$: C, 66.30; H, 6.36; N, 14.73. Found: C, 66.19; H, 6.45; N, 14.79.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-(pyrazin-2-yl)-1*H*-imidazol-4-yl]ethylcarbamate (12)

Yield: 244 mg (64%); oil; ee >95%; R_f = 0.33 (SiO_2 ; EtOAc–hexane, 5:1); $[\alpha]_{\text{D}}^{20}$ –12.0 (c 0.1, MeOH).

^1H NMR (500 MHz, CDCl_3): δ = 1.13 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.53 (d, J = 6.7 Hz, 3 H, CH_3CH), 3.49 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 4.88–4.92 (m, 1 H, CHNH), 5.07–5.12 (m, 2 H, CH_2Ph), 5.52 (d, J = 6.9 Hz, 1 H, NH), 5.86 (s, 2 H, OCH_2N), 7.09 (s, 1 H, 5- H_{im}), 7.27–7.35 (m, 5 H, Ph), 8.47 (s, 2 H, Prz), 9.39 (s, 1 H, Prz).

^{13}C NMR (90 MHz, CDCl_3): δ = 14.9 (CH_3CH_2), 21.7 (CH_3CH), 45.3 (CH), 64.6 (CH_3CH_2), 66.6 (PhCH_2), 77.0 (OCH_2N), 119.3, 128.0, 128.1, 128.5, 136.7, 141.9, 142.5, 143.0, 144.2, 144.8, 145.9, 155.5.

ESI-MS: m/z = 404 [M^+ + Na].

Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_3$: C, 62.98; H, 6.08; N, 18.36. Found: C, 62.61; H, 6.12; N, 18.59.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-(pyridazin-3-yl)-1H-imidazol-4-yl]ethylcarbamate (13)

Yield: 244 mg (64%); oil; ee >95%; R_f = 0.20 (SiO_2 ; EtOAc–hexane, 5:1); $[\alpha]_{\text{D}}^{20}$ –11.0 (c 0.1, MeOH).

^1H NMR (500 MHz, CDCl_3): δ = 1.14 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.53 (d, J = 6.6 Hz, 3 H, CH_3CH), 3.55 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.89–4.92 (m, 1 H, CHNH), 5.08–5.10 (m, 2 H, CH_2Ph), 5.52 (d, J = 6.5 Hz, 1 H, NH), 6.05 (s, 2 H, OCH_2N), 7.15 (s, 1 H, 5- H_{im}), 7.28–7.35 (m, 5 H, Ph), 7.49–7.52 (m, 1 H, PdZ), 8.30 (dd, J = 8.5, 1.5 Hz, 1 H, PdZ), 9.06 (dd, J = 5.0, 1.5 Hz, 1 H, ArH).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.1 (CH_3CH_2), 21.8 (CH_3CH), 45.4 (CH), 64.8 (CH_3CH_2), 66.7 (PhCH_2), 77.7 (OCH_2N), 119.3, 126.4, 126.9, 128.2, 128.3, 128.6, 132.1, 136.8, 141.8, 144.6, 150.4, 155.5.

ESI-MS: m/z = 404 [M^+ + Na].

Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_3$: C, 62.98; H, 6.08; N, 18.36. Found: C, 62.73; H, 6.35; N, 18.56.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-(pyrimidin-2-yl)-1H-imidazol-4-yl]ethylcarbamate (14)

Yield: 213 mg (56%); oil; ee >95%; R_f = 0.18 (SiO_2 ; acetone–hexane, 1:1); $[\alpha]_{\text{D}}^{20}$ –14.0 (c 0.1, MeOH).

^1H NMR (360 MHz, CDCl_3): δ = 1.09 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.51–1.54 (m, 3 H, CH_3CH), 3.44–3.48 (m, 2 H, CH_2CH_3), 4.86–4.90 (m, 1 H, CHNH), 5.00–5.07 (m, 2 H, CH_2Ph), 5.55 (d, J = 7.2 Hz, 1 H, NH), 5.92 (s, 2 H, OCH_2N), 7.09 (s, 1 H, 5- H_{im}), 7.17 (t, J = 4.9 Hz, 1 H, Pym), 7.21–7.29 (m, 5 H, Ph), 8.77 (d, J = 4.8 Hz, 2 H, Pym).

^{13}C NMR (90 MHz, CDCl_3): δ = 14.9 (CH_3CH_2), 21.8 (CH_3CH), 45.3 (CH), 64.7 (CH_3CH_2), 66.5 (PhCH_2), 77.6 (OCH_2N), 119.7, 128.0, 128.3, 128.6, 136.8, 148.1, 144.4, 155.8, 156.2, 157.4, 157.9.

