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PAPER

Coupling reaction between electron-rich pyrimidinones and α-amino acids promoted by phosphonium salts†

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Coupling reaction between electron-rich 2-morpholino-4(3*H*)-pyrimidinone and nucleophilic side chains of several natural α-amino acids promoted by phosphonium salt has been developed to prepare new optically active pyrimidin-4-yl amino acids. The best results were obtained using a two-step method through the easily available benzotriazolyl-1-oxy intermediate. A detailed optimization study of this reaction is discussed.

Introduction

Non-proteinogenic amino acids, especially unnatural synthetic α-amino acids, have played a significant role in drug development.[1] Their intrinsic biological properties and structural diversity make them both valuable pharmaceuticals[2] and useful building blocks in peptide chemistry[3] Thus unnatural α-amino acids have emerged as important synthetic targets and a variety of stereoselective methods have recently been developed for their preparation.[4] These methods are mainly based on an enantioselective transformation of prochiral starting materials[4e,5] or on chiral pool synthesis by transformation of natural α-amino acids.[6] As part of our research was aimed at synthesizing novel, modified antimicrobial peptides by incorporating unnatural α-amino acids, we focused our attention on the synthesis of novel, unnatural pyrimidinyl α-amino acids. Recently, we reported the synthesis of new pyrimidinyl α-amino acids **1** and **2**[7] based on methods we established[8] (Scheme 1). In particular, pyrimidin-4-yl α-amino acids **2** were synthesized by a Mitsunobu reaction between 4(3*H*)-pyrimidinones **3** and *N*-protected methyl serinate or threoninate. Subsequent oxidation of the compounds **4** obtained with *m*-CPBA, followed by treatment with nucleophiles gave the corresponding target compounds **2**. However, under Mitsunobu conditions serine and threonine amino acids could lead to the well-documented β-elimination reaction to obtain the dehydroalanine derivatives **5**,[9] and only with *N*-trityl serine methyl ester the expected compounds **4** could be isolated in high yields (Scheme 1).[7] Besides, the Mitsunobu reaction was limited to α-amino acids with a hydroxyl group in the side chain. Therefore, we sought a method that would allow incorporation of a range of amino acid residues at position 4 of the pyrimidine ring.

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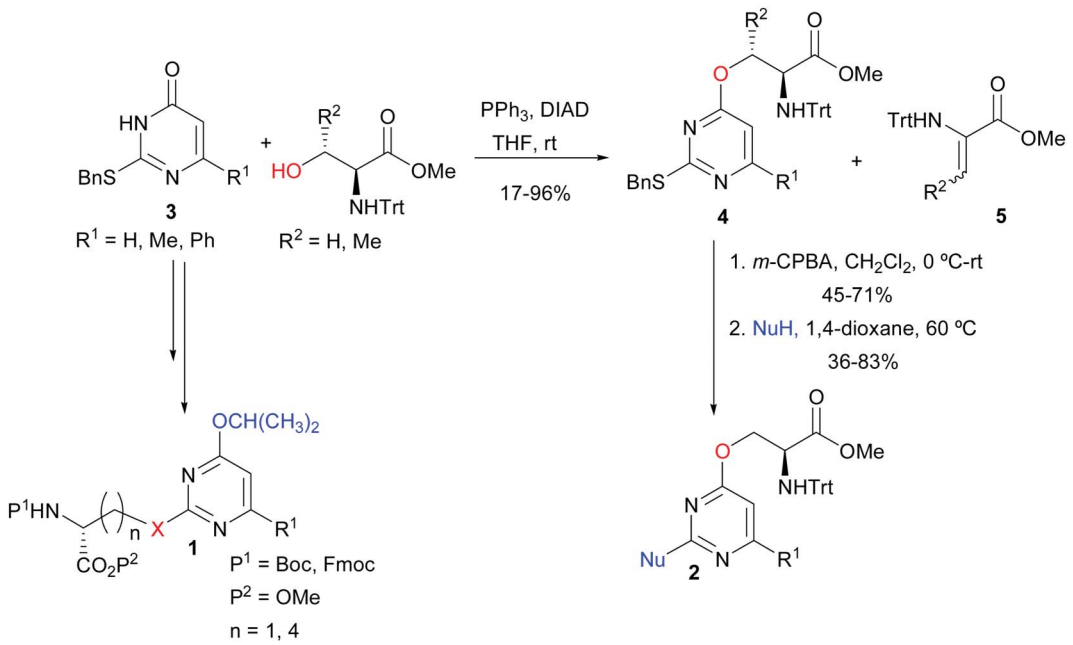
† Electronic supplementary information (ESI) available: experimental details and copies of NMR spectra (^{1}H, ^{13}C, dept, NOESY) for all new compounds.

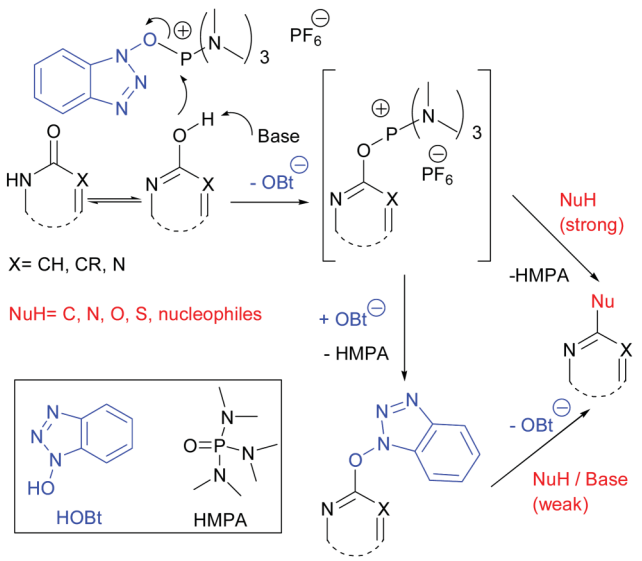
Phosphonium coupling has recently emerged as a new mild, efficient, and versatile method for direct C–C, C–N, C–O and C–S bond formations of tautomerizable heterocycles. It proceeds *via* C–OH bond activation of a tautomerizable heterocycle with a phosphonium salt, and subsequent functionalization with a nucleophile *via* S_NAr displacement.[10] Alkyl and aryl amines have been widely used as nucleophiles in this transformation, while phenol, alcohol, thiophenol, malonate, sulfonamide and nitrogen heterocyclic nucleophiles have been used less. Only a few examples of the direct amination of tautomerizable heterocycles with indoles or imidazoles *via* phosphonium coupling have been reported in the literature.[11] Mechanistic studies with phosponium reagents containing a benzotriazolyl-1-oxy (OBt) moiety, such as benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (BOP) or benzotriazole-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), showed that less reactive nucleophiles followed a stepwise pathway through OBt adducts (Scheme 2).[12] The OBt adducts were easily isolated and have been fully characterized. Phosphonium coupling with weak nucleophiles such as aryl amines, phenols or nitrogen heterocycles needed an additional base to perform the S_NAr displacement.

Results and discussion

Our studies began with the phosponium coupling of 4(3*H*)-pyrimidinone **3** with imidazole using bromo-tris-pyrrolidino-phosphonium hexafluorophosphate (PyBroP), PyBOP and BOP as coupling reagents, Et_3N or DBU as base, and acetonitrile and 1,4-dioxane as solvents. The reagent combination of BOP, DBU and acetonitrile was found to be the most effective in promoting this transformation (data not shown). We then used these optimized conditions for the coupling reaction of **3** with phenol, imidazole, n-propylamine and 3-methyl-1*H*-indole as models of amino acid side chains of tyrosine, histidine, lysine and tryptophan respectively. Pyrolidine was also used as a model of proline. As seen from Table 1, all reactions afforded the desired compounds **7** in moderate to good yields except for 3-methyl-1*H*-indole

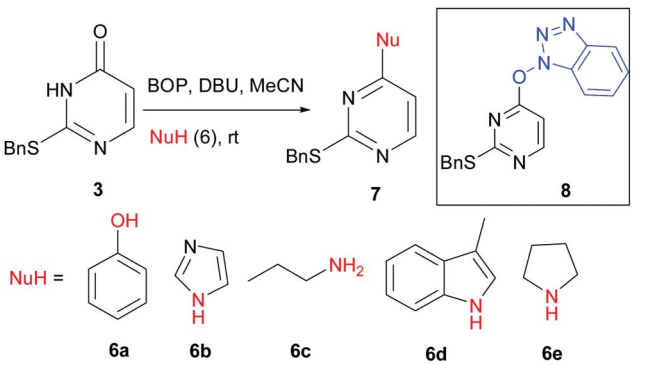


Scheme 1 Synthesis of pyrimidinyl amino acids **1** and **2**.



Scheme 2 Mechanism of phosphonium coupling using BOP.

