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 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 (alpha 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 (R¹ = H) already in hand,⁸ our retrosynthetic strategy leading to the target imidazoles involved the formation of the imidazole–(hetero)aromatic C(sp²)–C(sp²) 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
from the condensation of the corresponding α-bromoketones and formamidine in liquid ammonia, 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 chloromethyethyl ether in the presence of triethylamine afforded the protected imidazoles 4–6 in good yields (PG = ethoxymethyl, Scheme 1), 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–13C NMR spectroscopy employing HMQC and HMBC methods, which showed interactions between the CH group of the side chain, the imidazole carbons and the CH₂ group of the protecting group.

Since it is well known that N-substituted imidazole may be selectively lithiated at the C-2 position, 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, 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 involving lithiation of imidazoles 6a and 4a with n-BuLi at –78 °C was conducted; transmetallation with zinc bromide and subsequent Pd(PPh₃)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: Pd(PPh₃)₄/ZnBr₂:68% and PdCl₂(PPh₃)₂/ZnCl₂: 69%]. In addition, 2-iodopyrazine, 3-bromopyridazine, 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-idoimidazoles 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 coupling or palladium-catalyzed oxidative homocoupling 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 Pd(PPh₃)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 carboxylic 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
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. 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 rotation 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 μm) 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 × 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–NH4OAc, 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).

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

<table>
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<tr>
<th>Imidazole</th>
<th>Starting compd</th>
<th>R/a-amino acid</th>
<th>ArX/ArB(OH)2</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>[α]D20 (c 0.1, MeOH)</th>
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<td>4a</td>
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<td>48</td>
<td>–7.0</td>
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<tr>
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<td>4a</td>
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<td>20</td>
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<td>Me/(S)-Ala</td>
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<td>20</td>
<td>64</td>
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<tr>
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<td>4a</td>
<td>Me/(S)-Ala</td>
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<td>20</td>
<td>64</td>
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<tr>
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<td>56</td>
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<td>5a</td>
<td>i-Bu/(S)-Leu</td>
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<td>20</td>
<td>54</td>
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<td>16a</td>
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<td>72</td>
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<td></td>
<td>6</td>
<td>88</td>
<td>–39.0</td>
</tr>
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</table>

a Negishi reaction.
b Suzuki–Miyaura reaction.
(S)-Benzyl 1-(1-(Ethoxymethyl)-1H-imidazol-4-yl)ethylcarbamate (4a)
Yield: 466 mg (47%); oil; ee >95%; Rf = 0.75 [hexane–EtOAc–MeOH–NH3 (aq), 3:5:1:0.1]; Rf = 0.14 (EtOAc–hexane, 3:1); [α]20
–8.0 (c 0.1, MeOH).

1H NMR (360 MHz, CDCl3): δ = 1.13 (t, J = 7.0 Hz, 3 H, CH3), 1.46 (d, J = 6.8 Hz, 3 H, CH2CH3), 1.38 (q, J = 7.0 Hz, 2 H, CH2CH3), 1.47–2.48 (m, 1 H, CHN), 5.02–5.08 (m, 2 H, CH2Ph), 5.13 (s, 2 H, OCH3), 5.62–5.64 (m, 1 H, NH), 6.86 (s, 1 H, 5-Him), 7.25–7.31 (m, 5 H, Ph), 7.46 (s, 1 H, 2-Him).

EI-MS (70 eV): m/z (%) = 305 [M+1] (1), 195 (15), 180 (40), 168 (30), 151 (70), 122 (15), 108 (100), 91 (50), 79 (95), 59 (100), 51 (20).


(S)-Benzyl 1-(1-(Ethoxymethyl)-1H-imidazol-4-yl)-3-methylbutylcarbamate (5a)
Yield: 406 mg (36%); oil; ee >95%; Rf = 0.71 [hexane–EtOAc–MeOH–NH3 (aq), 3:5:1:0.1]; Rf = 0.18 (EtOAc–hexane, 3:1); [α]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, CH2CH3), 1.47–1.57 (m, 1 H, CH2CH3), 1.69 (t, J = 7.2 Hz, 2 H, CH2CH3), 3.34 (q, J = 6.3 Hz, 2 H, CH2CH3), 4.74–4.79 (m, 1 H, CHN), 4.98–5.12 (m, 4 H, CH2Ph and OCH3N), 5.86 (d, J = 8.8 Hz, 1 H, NH), 6.85 (s, 1 H, 5-Him), 7.25–7.30 (m, 5 H, Ph), 7.46 (s, 1 H, 2-Him).

EI-MS (70 eV): m/z (%) = 345 [M+1] (1), 288 (30), 244 (20), 194 (20), 180 (90), 153 (30), 135 (30), 122 (10), 108 (70), 91 (70), 79 (70), 59 (100), 41 (15).