ESI-MS: m/z = 404 [M^+ + Na].

Anal. Calcd for $\text{C}_{20}\text{H}_{23}\text{N}_5\text{O}_3$: C, 62.98; H, 6.08; N, 18.36. Found: C, 62.44; H, 6.36; N, 18.67.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-(quinolin-8-yl)-1H-imidazol-4-yl]-3-methylbutylcarbamate (15)

Yield: 255 mg (55%); oil; ee >95%; R_f = 0.36 (SiO_2 ; EtOAc–hexane, 5:1); $[\alpha]_{\text{D}}^{20}$ –27.0 (c 0.1, MeOH).

^1H NMR (360 MHz, CDCl_3): δ = 0.88–0.90 (m, 3 H, CH_3CH_2), 0.96 [d, J = 6.8 Hz, 6 H, (CH_3) $_2\text{CH}$], 1.55–1.74 [m, 1 H, (CH_3) $_2\text{CH}$], 1.80 (t, J = 6.4 Hz, 2 H, CH_2CH), 3.18 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 4.86–4.91 (m, 1 H, CHNH), 5.05–5.17 (m, 4 H, CH_2Ph and OCH_2N), 5.54 (d, J = 8.7 Hz, 1 H, NH), 7.14 (s, 1 H, 5- H_{im}), 7.27–7.33 (m, 5 H, Ph), 7.40–7.43 (m, 1 H, Qun), 7.62 (t, J = 7.3 Hz, 1 H, Qun), 7.93 (t, J = 8.2 Hz, 1 H, Qun), 8.19 (dd, J = 1.6, 8.3 Hz, 1 H, Qun), 8.88 (dd, J = 1.7, 4.1 Hz, 1 H, Qun).

^{13}C NMR (90 MHz, CDCl_3): δ = 14.8 (CH_3CH_2), 22.7 and 22.9 [(CH_3) $_2\text{CH}$], 25.1 [(CH_3) $_2\text{CH}$], 44.9 (CH_2CH), 47.9 (CHNH), 64.2 (CH_3CH_2), 66.6 (PhCH_2), 77.0 (OCH_2N), 116.6, 121.6, 126.6, 128.0, 128.1, 128.5, 128.6, 128.7, 129.9, 130.2, 133.1, 136.6, 137.0, 142.9, 146.4, 150.9, 156.1.

ESI-MS: m/z = 495 [M^+ + Na].

Anal. Calcd for $\text{C}_{28}\text{H}_{32}\text{N}_4\text{O}_3$: C, 71.16; H, 6.83; N, 11.86. Found: C, 71.02; H, 7.00; N, 12.05.

Benzyl (1S,1'S)-1,1'-[1,1'-Bis(ethoxymethyl)-1H,1'H-2,2'-biimidazole-4,4'-diyl]bis(ethane-1,1-diyl)dicarbamate (16)

Yield: 205 mg (34%); oil; ee >95%; R_f = 0.39 (SiO_2 ; acetone–hexane, 1:1); $[\alpha]_{\text{D}}^{20}$ –8.0 (c 0.1, MeOH).

^1H NMR (500 MHz, CDCl_3): δ = 1.03 (t, J = 6.5 Hz, 3 H, CH_3CH_2), 1.12 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.51 (d, J = 6.0 Hz, 3 H, CH_3CH), 1.58 (d, J = 5.5 Hz, 3 H, CH_3CH), 3.33–3.38 (m, 2 H, CH_2CH_3), 3.42–3.46 (m, 2 H, CH_2CH_3), 4.87–4.90 (m, 1 H, CHNH), 5.07–5.17 (m, 6 H, $2 \times \text{CH}_2\text{Ph}$ and CHNH), 5.29 (d, J = 8.0 Hz, 1 H, NH), 5.62–5.86 and 6.05–6.12 ($2 \times$ m, 4 H, $2 \times \text{OCH}_2\text{N}$), 7.02 (s, 2 H, $2 \times 5-H_{\text{im}}$), 7.30–7.35 (m, 10 H, Ph).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.0 and 15.1 (CH_3CH_2), 20.8 and 21.8 (CH_3CH), 42.1 and 45.4 (CHNH), 63.9 and 64.7 (CH_3CH_2), 66.9 and 67.1 (PhCH_2), 73.7 and 76.6 (OCH_2N), 117.0, 126.8, 128.3, 128.4, 128.7, 135.5, 136.5, 136.8, 137.8, 139.5, 143.3, 155.6, 155.9.

ESI-MS: m/z = 627 [M^+ + Na].