Table 1 Direct functionalitzation of 4(3*H*)-pyrimidinone **3** promoted by BOP



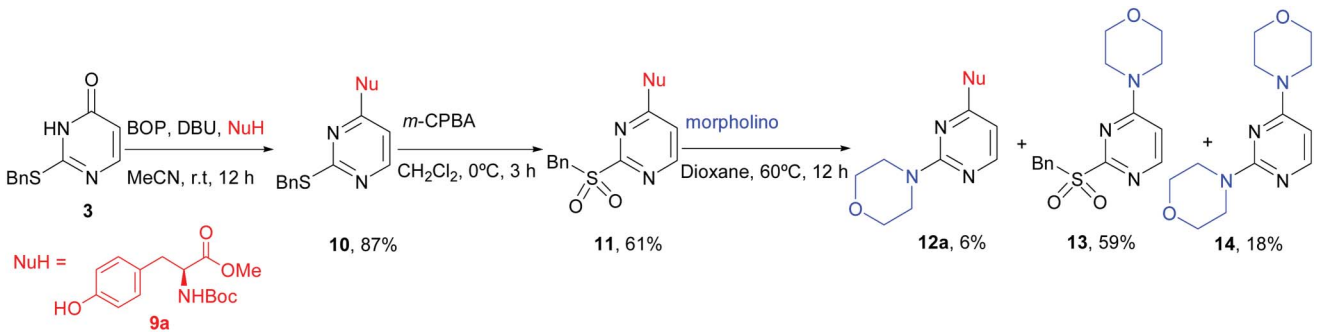
Entry	NuH	Conditions[a]	*T*/°C	*t*/h	**7**/yield (%)[b]
1	**6a**	B	rt	2	**7a**/61
2	**6b**	B	60	24	**7b**/60
3	**6c**	A	rt	12	**7c**/70
4[c]	**6d**	B	60	24	**7d**/—
5	**6e**	A	rt	3	**7e**/68

[a] Conditions **A**: **3** (1 equiv.), BOP (1.3 equiv.), DBU (1.5 equiv.), MeCN; **6** (1.3 equiv.). Conditions **B**: **3** (1 equiv.), BOP (1.3 equiv.), DBU (1.5 equiv.), MeCN; **6** (1.3 equiv.), DBU (1.5 equiv.). [b] Yields were calculated from isolated product after flash chromatography. [c] Only compound **8** (60%) was isolated.

6d. The coupling reaction with the strong nucleophiles n-propylamine, phenol and pyrrolidine proceeded efficiently at room temperature in short reaction times (entries 1, 3 and 5, Table 1). Although the coupling reaction with the weak nucleophile imidazole needed to be heated to 60 °C to reach completion, compound **7b** could be obtained in moderate yield (entry 2, Table 1). However, when we use 3-methyl-1*H*-indole **6d** as the nucleophile the reaction failed to give the expected product **7d** and only the OBt adduct **8** was isolated from the crude mixture (entry 4, Table 1).

Based on the model study, N^{α}-Boc methyl tyrosinate **9a** was engaged in a coupling reaction with 4(3*H*)-pyrimidinone **3** to afford the corresponding pyrimidin-4-yl amino ester **10** in 87% yield and without appreciable racemization[13] (Scheme 4).

Following the methodology described previously, we examined the functionalization of **10** at position 2 of the pyrimidine ring by nucleophilic displacement of the activated benzylsulfanyl group. Thus, amino ester **10** was treated with 2.5 equivalents of *m*-CPBA at 0 °C to afford the corresponding sulfone **11** in moderate yield. Unexpectedly, the subsequent *ipso*-substitution displacement of sulfone **11** with morpholine failed. The purification of the crude mixture only afforded a 6% yield of the desired compound **12a**

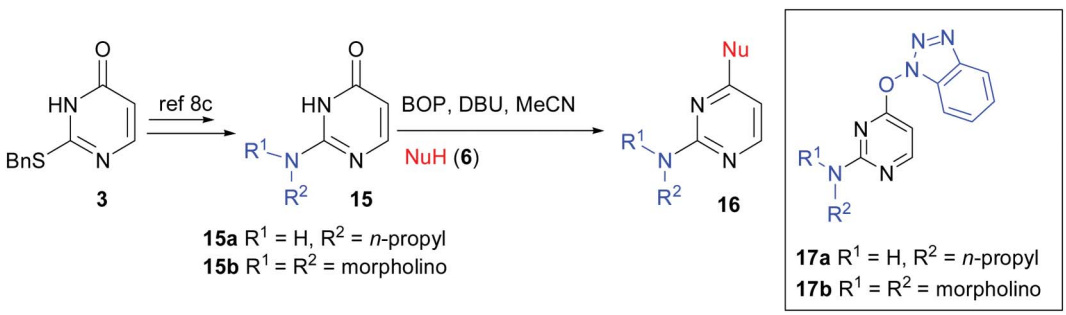


Scheme 3 Synthesis of pyrimidin-4-yl tyrosinate **12a**.

along with a large amount of compounds **13** and **14** (Scheme 3). These results clearly indicate that the phenoxy group in position 4 of pyrimidine ring undergoes aminolysis faster than bezylsulfonyl group at position 2. To circumvent this problem, we reasoned that a tyrosine residue or other amino acid residues should be incorporated at position 4 of the pyrimidine ring in the last synthetic reaction step.

Therefore, we continued to study the phosphonium coupling with 2-amino-4(3*H*)pyrimidinones **15** which were easily prepared from the pyrimidinone **3** using our previously described methodology.[8c] It has been reported that the electronic properties of the substrate likely dictate the outcome of phosphonium coupling reaction. This transformation is less efficient with electro-rich tautomerizable heterocycles.[10] For example, direct amination of 4-aminopyrimidin-2(1*H*)-one using BOP failed to yield the coupling products.[12b] Knowing this, we first examined phosphonium coupling with compound **15** using the model nucleophiles **6** (Table 2). Compared to substrate **3**, the phosphonium coupling of **15** proceeded more slowly. In all cases, heating and addition of an extra base was required to promote S_NAr displacement even though alkylamines were used. The best results were obtained for the reaction of **15b** which afforded the expected pyrimidines **16ba–e** in moderate to good yields (entries 6–11, Table 2). A direct coupling reaction between **15** and the weak nucleophile, 3-methyl-1*H*-indole **6d** could not be achieved. There was no reaction with **15a**, and only the OBt adduct **17b** was isolated when the reaction was carried out with substrate **15b** (entries 4 and 9, Table 2). To further confirm structures **17**, pyrimidinones **15** were treated with BOP (1.5 equiv.) and DBU (1.5 equiv.) at room temperature without the presence of nucleophiles **6**. While the expected OBt adduct **17a** could not be detected and only uncharacterized compounds were isolated from the crude reaction, compound **17b** was obtained in 90% yield. Next, the reaction of the OBt adduct **17b** with **6d** in the presence of K_2CO_3 led to

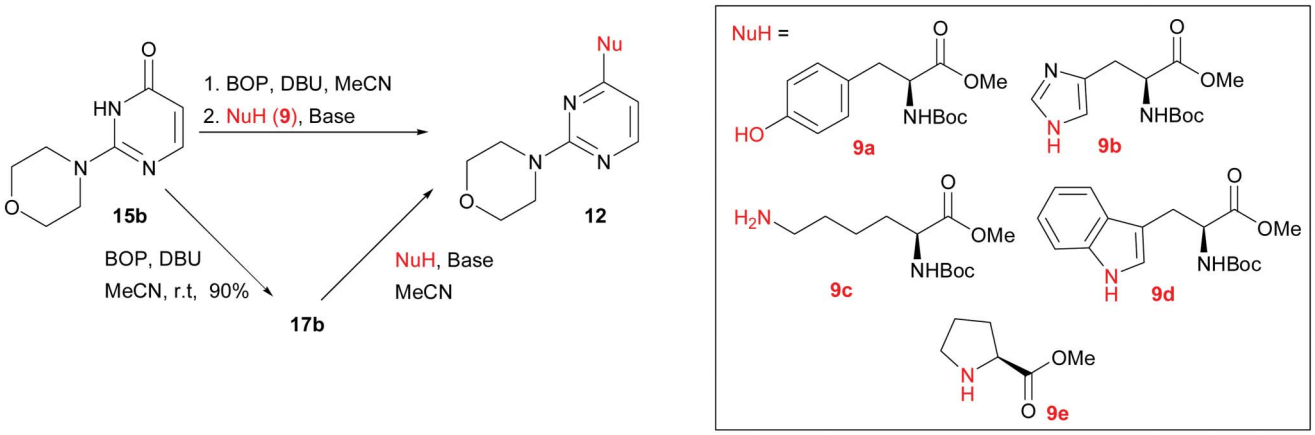
Table 2 Synthesis of pyrimidines **16**[a]



Entry	**15** or **17**	NuH	*t*/h	**16**/yield (%)[b]
1	**15a**	**6a**	48	**16aa**/63
2[c]	**15a**	**6b**	54	**16ab**/40
3	**15a**	**6c**	72	**16ac**/51
4[d]	**15a**	**6d**	60	**16ad**/—
5	**15a**	**6e**	24	**16ae**/68
6	**15b**	**6a**	24	**16ba**/68
7	**15b**	**6b**	24	**16bb**/55
8	**15b**	**6c**	24	**16bc**/82
9[e]	**15b**	**6d**	40	**16bd**/—
10[f]	**17b**	**6d**	15	**16bd**/47
11	**15b**	**6e**	24	**16be**/89

[a] Reaction conditions: **15** (1 equiv.), BOP, (1.5 equiv.), DBU (1.5 equiv.), MeCN; **6** (1.5 equiv.), DBU (1.5 equiv.), 60 °C. [b] Yields were calculated from isolated product after flash chromatography. [c] Reaction temperature was 90 °C, at 60 °C only traces of **16ab** were obtained. [d] Intermediate **17a** was not observed. [e] Only compound **17b** was isolated. [f] Reaction conditions: **17b** (1 equiv.), **6d** (1.5 equiv.), K_2CO_3 (4 equiv.), MeCN, 60 °C.