(S)-Benzyl 1-(1-(Ethoxymethyl)-1H-imidazol-4-yl)-2-phenyl-ethylcarbamate (6a)
Yield: 446 mg (36%); oil; ee >95%; Rf = 0.58 [hexane–EtOAc–MeOH–NH3 (aq), 3:5:1:0.1]; Rf = 0.25 (EtOAc–hexane, 3:1); [α]20
–30.0 (c 0.1, MeOH).

1H NMR (360 MHz, CDCl3): δ = 1.10 (t, J = 6.9 Hz, 3 H, CH3), 1.39–3.13 (dd, J = 9.2, 5.8 Hz, 1 H, CH2CHPh), 3.22–3.25 (m, 3 H, CH2CHPh and CH2CH3), 4.94–4.99 (m, 1 H, CHN), 5.02–5.09 (m, 4 H, CH2Ph and OCH3N), 5.67–6.21 (m, 1 H, NH), 5.68 (s, 1 H, 5-Him), 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-Him).

EI-MS (70 eV): m/z (%) = 349 [M+1] (1), 322 (20), 285 (20), 268 (20), 241 (15), 224 (15), 207 (15), 190 (15), 173 (15), 156 (100), 145 (100), 138 (5-Cim), 136.5 (Ph), 138.5 (2-Cim), 155.8 (CO).

(S)-Benzyl 1-[1-(Ethoxymethyl)-1H-imidazol-5-yl)-2-phenylethylcarbamate (6b)
Yield: 446 mg (36%); oil; ee >95%; Rf = 0.52 [hexane–EtOAc–MeOH–NH3 (aq), 3:5:1:0.1]; Rf = 0.1 (EtOAc–hexane, 3:1); [α]20
–230.0 (c 0.1, MeOH).

1H NMR (360 MHz, CDCl3): δ = 1.07 (t, J = 7.0 Hz, 3 H, CH3), 3.15–3.30 (m, 4 H, CH2Ph and CH2CH3), 5.97–5.07 (m, 3 H, CH2CHPh and CH2CH3), 5.12–5.20 (m, 2 H, 2 H, NH and OCH3N), 5.31 (d, J = 10.0 Hz, 1 H, OCH3N), 7.00 (s, 1 H, 4-Him), 7.13–7.32 (m, 10 H, Ph and ArH), 7.54 (s, 1 H, 2-Him).

1C NMR (90 MHz, CDCl3): δ = 14.8 (CH3), 41.9 (CH2CH3), 50.9 (CH), 64.2 (CH2CH3), 66.6 (PhCH2O), 76.2 (OCH3N), 115.9 (5-Cim), 126.5 (Ar), 128.0 (Ph), 128.1 (Ph), 128.5 (Ph), 129.5 (Ar), 135.8 (Ph), 137.4 (2-Cim), 141.3 (Ar), 142.1 (4-Cim), 155.9 (CO).


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, 1.0 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 Na₂S₂O₃ (sat., 20 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried (Na₂SO₄), the solvent evaporated and the crude product was purified by column chromatography (SiO₂; EtOAc–hexane, 1:2).

(5)-Benzyl 1-[(Ethoxymethyl)-2-iodo-1H-imidazol-4-yl]ethylcarbamate (8)

Yield: 524 mg (37%); oil; ee >95%; R f = 0.27 (SiO₂; EtOAc–hexane, 1:2); [α] D 20 –30.0 (c 0.1, MeOH).

1H NMR (500 MHz, CDCl₃): δ = 1.11 (t, J = 6.8 Hz, 3 H, CH₃CH₂), 1.18 (d, J = 6.9 Hz, 3 H, CH₂CH₃), 1.51–1.58 (m, 1 H, CH₂CH₂), 1.68 [1, δ = 7.1 Hz, 2 H, CH₂CH₂CH₂CH₃], 3.46 (q, J = 7.0 Hz, 2 H, CH₂CH₂CH₂CH₃), 4.06–4.73 (m, 1 H, CH₃NH₂), 5.02–5.08 (m, 2 H, CH₂Ph), 5.16 (s, 2 H, CH₂O), 6.74 (d, J = 6.9 Hz, 1 H, CH₃NH₂), 7.02 (s, 1 H, 5-H), 7.16–7.25 (m, 5 H, Ph), 7.22–7.34 (m, 3 H, 5-H), 7.42–7.48 (m, 3 H, 2-Ar). ESI-MS: m/z = 478 [M⁺ + Na⁺].


(5)-Benzyl 1-[(Ethoxymethyl)-2-iodo-1H-imidazol-4-yl]ethylcarbamate (9)

Yield: 524 mg (37%); oil; ee >95%; R f = 0.25 (SiO₂; acetone–hexane, 1:2); [α] D 20 –30.0 (c 0.1, MeOH).