Anal. Calcd for $\text{C}_{32}\text{H}_{40}\text{N}_6\text{O}_6$: C, 63.56; H, 6.67; N, 13.90. Found: C, 63.42; H, 6.77; N, 14.05.

Suzuki–Miyaura Cross-Coupling to Generate Target Imidazoles 17, 18; General Procedure

$\text{Pd}(\text{PPh}_3)_4$ (15.9 mg, 0.014 mmol), $\text{ArB}(\text{OH})_2$ (0.36 mmol) and an aqueous solution of Na_2CO_3 (0.2 mL, 2M) were successively added to a degassed solution of 2-iodoimidazole **7** or **8** (0.28 mmol) in THF– H_2O (4:1, 20 mL). The reaction mixture was refluxed until TLC showed that the reaction was complete (see Table 1 for the reaction times). The product was extracted with CH_2Cl_2 (3×20 mL), the solvent evaporated and the crude product purified by column chromatography.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-phenyl-1H-imidazol-4-yl]ethylcarbamate (17)

Yield: 78 mg (74%); oil; ee >95%; R_f = 0.63 (SiO_2 ; acetone–hexane, 1:1); $[\alpha]_{\text{D}}^{20}$ –11.0 (c 0.1, MeOH).

^1H NMR (500 MHz, CDCl_3): δ = 1.22 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.54 (d, J = 6.7 Hz, 3 H, CH_3CH), 3.51 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 4.84–4.91 (m, 1 H, CHNH), 5.08–5.14 (m, 2 H, CH_2Ph), 5.19 (s, 2 H, OCH_2N), 5.49 (d, J = 6.3 Hz, 1 H, NH), 6.97 (s, 1 H, 5- H_{im}), 7.27–7.34 (m, 5 H, Ph), 7.40–7.46 (m, 3 H, 2-ArH), 7.71 (d, J = 8.0 Hz, 2 H, 2-ArH).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.1 (CH_3CH_2), 22.0 (CH_3CH), 45.5 (CH), 64.7 (CH_3CH_2), 66.7 (PhCH_2), 76.0 (OCH_2N), 117.3, 128.2, 128.3, 128.7, 128.9, 129.2, 129.3, 130.3, 136.9, 143.7, 148.7, 155.9.

ESI-MS: m/z = 402 [M^+ + Na].

Anal. Calcd for $\text{C}_{22}\text{H}_{25}\text{N}_3\text{O}_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.41; H, 6.82; N, 11.02.

(S)-Benzyl 1-[1-(Ethoxymethyl)-2-(furan-2-yl)-1H-imidazol-4-yl]-3-methylbutylcarbamate (18)

Yield: 101 mg (88%); oil; ee >95%; R_f = 0.1 (SiO_2 ; EtOAc–hexane, 1:4); $[\alpha]_{\text{D}}^{20}$ –39.0 (c 0.1, MeOH).

^1H NMR (360 MHz, CDCl_3): δ = 0.92 [d, J = 6.2 Hz, 6 H, (CH_3) $_2\text{CH}$], 1.17 (t, J = 6.9 Hz, 3 H, CH_3CH_2), 1.54–1.61 [m, 1 H, (CH_3) $_2\text{CH}$], 1.75 (t, J = 6.8 Hz, 2 H, CH_2CH), 3.49 (q, J = 6.9 Hz, 2 H, CH_2CH_3), 4.75–4.82 (m, 1 H, CHNH), 5.03–5.14 (m, 2 H, CH_2Ph), 5.36 (s, 2 H, OCH_2N), 5.41 (d, J = 8.7 Hz, 1 H, NH), 6.48–6.49 (m, 1 H, Fur), 6.87 (d, J = 2.8 Hz, 1 H, Fur), 6.92 (s, 1 H, 5- H_{im}), 7.27–7.32 (m, 5 H, Ph), 8.51 (d, J = 1.0 Hz, 1 H, Fur).

^{13}C NMR (90 MHz, CDCl_3): δ = 15.0 (CH_3CH_2), 22.6 and 22.7 [$(\text{CH}_3)_2\text{CH}$], 25.0 [$(\text{CH}_3)_2\text{CH}$], 44.7 (CH_2CH), 47.6 (CHNH), 64.5 (CH_3CH_2), 66.6 (PhCH_2), 76.1 (OCH_2N), 110.6, 111.6, 117.7, 128.1, 128.2, 128.6, 136.9, 139.8, 142.8, 143.3, 144.8, 156.0.

ESI-MS: m/z = 434 [$\text{M}^+ + \text{Na}$].

Anal. Calcd for $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_4$: C, 67.13; H, 7.10; N, 10.21. Found: C, 66.96; H, 7.23; N, 10.37.

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