Table 3 Synthesis of pyrimidin-4-yl α-amino esters **12**



Entry	NuH	Conditions[a]	T/°C	t/h	**12**/yield (%)[b]
1	**9e**	A	60	24	**12e**/89
2	**9a**	A	60	72	**12a**/29[c,d]
3	**9a**	B	50	24	**12a**/85
4	**9b**	C	50	32	**12b**/62[c]
5[e]	**9b**	C	rt	40	**12b**/34[c]
6	**9b**	B	50	48	**12b**/20
7	**9b**	D	50	19	**12b**/72[e]
8	**9c**	B	50	48	**12c**/67[c]
9	**9c**	B	rt	76	**12c**/43
10	**9c**	B	40	42	**12c**/66
11	**9c**	D	40	24	**12c**/84[e]
12	**9d**	B	50	24	**12d**/22
13	**9d**	D	50	6 days	**12d**/11[e]

[a] Conditions A: substrate **15b** (1 equiv.), BOP (1.5 equiv.), DBU (1.5 equiv.), MeCN; **9** (1.5 equiv.), DBU (1.5 equiv.). Conditions B: substrate **17b** (1 equiv.), **9** (1.5 equiv.), K_2CO_3 (4 equiv.), MeCN. Conditions C: substrate **17b** (1 equiv.), **9** (1.5 equiv.), DBU (1.5 equiv.), MeCN. Conditions D: substrate **17b** (2.2 equiv.), **9** (1 equiv.), K_2CO_3 (4 equiv.), MeCN. [b] Yields were calculated from isolated product after flash chromatography. [c] Partial racemization was observed. [d] Compound **17b** (40%) was also isolated. [e] The excess amount of **17b** recovered by flash chromatography.

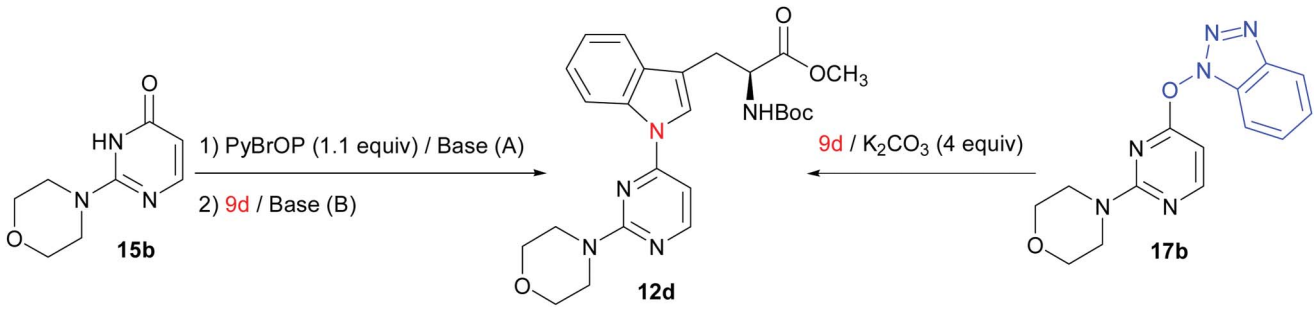
the formation of pyrimidine **16bd** in moderate yield (entry 10, Table 2).

In order to get the target pyrimidin-4-yl amino esters **12**, we extended the phosphonium coupling reaction to amino esters **9** using substrate **15b**, which afforded better results. Following the previous optimized conditions (conditions A, Table 3), we first examined N^{α}-Boc methyl tyrosinate **9a** and methyl prolinate **9e**. In the case of **9e**, the desired compound **12e** was obtained in good yield and without appreciable racemization (entry 1, Table 3). However, using **9a** the expected product **12a** was obtained in only 29% yield and partial racemization was detected (entry 2, Table 3). The long reaction time under basic conditions probably caused racemization of the tyrosinate residue. The major compound isolated in this reaction was the OBt adduct **17b**. Therefore, we decided to explore the synthesis of compounds **12** following a two-step strategy through the OBt adduct intermediate **17b**. Thus, when **9a** was treated with **17b** in the presence of K_2CO_3 at 50 °C, compound **12a** was isolated in high yield and without appreciable racemization (conditions B, entry 3, Table 3). Treatment of **17b** with N^{α}-Boc methyl histidinate **9b** using DBU as a base afforded compound **12b** in moderate yield and with considerable racemization, even at room temperature (conditions C, entries 4 and 5, Table 3). The racemization of **12b** could be completely avoided using K_2CO_3 as a base at 50 °C but the yield was lower (conditions B, entry 6, Table 3). This result was significantly improved when an excess of **17b** (2.2 equiv.) was used under the same reaction conditions (conditions D, entry 7, Table 3). It should be noted that the excess amount of **17b** was easily recovered during the purification step and could be reused.

The two nitrogen atoms of the imidazole ring of histidine are not equivalent. The nucleophilic attack could, in principle, take place by $N(\pi)$ or $N(\tau)$ atoms and consequently two regioisomers of compound **12a** would be isolated. However, all the tested reactions were completely regioselective in favor of $N(\tau)$ derivative **12a** according to a NOESY experiment. A strong NOESY correlation between H5/H5′ and H5/H2′ was observed. This result was only consistent with $N(\tau)$ regioisomer (Fig. 1).

After screening the conditions B and D at different temperatures for N^{α}-Boc methyl lysinate **9c**, the best result was achieved using an excess of **17b** (conditions D, entry 11, Table 3) and, more importantly, at a temperature below 50 °C to insure the optical purity of compound **12c** (entries 8–11, Table 3). When the reaction was carried out with N^{α}-Boc methyl tryptophanate **9d** under conditions B and D, the corresponding compound **12d** was obtained in poor yield probably due to the low nucleophilicity of the indole nitrogen atom (entries 12 and 13, Table 3). In addition, HPLC-monitoring of the progress of these reactions showed around 20–30% conversion of the starting material after

Table 4 Synthetic study of compound **12d**



Entry	**15b** or **17b** (equiv.)	**9d** (equiv.)	Base (A) (equiv.) Base (B) (equiv.)	Solvent	*T*/°C; *t* (h)	**12d**/yield (%)[a]
1	**17b** (1)	2		DMF	50 °C; 24 h	16%
2	**17b** (1)	1.5		MeCN	MW: 80 °C; 1 h	—
3	**17b** (1)	1.5		MeCN	MW: 110 °C; 1 h	traces[c]
4[b]	**15b** (1)	1.3	Et_3N (2.5) KO*t*Bu (1.3)	dioxane	rt; 45 h	—
5	**15b** (1)	1.3	Et_3N (2.5) K_2CO_3 (4)	dioxane	50 °C; 42 h	—
6	**15b** (1)	1.3	Et_3N (2.5) K_2CO_3 (4)	MeCN	MW: 80 °C; 1 h	10%
7	**15b** (1)	2	DBU (2.5) DBU (2.0)	MeCN	MW: 80 °C; 1 h	—

[a] Yields were calculated from isolated product after flash chromatography. [b] Experimental conditions reported by Kang *et al.*[11] [c] Determined by HPLC of crude material.