1H NMR (300 MHz, CDCl₃): δ = 1.11 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 1.15 (dd, J = 8.5, 4.4 Hz, 1 H, CH₂CH₂Ph), 3.28–3.38 (m, 3 H, CH₂CH₂Ph and CH₂CH₃), 4.94–5.00 (m, 1 H, CHNH₂), 5.09 (s, 2 H, OCH₂), 5.16–5.12 (m, 2 H, CH₂Ph), 5.70 (d, J = 7.5 Hz, 1 H, NH), 6.63 (s, 1 H, 5-H), 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), 7.45–7.48 (m, 3 H, 2-ArH). ESI-MS: m/z = 478 [M⁺ + Na⁺].


(5)-Benzyl 1-[(Ethoxymethyl)-2-iodo-1H-imidazol-4-yl]ethylcarbamate (10)

Yield: 203 mg (48%); oil; ee >95%; R f = 0.66 (SiO₂; EtOAc–hexane, 5:1); [α] D 20 –7.0 (c 0.1, MeOH).

1H NMR (300 MHz, CDCl₃): δ = 1.21 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 1.53 (dd, J = 6.6 Hz, 3 H, CH₂CH₂), 1.93 (s, 2 H, CH₂O), 4.76–4.83 (m, 2 H, CH₂Ph), 5.24–5.35 (m, 2 H, CH₂Ph), 5.78 (d, J = 6.4 Hz, 1 H, NH), 6.24 (d, J = 8.9 Hz, 2 H, 2-ArH), 6.51 (s, 1 H, 5-H), 6.72–6.74 (m, 2 H, Ph), 7.58 (d, J = 8.9 Hz, 2 H, 2-ArH). ESI-MS: m/z = 445 [M⁺ + Na⁺].


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

Yield: 258 mg (68%); oil; ee >95%; R f = 0.48 (SiO₂; EtOAc–hexane, 5:1); [α] D 20 –10.0 (c 0.1, MeOH).

1H NMR (300 MHz, CDCl₃): δ = 1.13 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 1.53 (dd, J = 6.7 Hz, 3 H, CH₂CH₂), 3.47 (q, J = 6.9 Hz, 2 H, CH₂CH₂), 4.87–4.89 (m, 1 H, CHNH₂), 5.07–5.12 (m, 2 H, CH₂Ph), 5.57 (d, J = 6.3 Hz, 1 H, NH₂), 5.95 (s, 2 H, OCH₂), 7.03 (s, 1 H, 5-H), 7.15 (t, J = 4.9 Hz, 1 H, Py), 7.20–7.37 (m, 5 H, Ph), 7.67 (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). ESI-MS: m/z = 403 [M⁺ + Na⁺].


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

Yield: 244 mg (64%); oil; ee >95%; R f = 0.33 (SiO₂; EtOAc–hexane, 5:1); [α] D 20 –12.0 (c 0.1, MeOH).

1H NMR (500 MHz, CDCl₃): δ = 1.13 (t, J = 7.0 Hz, 3 H, CH₃CH₂), 1.53 (dd, J = 6.7 Hz, 3 H, CH₂CH₂), 3.49 (q, J = 6.9 Hz, 2 H, CH₂CH₂), 4.88–4.92 (m, 1 H, CHNH₂), 5.07–5.12 (m, 2 H, CH₂Ph), 5.52 (d, J = 6.9 Hz, 1 H, NH), 5.86 (s, 2 H, OCH₂), 7.09 (s, 1 H, 5-H), 7.27–7.35 (m, 5 H, Ph), 8.47 (s, 2 H, Prz), 9.39 (s, 1 H, Prz).

[1H NMR (360 MHz, CDCl3): δ = 1.14 (t, J = 7.0 Hz, 3 H, CH3(CH)=), 1.53 (d, J = 6.6 Hz, 3 H, CH3(CH3)2), 3.55 (q, J = 7.0 Hz, 2 H, CH2(OH)), 4.89–4.92 (m, 1 H, CHN), 5.08–5.10 (m, 2 H, CH2(N)), 5.52 (d, J = 6.5 Hz, 1 H, NH), 6.05 (s, 2 H, OCH2N), 7.15 (s, 1 H, 5-Hm), 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 ArH).]

[11C NMR (90 MHz, CDCl3): δ = 15.1 (CH3(CH)=), 21.8 (CH3(CH)=), 45.4 (CH3), 64.8 (CH3(CH)=), 66.7 (PhCH3), 77.7 (OCH2N), 119.3, 126.4, 126.9, 128.2, 128.3, 128.6, 132.1, 136.8, 141.4, 144.8, 150.4, 155.5.]

[ESI-MS: m/z = 404 [M* + Na].] Anal. Calcd for C28H32N4O3: C, 71.16; H, 6.83; N, 11.86. Found: C, 71.02; H, 7.00; N, 12.05.

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

Yield: 244 mg (64%); oil; ee ≥95%; Rf = 0.20 (SiO2; EtOAc–hexane, 5:1); [α]D20 = 11.0 (c 0.1, MeOH).

[1H NMR (500 MHz, CDCl3): δ = 1.03 (t, J = 6.5 Hz, 3 H, CH3(CH)=), 1.12 (t, J = 7.0 Hz, 3 H, CH3(CH)=), 1.51 (d, J = 6.0 Hz, 3 H, CH3(CH)=), 1.58 (d, J = 5.5 Hz, 3 H, CH3(CH)=), 3.33–3.38 (m, 2 H, CH2(N)), 3.42–3.46 (m, 2 H, CH2(N)), 4.87–4.90 (m, 1 H, CHN), 5.07–5.17 (m, 6 H, 2 × CH2Ph and CHN), 5.29 (d, J = 8.0 Hz, 1 H, NH), 5.62–5.86 and 6.05–6.12 (2 × m, 4 H, 2 × OCH2N), 7.02 (s, 2 H, 2 × 5-Hm), 7.30–7.35 (m, 10 H, Ph).]

[13C NMR (90 MHz, CDCl3): δ = 15.0 and 15.1 (CH3(CH)=), 20.8 and 21.8 (CH3(CH)=), 42.1 and 45.4 (CH(N)), 63.9 and 64.7 (CH3(CH)=), 66.9 and 67.1 (PhCH3), 73.7 and 76.6 (OCH2N), 117.0, 126.8, 128.3, 128.4, 128.7, 135.5, 136.5, 136.8, 137.8, 139.5, 144.3, 155.6, 155.9.]

[ESI-MS: m/z = 627 [M* + Na].] Anal. Calcd for C36H36N4O4: 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

Pd(PPh3)4 (15.9 mg, 0.014 mmol), ArB(OH)2 (0.36 mmol) and an aqueous solution of Na2CO3 (0.2 mL, 2M) were successively added to a degassed solution of 2-iodimidazole 7 or 8 (0.28 mmol) in THF–H2O (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 CH2Cl2 (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 (14)

Yield: 78 mg (74%); oil; ee ≥95%; Rf = 0.63 (SiO2; acetone–hexane, 1:1); [α]D20 = –11.0 (c 0.1, MeOH).

[1H NMR (500 MHz, CDCl3): δ = 1.22 (t, J = 7.0 Hz, 3 H, CH3(CH)=), 1.54 (d, J = 6.7 Hz, 3 H, CH3(CH)=), 3.51 (q, J = 6.9 Hz, 2 H, CH2(N)), 4.84–4.91 (m, 1 H, CHN), 5.08–5.14 (m, 2 H, CH2(N)), 5.19 (s, 2 H, OCH2N), 5.48 (d, J = 6.3 Hz, 1 H, NH), 6.97 (s, 1 H, 5-Hm), 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).]

[13C NMR (90 MHz, CDCl3): δ = 15.1 (CH3(CH)=), 22.0 (CH3(CH)=), 45.5 (CH), 64.7 (CH3(CH)=), 66.7 (PhCH3), 76.0 (OCH2N), 117.3, 128.2, 128.3, 128.7, 129.2, 129.3, 130.3, 136.9, 143.7, 148.7, 155.9.]


(S)-Benzyl 1-[1-(Ethoxymethyl)-2-(furan-2-yl)-1H-imidazol-4-yl]ethylcarbamate (15)

Yield: 255 mg (55%); oil; ee ≥95%; Rf = 0.36 (SiO2; EtOAc–hexane, 5:1); [α]D20 = –27.0 (c 0.1, MeOH).

[1H NMR (360 MHz, CDCl3): δ = 0.88–0.90 (m, 3 H, CH3(CH)=), 0.96 (d, J = 6.8 Hz, 6 H, (CH2)3CH), 1.55–1.74 (m, 1 H, (CH2)3CH), 1.80 (t, J = 6.4 Hz, 2 H, CH2(N)), 3.18 (q, J = 7.0 Hz, 2 H, CH2(N)), 4.86–4.91 (m, 1 H, CHN), 5.05–5.17 (m, 4 H, CH2(N) and OCH2N), 5.54 (d, J = 8.7 Hz, 1 H, NH), 7.14 (s, 1 H, 5-Hm), 7.27–7.33 (m, 3 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).]

[13C NMR (90 MHz, CDCl3): δ = 14.8 (CH3(CH)=), 22.7 and 22.9 [(CH3)2CH], 25.1 [(CH3)2CH], 44.9 (CH3(CH)=), 47.9 (CHN), 64.2 (CH2(N)), 66.6 (PhCH3), 77.0 (OCH2N), 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, 144.6, 150.9, 156.1.]

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