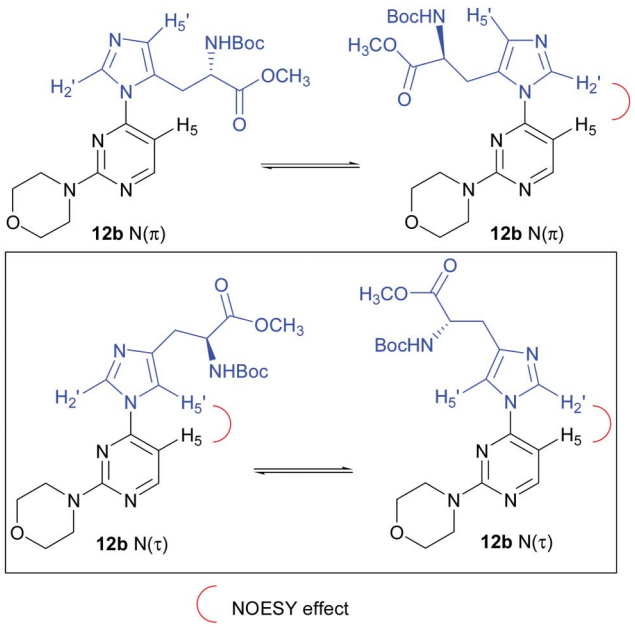


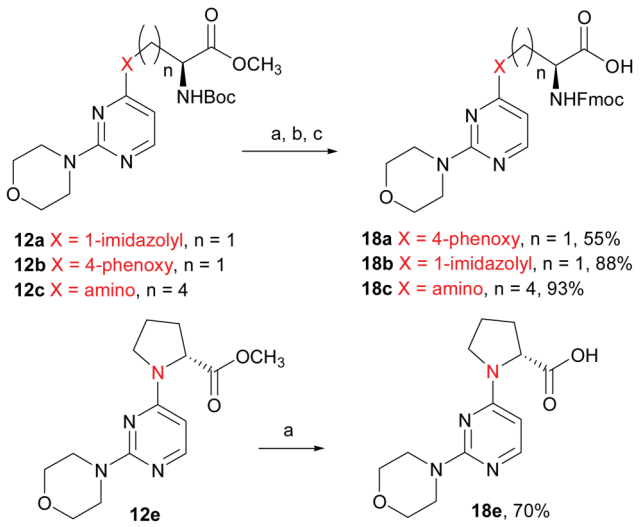
Fig. 1 NOESY experiment of compound **12b**.

24 h. Reaction times up to 24 h did not increase these reaction conversions. In an attempt to improve these results, a variety of reaction conditions were assayed (Table 4). A similar result was obtained when the reaction was carried out in DMF under conditions B (entry 1, Table 4). No reaction took place when OBt adduct **17b** was treated with **9d** using the above reaction conditions under microwave heating[14] (entries 2 and 3, Table 4). We also tested the direct coupling reaction between **15b** and **9d** using PyBroP as activating agent. PyBroP had been successfully employed by Kang *et al.* to achieve the coupling between an electro-deficient pyrimidin-2(1*H*)-one and indole.[11] However, in the case of the electron rich 2-morpholino-4(3*H*)pyrimidinone **15b**, the direct coupling reaction with **9d** promoted by PyBroP failed in each of the experimental reaction conditions tested (entries 4–7, Table 4). In general, the starting substrate **15b** was totally recovered and only a 10% yield of **12d** was obtained when Et_3N and K_2CO_3 were used as bases in MeCN at 80 °C under microwave heating (entry 6, Table 4).

To obtain useful building blocks for solid-phase peptide synthesis following Fmoc/*tert*-butyl strategy, compounds **12a–c** were converted into their corresponding N^{α}-Fmoc amino acids **18**. Thus, the methyl ester of compound **12** was deprotected using lithium hydroxide. After cleavage of the N^{α}-Boc protecting group by treatment with TFA, the free amino group was reprotected with Fmoc-Osu leading to expected compounds **18a–c** in high yields (Scheme 4). Pyrimidinyl amino acid **18e** may be also used as building block in solid-phase peptide synthesis, but it could only be incorporated into a peptide sequence as the last amino acid (Scheme 4).

Conclusion

In summary, we were able to incorporate a range of nucleophiles including amino esters residues at position 4 of an electron-rich 2-amino-4(3*H*)-pyrimidinone through a coupling reaction promoted by phosphonium salts. Except for the tryptophan derivative **12d**, the target pyrimidin-4-yl amino esters **12** were obtained in high yields using a two-step method *via* the easily available OBt adduct intermediate. We demonstrated that the



12a X = 1-imidazolyl, n = 1
12b X = 4-phenoxy, n = 1
12c X = amino, n = 4

18a X = 4-phenoxy, n = 1, 55%
18b X = 1-imidazolyl, n = 1, 88%
18c X = amino, n = 4, 93%

Scheme 4 Synthesis of N^{α}-Fmoc-pyrimidin-4-yl amino acids **18**. *Reagents and conditions*: (a) LiOH, THF : MeOH : H_2O, rt; (b) TFA : CH_2Cl_2 (1 : 1), 0 °C–rt; (c) Fmoc-OSu, $NaHCO_3$, 1,4-dioxane, rt.

base, the reaction temperature and reagent equivalents play a crucial role in obtaining compounds **12** in good yields and without racemization. This investigation shows that the phosphonium-mediated bond-forming reactions are governed by both the electronic properties of the substrates and the strength of the nucleophiles. In the case of histidine derivative **12b**, the described reaction proved to be totally regioselective in favor of $N(\tau)$ regioisomer. N^{α}-Boc-pyrimidin-4-yl amino esters **12** were easily converted into N^{α}-Fmoc-pyrimidin-4-yl amino acids **18** using standard deprotecting and protecting group procedures. The N^{α}-Fmoc-protected derivatives **18** are useful building-blocks for the solid-phase peptide synthesis following Fmoc/*tert*-butyl strategy. The study of the effect of its incorporation into bioactive peptides is currently underway.

Experimental

General remarks

All commercially available chemicals were used as purchased without further purification. Melting points (capillary tube) were measured with an Electrothermal digital melting point apparatus IA 91000 and are uncorrected. IR spectra were recorded on a Mattson-Galaxy Satellite FT-IR using a single reflection ATR system as a sampling accessory. NMR spectra were recorded on a Brucker DPX200 Advance spectrometer. ^{1}H NMR spectra were recorded at 200 or 400 MHz. ^{13}C NMR spectra and DEPT experiments were determined at 50 or 100 MHz. Spectra recorded in $CDCl_3$ were referenced to residual $CHCl_3$ at 7.26 ppm for ^{1}H or 77.0 ppm for ^{13}C. Spectra recorded in DMSO-*d6* were referenced to residual DMSO at 2.50 ppm for ^{1}H or 39.5 ppm for ^{13}C. ESI mass spectra were recorded using a Navigator quadrupole instrument. High resolution mass spectra (HRMS) were determined under conditions of ESI on a Bucker Micro Q-Tof instrument using a hybrid quadrupole time-of-flight mass spectrometer. Optical rotations were measured on a Perkin Elmer 343 Plus polarimeter, using the sodium D line. Specific rotations $[\alpha]_D$ are given in 10^{-1} cm^2 g^{-1}, and the concentration (c) is expressed in g per 100 mL. Analytical thin layer chromatography (TLC) was performed on precoated TLC plates, silica gel 60 F_{254} (Merck). Spots on TLC plates were visualized with UV/visible light (254 nm) and/or with a solution of potassium permanganate (1.5 g/100 mL H_2O). Flash chromatography (FC) purifications were performed on silica gel 60 (230–400 mesh, Merck).

General procedure for the synthesis of 2-(benzylfanyl)pyrimidines (7)

To a solution of 2-(benzylsulfanyl)pyrimidin-4(3*H*)-one **3** (100 mg, 0.46 mmol, 1.0 equiv.) and DBU (0.11 mL, 0.69 mmol, 1.5 equiv.) in acetonitrile (1.5 mL) was added BOP (265 mg, 0.6 mmol, 1.3 equiv.) and the solution was stirred at room temperature for 15 min. Next the appropriate nucleophile **6** (0.69 mmol, 1.5 equiv.) was added and the resulting mixture was stirred at the temperature specified for each compound. Upon completion of the reaction (TLC monitoring, 3–24 h), the solvent was removed under reduced pressure, and the crude material was purified by flash chromatography (n-hexane/ethyl acetate 15 : 1 to 1 : 1) to afford compounds **7**.

2-(Benzylsulfanyl)-4-phenoxypyrimidine (7a). By the general procedure, **6a** (65 mg, 0.69 mmol), and DBU (0.11 mL, 0.69 mmol) at room temperature for 2 h provided **7a** (83 mg, 61%) as a colorless solid: mp 65–69 °C; TLC: *Rf* (ethyl acetate/n-hexane, 1 : 1) 0.78; IR (neat) 3053 (CH), 2922 (CH), 1556 (CC), 1487, 1425 (CC, CN) cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.18 (s, 2H, SCH_2), 6.56 (d, J = 5.6 Hz, 1H, $H(5)_{pyrim}$), 7.14–7.34 (m, 8H, CH_{aryl}), 7.42–7.47 (m, 2H, CH_{aryl}), 8.37 (d, J = 5.6 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 34.9 (t), 103.3 (d), 121.8 (d, 2C), 125.7 (d), 126.9 (d), 128.3 (d, 2C), 128.9 (d, 2C), 129.6 (d, 2C), 137.5 (s), 152.2 (s), 158.7 (d), 168.9 (s), 171.8 (s); HRMS (ESI) *m/z*: calculated for $C_{17}H_{15}N_2OS$ $[M+H]^+$ 295.0900, found: 295.0886.

2-(Benzylsulfanyl)-4-(1*H*-imidazol-1-yl)pyrimidine (7b). By the general procedure, **6b** (47 mg, 0.69 mmol), and DBU (0.11 mL, 0.69 mmol) at 60 °C for 24 h provided **7a** (74 mg, 60%) as a colorless solid: mp 91–95 °C; TLC: *Rf* (ethyl acetate/n-hexane, 1 : 1) 0.25; IR (neat) 3136 (CH), 3070 (CH), 2955 (CH), 1573 (CC), 1484, 1446 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.42 (s, 2H, SCH_2), 6.93 (d, J = 5.4 Hz, 1H, $H(5)_{pyrim}$), 7.19 (s, 1H, $H(4)_{imd}$), 7.24–7.44 (m, 5H, CH_{aryl}), 7.60 (s, 1H, $H(5)_{imd}$), 8.37 (s, 1H, $H(2)_{imd}$), 8.54 (d, J = 5.4 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 35.4 (t), 103.5 (d), 115.6 (d), 127.3 (d), 128.6 (d, 2C), 128.7 (d, 2C), 131.4 (d), 135.0 (s), 136.8 (d), 154.5 (s), 159.3 (d), 173.0 (s). HRMS (ESI) *m/z*: calculated for $C_{14}H_{13}N_4S$ $[M+H]^+$ 269.0855, found: 269.0864.

2-(Benzylsulfanyl)-*N*-propylpyrimidin-4-amine (7c). By general procedures, **6c** (57 µL, 0.69 mmol) at room temperature for 12 h provided **7c** (83 mg, 70%) as a colorless solid: mp 39–41 °C; TLC: *Rf* (ethyl acetate/n-hexane, 1 : 1) 0.67. IR (neat) 3228 (NH), 3022 (CH), 2959 (CH), 1591 (CC), 1572, 1484 (CC, CN) cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H, CH_3), 1.61 (sext, J = 7.4 Hz, 2H, CH_2), 3.25 (q, J = 6.6 Hz, 2H, NCH_2), 4.37 (s, 2H, SCH_2), 4.92 (br, 1H, NH), 6.01 (d, J = 6.0 Hz, 1H, $H(5)_{pyrim}$), 7.21–7.44 (m, 5H, CH_{aryl}), 7.98 (d, J = 6.0 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 11.3 (q), 22.5 (t), 35.0 (t), 43.0 (t), 99.4 (d), 126.9 (d), 128.3 (d, 2C), 128.9 (d, 2C), 138.1

(s), 155.3 (d), 161.9 (s), 170.7 (s); HRMS (ESI) *m/z*: calculated for $C_{14}H_{18}N_3S$ $[M+H]^+$ 260.1216, found: 260.1218.

2-(Benzylsulfanyl)-4-(pyrrolidin-1-yl)pyrimidine (7e). By the general procedure, **6e** (57 μL, 0.69 mmol) at room temperature for 3 h provided **7e** (84 mg, 68%) as a colorless solid: mp 50–52 °C; TLC: *Rf* (ethyl acetate/n-hexane, 1 : 1): 0.75; IR (neat) 3026 (CH), 2948 (CH), 1575 (CC), 1540, 1482 (CC, CN) cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.98–2.04 (br, 4H, 2 × CH_2), 3.29–3.60 (br, 4H, 2 × NCH_2), 4.39 (s, 2H, SCH_2), 5.97 (d, J = 6.0 Hz, 1H, $H(5)_{pyrim}$), 7.20–7.31 (m, 3H, CH_{aryl}), 7.42–7.44 (m, 2H, CH_{aryl}), 7.98 (d, J = 6.0 Hz, 1H, $H(6)_{pyrim}$). ^{13}C-NMR (50 MHz, $CDCl_3$) δ 24.8 (t), 25.8 (t), 34.9 (t), 46.2 (t, 2C), 99.4 (d), 126.7 (d) 128.2 (d, 2C), 128.8 (d, 2C), 138.4 (s), 154.6 (d), 159.2 (s), 170.1 (s). HRMS (ESI) *m/z*: calculated for $C_{15}H_{17}N_3NaS$ $[M+Na]^+$ 294.1035, found: 294.1066; calculated for $C_{15}H_{18}N_3S$ $[M+H]^+$ 272.1216, found: 272.1226.

1-(2-(Benzylsulfanyl)pyrimidin-4-yloxy)-1*H*-benzo[*d*][1,2,3]triazole (8). Colorless solid: mp 131–132 °C; TLC: *Rf* (ethyl acetate/n-hexane, 1 : 1) 0.46; IR (neat) 3094 (CH), 2961 (CH), 1592 (CC), 1574 (CC), 1537, 1491, 1423 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 2H, SCH_2), 6.80 (d, J = 5.7 Hz, 1H, $H(5)_{pyrim}$), 6.90–6.93 (m, 2H, CH_{aryl}), 7.12–7.14 (m, 3H, CH_{aryl}), 7.43–7.47 (m, 2H, CH_{aryl}), 7.54–7.58 (m, 1H, CH_{aryl}), 8.08–8.10 (m, 1H, CH_{aryl}), 8.54 (d, J = 5.7 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 35.0 (t), 100.4 (d), 108.6 (d), 120.6 (d), 125.0 (d), 127.2 (d), 128.3 (d, 2C), 128.5 (d, 2C), 128.8 (s), 128.9 (d), 136.3 (s), 143.3 (s), 159.9 (d), 168.7 (s), 173.0 (s); HRMS (ESI) *m/z*: calculated for $C_{17}H_{13}N_5NaOS$ $[M+Na]^+$ 358.0733, found: 358.0717; calculated for $C_{17}H_{14}N_5OS$ $[M+H]^+$ 336.0914, found: 336.0911.

Synthesis of *tert*-butyl (*S*)-1-(methoxycarbonyl)-2-(4-(2-(benzylsulfanyl)pyrimidin-4-yloxy)phenyl)ethylcarbamate (10)

To a solution of 2-(benzylsulfanyl)pyrimidin-4(3*H*)-one **3** (100 mg, 0.46 mmol, 1.0 equiv.) and DBU (0.11 mL, 0.69 mmol, 1.5 equiv.) in acetonitrile (1.5 mL) was added BOP (265 mg, 0.6 mmol, 1.3 equiv.) and the solution was stirred at room temperature for 15 min. Then, N^{α}-Boc-(*S*)-tyrosine methyl ester **9a** (204 mg, 0.69 mmol, 1.5 equiv.) and DBU (0.11 mL, 0.69 mmol, 1.5 equiv.) were added as an acetonitrile solution (0.5 mL). The resulting mixture was stirred at room temperature. Upon completion of the reaction (TLC monitoring, 12 h), the solvent was removed under reduced pressure and the crude material was purified by flash chromatography (n-hexane/ethyl acetate, 15 : 1 to 1 : 1) affording 198 mg (87%) of compound **10** as a colorless solid: TLC: *Rf* (n-hexane/ethyl acetate, 1 : 1) 0.68; $[\alpha]_D^{20}$ +3.92 (*c* 1.95, $CHCl_3$); IR (neat) 3357 (NH), 3038 (CH), 2978 (CH), 1736 (CO), 1698 (CO), 1557, 1443 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H, C(CH_3)$_3$), 3.02 (dd, J = 13.88 Hz, J' = 5.90 Hz, 1H, C$H_{2\beta}$), 3.15 (dd, J = 13.88 Hz, J' = 5.62 Hz, 1H, C$H_{2\beta}$), 3.68 (s, 3H, OCH_3), 4.16 (s, 2H, SCH_2), 4.57–4.59 (m, 1H, CH_{α}), 5.00 (d, J = 7.6 Hz, 1H, NH), 6.50 (d, J = 5.80 Hz, 1H, $H(5)_{pyrim}$), 7.07 (d, J = 8.8 Hz, 2H, CH_{aryl}), 7.15–7.23 (m, 7H, CH_{aryl}), 8.33 (d, J = 5.80 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$, 25 °C) δ 28.2 (q, 3C), 35.0 (t), 37.8 (t), 52.2 (q), 54.4 (d), 80.0 (s), 103.3 (d), 121.7 (d, 2C), 127.0 (d), 128.2 (d, 2C), 128.9 (d, 2C), 130.4 (d, 2C), 133.7 (s), 137.5 (s), 151.2 (s), 154.9 (s), 158.7 (d), 168.7 (s), 171.8 (s), 172.0 (s); HRMS (ESI) *m/z*: calculated for $C_{26}H_{29}KN_3O_5S$ $[M+K]^+$ 534.1460, found 534.1460; calculated for $C_{26}H_{29}N_3NaO_5S$ $[M+Na]^+$ 518.1720, found 518.1724; calculated for $C_{26}H_{30}N_3O_5S$ $[M+H]^+$ 496.1901, found 496.1910.

Synthesis of *tert*-butyl (*S*)-1-(methoxycarbonyl)-2-(4-(2-(benzylsulfonyl)pyrimidin-4-yloxy)phenyl)ethylcarbamate (11)

Compound **10** (120 mg, 0.24 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (2.5 mL). The solution was cooled in an ice bath and *m*-CPBA (118 mg, 5.23 mmol, 2.2 equiv.) was added in small portions. The resulting mixture was warmed to room temperature and stirred during 3 h. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the residue was dissolved in AcOEt (10 mL), washed with saturated $NaHCO_3$ solution (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (n-hexane/ethyl acetate, 10 : 1 to 1 : 1) affording 78 mg (61%) of compound **11** as a colorless solid: TLC: *Rf* (n-hexane/ethyl acetate, 1 : 1) 0.40; $[\alpha]_D^{20}$ +10.28 (*c* 0.7, $CHCl_3$); IR (neat) 3380 (NH), 3040 (CH), 2972 (CH), 1741 (CO), 1711 (CO), 1570, 1543, 1434, (CC, CN), 1310 (SO) cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1.42 (s, 9H, C(CH_3)$_3$), 3.06 (dd, J = 13.80 Hz, J' = 6.50 Hz, 1H, C$H_{2\beta}$), 3.17 (dd, J = 13.80 Hz, J' = 5.7 Hz, 1H, C$H_{2\beta}$), 3.70 (s, 3H, OCH_3), 4.59 (br. s, 3H, SCH_2 and CH_{α}), 5.03 (d, J = 7.8 Hz, 1H, NH), 6.98 (d, J = 5.80 Hz, 1H, $H(5)_{pyrim}$), 7.11 (d, J = 8.5 Hz, 2H, CH_{aryl}), 7.22–7.30 (m, 7H, CH_{aryl}), 8.67 (d, J = 5.80 Hz, 1H, $H(6)_{pyrim}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.3 (q, 3C), 38.0 (t), 52.3 (q), 54.5 (d), 57.1 (t), 80.1 (s), 110.8 (d), 121.3 (d, 2C), 126.7 (s), 128.6 (d, 2C), 128.8 (d), 130.9 (d, 2C), 131.3 (d, 2C), 134.8 (s), 150.7 (s), 155.0 (s), 159.6 (d), 164.9 (s), 169.9 (s), 172.0 (s); HRMS (ESI) *m/z*: calculated for calculated for $C_{26}H_{29}N_3NaO_7S$ $[M+Na]^+$ 550.1618, found 550.1621.

General procedure for the synthesis of 2-aminopyrimidines (16)

The appropriate 2-aminopyrimidin-4(3*H*)-one **15** (1.0 equiv.), DBU (1.5 equiv.) and BOP (1.5 equiv.) were dissolved in acetonitrile (3 mL $mmol^{-1}$) and the resulting solution was stirred at room temperature for 15 min. Next the corresponding nucleophile **6** (1.5 equiv.) and DBU (1.5 equiv.) were added and the resulting mixture was stirred at the temperature specified for each compound. Upon completion of the reaction (TLC monitoring, 24–72 h), the solvent was removed under reduced pressure, and the crude material was purified by flash chromatography (n-hexane/ethyl acetate 15 : 1 to 1 : 2) to afford compounds **16**.

4-Phenoxy-*N*-propylpyrimidin-2-amine (16aa). By the general procedure, **15a** (100 mg, 0.65 mmol), BOP (433 mg, 0.98 mmol), DBU (0.29 mL, 1.95 mmol) and **6a** (93 mg, 0.98 mmol) at 90 °C for 54 h provided **16aa** (94 mg, 63%) as a colorless oil: TLC: *Rf* (CH_2Cl_2/CH_3OH, 10 : 1) 0.44; IR (neat) 3262 (NH), 3039 (CH), 2961 (CH), 1626 (CC), 1581, 1530, 1454 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H, CH_3), 1.65 (sext, J = 7.3 Hz, 2H, CH_2), 3.40 (br, 2H, NCH_2), 5.21 (br, 1H, NH), 5.98 (d, J = 5.4 Hz, 1H, $H(5)_{pyrim}$), 7.12–7.14 (m, 2H, CH_{aryl}), 7.20–7.26 (m, 1H, CH_{aryl}), 7.36–7.41 (m, 2H, CH_{aryl}), 8.09 (d, J = 5.4 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.3 (q), 22.7 (t), 43.2 (t), 96.1 (d), 121.7 (d, 2C), 125.3 (d), 129.5 (d, 2C), 152.6 (s),

159.5 (d), 162.6 (s), 170.1 (s); HRMS (ESI) *m/z*: calculated for $C_{13}H_{16}N_3O$ $[M+H]^+$ 230.1288, found: 230.1288.

4-(1*H*-Imidazol-1-yl)-*N*-propylpyrimidin-2-amine (16ab). By the general procedure, **15a** (100 mg, 0.65 mmol), BOP (433 mg, 0.98 mmol), DBU (0.29 mL, 1.95 mmol) and **6b** (67 mg, 0.98 mmol) at 60 °C for 48 h provided **16ab** (53 mg, 40%) as a colorless solid: mp 103–105 °C; TLC: *Rf* (CH_2Cl_2/CH_3OH, 10 : 1) 0.42; IR (neat) 3246 (NH), 3072 (CH), 2959 (CH), 1626 (CC), 1607, 1582, 1538, 1498 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.2 Hz, 3H, CH_3), 1.65 (sext, J = 7.2 Hz, 2H, CH_2), 3.40 (q, J = 6.7 Hz, 2H, NCH_2), 5.64 (br, 1H, N*H*), 6.52 (d, J = 5.2 Hz, 1H, $H(5)_{pyrim}$), 7.18 (s, 1H, $H(4)_{imd}$), 7.61 (s, 1H, $H(5)_{imd}$), 8.31 (s, 1H, $H(2)_{imd}$), 8.54 (br, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.4 (q), 22.6 (t), 43.3 (t), 97.0 (d), 115.8 (d), 130.6 (d), 135.1 (d), 155.5 (s), 160.1 (d), 162.3 (s); HRMS (ESI) *m/z*: calculated for $C_{10}H_{14}N_5$ $[M+H]^+$ 204.1244, found: 204.1242.

***N*^{2},*N*^{4}-Dipropylpyrimidin-2,4-diamine (16ac).** By the general procedure, **15a** (100 mg, 0.65 mmol), BOP (433 mg, 0.98 mmol), DBU (0.29 mL, 1.95 mmol) and **6c** (80 µL, 0.98 mmol) at 60 °C for 72 h provided **16ac** (64 mg, 51%) as a colorless oil: TLC: *Rf* (CH_2Cl_2/CH_3OH, 9 : 1) 0.39; IR (neat) 3277 (NH), 2959 (CH), 1585 (CC), 1498, 1460, 1436 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4 Hz, 3H, CH_3), 0.95 (t, J = 7.4 Hz, 3H, CH_3), 1.53–1.64 (m, 4H, 2 × CH_2), 3.19–3.21 (m, 2H, NCH_2), 3.27–3.32 (m, 2H, NCH_2), 4.72 (br, 1H, N*H*), 4.90 (br, 1H, N*H*), 5.66 (d, J = 5.6 Hz, 1H, $H(5)_{pyrim}$), 7.80 (d, J = 5.6 Hz, 1H, $H(6)_{pyrim}$). ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.4 (q), 11.5 (q), 22.7 (t), 23.0 (t), 43.0 (t), 43.1 (t), 93.7 (d), 156.0 (d), 162.2 (s), 163.1 (s); HRMS (ESI) *m/z*: calculated for $C_{10}H_{19}N_4$ $[M+H]^+$ 195.1604, found: 195.1598.

***N*-Propyl-4-(pyrrolidin-1-yl)pyrimidin-2-amine (16ae).** By the general procedure, **15a** (100 mg, 0.65 mmol), BOP (433 mg, 0.98 mmol), DBU (0.29 mL, 1.95 mmol) and **6e** (80 µL, 0.98 mmol) at 60 °C for 24 h provided **16ae** (91 mg, 68%) as a colorless solid: mp 97–98 °C; TLC: *Rf* (CH_2Cl_2/CH_3OH, 10 : 1) 0.40; IR (neat) 3237 (NH), 2959 (CH), 1596 (CC), 1569, 1527, 1416 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J = 7.4 Hz, 3H, CH_3), 1.60 (sext, J = 7.2 Hz, 2H, CH_2), 1.95 (br, 4H, 2 × CH_2), 3.30–3.34 (m, 2H, NCH_2), 3.42 (br, 4H, 2 × CH_2), 5.11 (br, 1H, N*H*), 5.65 (d, J = 6.0 Hz, 1H, $H(5)_{pyrim}$), 7.77 (d, J = 6.0 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.5 (q), 22.9 (t), 25.2 (t, 2C), 43.1 (t), 46.1 (t, 2C), 94.0 (d), 156.0 (d), 160.5 (s), 161.3 (s); HRMS (ESI) *m/z*: calculated for $C_{11}H_{19}N_4$ $[M+H]^+$ 207.1604, found: 207.1609.

2-Morpholino-4-phenoxypyrimidine (16ba). By the general procedure, **15b** (100 mg, 0.55 mmol), BOP (367 mg, 0.83 mmol), DBU (0.25 mL, 1.65 mmol) and **6a** (78 mg, 0.83 mmol) at 60 °C for 24 h provided **16ba** (96 mg, 68%) as a colorless solid: mp 99–103 °C; TLC: *Rf* (CH_2Cl_2/CH_3OH, 20 : 1) 0.80; IR (neat) 2956 (CH), 2921 (CH), 1583 (CC), 1551, 1462 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.63–3.73 (m, 8H, CH_{2morph}) 6.03 (d, J = 5.6 Hz, 1H, $H(5)_{pyrim}$), 7.12–7.14 (m, 2H, CH_{aryl}), 7.21–7.26 (m, 1H, CH_{aryl}), 7.37–7.41 (m, 2H, CH_{aryl}), 8.17 (d, J = 5.6 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 44.2 (t, 2C), 66.6 (t, 2C), 96.2 (d), 121.6 (d, 2C), 125.4 (d), 129.5 (d, 2C), 152.5 (s), 158.7 (d), 161.2 (s), 170.0 (s); HRMS (ESI) *m/z*: calculated for $C_{14}H_{16}N_3O_2$ $[M+H]^+$ 258.1237, found: 258.1248.

4-(1*H*-Imidazol-1-yl)-2-morpholinopyrimide (16bb). By the general procedure, **15b** (100 mg, 0.55 mmol), BOP (367 mg, 0.83 mmol), DBU (0.25 mL, 1.65 mmol) and **6b** (56 mg, 0.83 mmol) at 60 °C for 24 h provided **16bb** (70 mg, 55%) as a colorless solid: mp 114–116 °C; TLC: *Rf* (CH_2Cl_2/CH_3OH, 10 : 1) 0.48; IR (neat) 3012 (CH), 2959 (CH), 1626 (CC), 1607, 1582, 1538, 1498 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.76–3.79 (m, 4H, 2 × $NCH_{2\,morph}$), 3.83–3.86 (m, 4H, 2 × $OCH_{2\,morph}$), 6.53 (d, J = 5.2 Hz, 1H, $H(5)_{pyrim}$), 7.17 (s, 1H, $H(4)_{imd}$), 7.58 (d, J = 0.8 Hz, 1H, $H(5)_{imd}$), 8.35 (s, 1H, $H(2)_{imd}$), 8.36 (d, J = 5.2 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 44.4 (t, 2C), 66.9 (t, 2C), 97.2 (d), 115.9 (d), 131.2 (d), 135.2 (d), 155.5 (s), 160.4 (d), 161.7 (s); HRMS (ESI) *m/z*: calculated for $C_{11}H_{14}N_5O$ $[M+H]^+$ 232.1193, found: 232.1183.

2-Morpholino-*N*-propylpyrimidin-4-amine (16bc). By the general procedure, **15b** (100 mg, 0.55 mmol), BOP (367 mg, 0.83 mmol), DBU (0.25 mL, 1.65 mmol) and **6c** (68 µL, 0.83 mmol) at 60 °C for 24 h provided **16bc** (99 mg, 82%) as a colorless oil: TLC: *Rf* (CH_2Cl_2/CH_3OH, 9 : 1) 0.48; IR (neat) 3347 (NH), 2958 (CH), 1579 (CC), 1478, 1432 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0.97 (t, J = 7.4 Hz, 3H, CH_3), 1.60 (sext, J = 7.3 Hz, 2H, CH_2), 3.24–3.26 (m, 2H, NCH_2), 3.68–3.79 (m, 8H, CH_{2morph}), 4.92 (br, 1H, N*H*), 5.73 (d, J = 5.6 Hz, 1H, $H(5)_{pyrim}$), 7.85 (d, J = 5.6 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 11.6 (q), 22.7 (t), 43.0 (t), 44.4 (t, 2C), 66.9 (t, 2C), 94.3 (d), 154.8 (d), 160.9 (s), 162.8 (s); HRMS (ESI) *m/z*: calculated for $C_{11}H_{19}N_4O$ $[M+H]^+$ 223.1553, found: 223.1554.

2-Morpholino-*N*-propylpyrimidin-4-amine (16be). By the general procedure, **15b** (100 mg, 0.55 mmol), BOP (367 mg, 0.83 mmol), DBU (0.25 mL, 1.65 mmol) and **6e** (68 µL, 0.83 mmol) at 60 °C for 15 h provided **16be** (115 mg, 89%) as a colorless solid: mp 97–102 °C; TLC: *Rf* (CH_2Cl_2/CH_3OH, 9 : 1) 0.60; IR (neat) 2957 (CH), 1582 (CC), 1551, 1462, 1434 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.99 (br, 4H, 2 × CH_2), 3.36–3.53 (m, 4H, 2 × NCH_2), 3.72–3.82 (m, 8H, CH_{2morph}), 5.71 (d, J = 5.8 Hz, 1H, $H(5)_{pyrim}$), 7.85 (d, J = 5.8 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 25.1 (t, 2C), 44.3 (t, 2C), 45.9 (t, 2C), 66.9 (t, 2C), 94.2 (d), 154.9 (d), 160.3 (s), 161.2 (s); HRMS (ESI) *m/z*: calculated for $C_{12}H_{19}N_4O$ $[M+H]^+$ 235.1553, found: 235.1557.

Synthesis of 1-(2-morpholinopyrimidin-4yloxy)-1*H*-benzo[*d*]-[1,2,3] triazole (17b). To a solution of 2-morpholinopyrimidin-4(3*H*)-one **15b** (1.5 g, 8.28 mmol, 1 equiv.) and DBU (1.86 mL, 12.42 mmol, 1.5 equiv.) in acetonitrile (25 mL) was added BOP (4.4 g, 9.94 mmol, 1.2 equiv.) and the resulting mixture was stirred at room temperature. Upon completion of the reaction (TLC monitoring, 5 h), the solvent was removed under reduced pressure and the crude material was purified by flash chromatography (n-hexane/ethyl acetate, 20 : 1 to 15 : 1) affording 2.22 g (90%) of compound **17b** as a colorless solid: mp 105–106 °C; TLC: *Rf* (n-hexane/ethyl acetate, 1 : 1) 0.38; IR (neat) 3073 (CH), 2982 (CH), 1619 (CC), 1539, 1510, 1435 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.33–3.49 (m, 8H, CH_{2morph}), 6.27 (d, J = 5.52 Hz, 1H, $H(5)_{pyrim}$), 7.38–7.44 (m, 3H, CH_{aryl}), 7.48–7.52 (m, 1H, CH_{aryl}), 8.06 (d, J = 8.38 Hz, 1H, CH_{aryl}), 8.29 (d, J = 5.52 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 44.1 (t, 2C), 66.6 (t, 2C), 93.1 (d), 109.1 (d), 120.6 (d), 124.9 (d), 128.7 (d), 129.2 (s), 143.49 (s), 160.9 (d), 161.3 (s), 169.8 (s); HRMS (ESI) *m/z*:

calculated for $C_{14}H_{14}N_6NaO_2$ $[M+Na]^+$ 321.1070, found 321.1072; calculated for $C_{14}H_{15}N_6O_2$ $[M+H]^+$ 299.1251, found: 299.1243.

Synthesis of 3-methyl-1-(2-morpholinopyrimidin-4-yl)-1*H*-indole (16bd)

3-Methyl-1*H*-indole **6d** (65 mg, 0.5 mmol, 1.5 equiv.) and K_2CO_3 (91 mg, 0.66 mmol, 4 equiv.) were dissolved in acetonitrile (1 mL) and the resulting mixture was stirred at room temperature for 15 min. Then, OBt-adduct **17b** (100 mg, 0.33 mmol, 1 equiv.) was added as an acetonitrile solution (0.5 mL) and the reaction mixture was stirred at 60 °C. Upon completion of the reaction (TLC monitoring, 15 h), the solvent was removed under reduced pressure and the crude material was purified by flash chromatography (n-hexane/ethyl acetate, 20 : 1 to 10 : 1) affording 46 mg (47%) of compound **16bd** as a colorless solid: mp 122–124 °C; TLC: *Rf* (n-hexane/ethyl acetate, 1 : 1) 0.44; IR (neat) 3035 (CH), 2971 (CH), 1599 (CC), 1553, 1550, 1478, 1459 (CC, CN) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 2.34 (d, J = 1.2 Hz, 3H, CH_3), 3.82–3.84 (m, 4H, 2 × NCH_{2morph}), 3.89–3.92 (m, 4H, 2 × OCH_{2morph}), 6.63 (d, J = 5.6 Hz, 1H, $H(5)_{pyrim}$), 7.23–7.27 (m, 1H, CH_{aryl}), 7.31–7.35 (m, 1H, 1H, CH_{aryl}), 7.47 (d, J = 1.2 Hz, 1H, $H(2)_{indol}$), 7.56–7.58 (m, 1H, 2H, CH_{aryl}), 8.31 (d, J = 5.6 Hz, 1H, $H(6)_{pyrim}$), 8.34–8.36 (m, 1H, 2H, CH_{aryl}); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 9.7 (q), 44.5 (t, 2C), 66.9 (t, 2C), 98.3 (d), 114.8 (d), 116.4 (s), 119.2 (d), 121.7 (d), 122.1 (d), 123.7 (d), 131.7 (s), 135.3 (s), 158.5 (s), 158.6 (d), 161.8 (s); HRMS (ESI) m/z: calculated for $C_{17}H_{19}N_4O$ $[M+H]^+$ 295.1553, found: 295.1559.

General procedures for the synthesis of pyrimidin-4-yl amino esters 12

Method A: to a solution of 2-morpholinopyrimidin-4(3*H*)-one **15b** (84 mg, 0.46 mmol, 1.0 equiv.) and DBU (0.11 mL, 0.69 mmol, 1.5 equiv.) in acetonitrile (1.5 mL) was added BOP (305 mg, 0.69 mmol, 1.5 equiv.) and the solution was stirred at room temperature for 15 min. Then, the appropriate amino ester **9** (0.69 mmol, 1.5 equiv.) and DBU (0.11 mL, 0.69 mmol, 1.5 equiv.) were added as an acetonitrile solution (0.5 mL). The resulting mixture was stirred at 60 °C. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude material was purified by flash chromatography (n-hexane/ethyl acetate, 15 : 1 to 1 : 1) to afford compounds **12**. **Method B**: the appropriate amino esters **9** (1.5 equiv.) and K_2CO_3 (4 equiv.) were dissolved in acetonitrile (2.5 mL $mmol^{-1}$ of **9**). The resulting mixture was stirred at room temperature for 15 min. Then, OBt-adduct **17b** (1 equiv.) was added as an acetonitrile solution (0.5 mL $mmol^{-1}$ of **17b**) and the reaction mixture was stirred at the temperature specified for each compound. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude material was purified by flash chromatography (n-hexane/ethyl acetate, 15 : 1 to 1 : 1) to afford compounds **12**. **Method C**: the appropriate amino ester **9** (1.5 equiv.) and DBU (1.5 equiv.) were dissolved in acetonitrile (2.5 mL $mmol^{-1}$ of **9**) and the resulting mixture was stirred at room temperature for 15 min. Then, OBt-adduct **17b** (1 equiv.) was added as an acetonitrile solution (0.5 mL $mmol^{-1}$ of **17b**) and the reaction mixture was stirred at the temperature specified for each compound. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude material was purified by flash chromatography (n-hexane/ethyl acetate, 15 : 1 to 1 : 1) to afford compounds **12**. **Method D**: the appropriate amino ester **9** (1.0 equiv.) and K_2CO_3 (4 equiv.) were dissolved in acetonitrile (2.5 mL $mmol^{-1}$ of **9**) and the resulting mixture was stirred at room temperature for 15 min. Then, OBt-adduct **17b** (2.2 equiv.) was added as an acetonitrile solution (0.5 mL $mmol^{-1}$ of **17b**) and the reaction mixture was stirred at the temperature specified for each compound. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure and the crude material was purified by flash chromatography (n-hexane/ethyl acetate, 15 : 1 to 1 : 1) to afford compounds **12**.

***tert*-Butyl (*S*)-1-(methoxylcarbonyl)-2-(4-(2-morpholinopyrimidin-*N*-yloxy) phenyl) ethylcarbamate (12a).** Synthesized according to general procedure method **B** from N^{α}-Boc-(*S*)-tyrosine methyl ester **9a** (146 mg, 0.49 mmol), K_2CO_3 (91 mg, 0.66 mmol) and OBt-adduct **17b** (100 mg, 0.33 mmol) at 50 °C during 24 h. Before flash chromatography, the crude material was diluted in ethyl acetate (10 mL) and washed with 1 M NaOH (2 × 5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure.[15] Finally, the resulting residue was purified by flash chromatography affording 128 mg (85%) of compound **12a** as a colorless solid: mp 118–119 °C; TLC: *Rf* (n-hexane/ethyl acetate, 1 : 1) 0.41; $[\alpha]_D^{25}$ +25.48 (*c* 0.11, MeOH); IR (neat) 3339 (NH), 1735 (CO), 1683 (CO), 1588 (CC), 1499, 1438, (CC, CN), 1290, 1230, 1163 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H, C(CH_3)$_3$), 3.02 (dd, J = 14.01 Hz, J' = 6.31 Hz, 1H, C$H_{2\beta}$), 3.11 (dd, J = 14.01 Hz, J' = 5.55 Hz, 1H, C$H_{2\beta}$), 3.65–3.68 (m, 8H, CH_{2morph}), 3.69 (s, 3H, OCH_3), 4.57 (m, 1H, CH_{α}), 4.99 (d, J = 8.0 Hz, 1H, NH)), 5.99 (d, J = 5.58 Hz, 1H, $H(5)_{pyrim}$), 7.03 (d, J = 8.51 Hz, 2H, CH_{aryl}), 7.12 (d, J = 8.51 Hz, 2H, CH_{aryl}), 8.13 (d, J = 5.58 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.9 (q, 3C), 38.5 (t), 44.7 (t, 2C), 52.8 (q), 55.0 (d), 67.3 (t, 2C), 80.6 (s), 96.7 (d), 122.4 (d, 2C), 130.9 (d, 2C), 133.8 (s), 152.3 (s), 155.6 (s), 159.9 (d), 162.3 (s), 170.5 (s), 172.7 (s); HRMS (ESI) m/z: calculated for $[M+Na]^+$ 481.2058, found 481.2053; calculated for $C_{23}H_{31}N_4O_6$ $[M+H]^+$ 459.2238, found 459.2240.

***tert*-Butyl (*S*)-1-(methoxylcarbonyl)-2-(1-(2-morpholinopyrimidin-*N*-yl)-1*H*-imidaz-4-yl)ethylcarbamate (12b).** By the general procedure method **D**, N^{α}-Boc-(*S*)-histidine methyl ester **9b** (89 mg, 0.33 mmol), K_2CO_3 (96 mg, 0.67 mmol) and OBt-adduct **17b** (200 mg, 0.67 mmol), at 50 °C for 19 h provided **12b** (102 mg, 72%) as a colorless solid: mp 60–62 °C; TLC: *Rf* (n-hexane/ethyl acetate, 1 : 1): 0.47; $[\alpha]_D^{25}$ +10.65 (*c* 0.17, MeOH); IR (neat) 3692 (NH), 1741 (CO), 1706 (CO), 1595 (CC), 1552, 1479, 1442, (CC, CN), 1345, 1161 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H, C(CH_3)$_3$), 3.09–3.17 (m, 2H, C$H_{2\beta}$), 3.70 (s, 3H, OCH_3), 3.74–3.89 (m, 8H, CH_{2morph}), 4.61–4.66 (m, 1H, CH_{α}), 5.81 (d, J = 8 Hz, 1H, NH), 6.50 (d, J = 5.4 Hz, 1H, $H(5)_{pyrim}$), 7.41 (d, J = 1.12 Hz, 1H, $H(5)_{imd}$), 8.23 (d, J = 1.12 Hz, $H(2)_{imd}$), 8.38 (d, J = 5.4 Hz, 1H, $H(6)_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 28.4 (q, C), 30.5 (t), 44.3 (t, 2C), 52.4 (q), 53.3 (d), 66.8 (t, 2C), 79.8 (s), 96.8 (d), 113.3 (d), 134.8 (d), 139.4 (s), 155.1 (s), 155.6 (s), 160.3 (d), 161.5 (s), 172.5 (s); HRMS (ESI) m/z: calculated for $[M+Na]^+$ 455.2056, found 455.2038; calculated for $C_{20}H_{29}N_6O_5$ $[M+H]^+$ 433.2194, found 433.2208.

***tert*-Butyl (*S*)-1-(methoxylcarbonyl)-5-(1-(2-morpholinopyrimidin-*N*-ylamino)pentylcarbamate (12c).** By the general procedure method **D**, N^{α}-Boc-(*S*)-lysine methyl ester **9c** (855.4 mg, 0.33 mmol), K_2CO_3 (96 mg, 0.67 mmol) and OBt-adduct **17b** (200 mg, 0.67 mmol) at 40 °C for 24 h provided **12c** (117 mg, 84%) as a colorless oil: TLC: *Rf* (n-hexane/ethyl acetate, 1 : 4): 0.40; $[\alpha]_D^{25}$ −6.07 (*c* 0.28, MeOH); IR (neat) 3364 (NH), 2982 (CH), 1740 (CO), 1708 (CO), 1583, 1480, 1434, (CC, CN), 1244, 1159 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.38–1.46 (m, 2H, CH_2), 1.41 (s, 9H, C(CH_3)$_3$), 1.52–1.85 (m, 4H, 2 × CH_2), 3.19–3.28 (m, 2H, NCH_2), 3.71–3.72 (m, 11H, CH_{2morph} and OCH_3), 4.27–4.29 (m, 1H, CH_{α}), 4.73 (br, 1H, N*H*), 5.06 (d, *J* = 7.6 Hz, 1H, N*H*), 5.66 (d, *J* = 6.4 Hz, 1H, *H*(5)$_{pyrim}$), 7.85 (d, *J* = 6.4 Hz, 1H, *H*(6)$_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 22.7 (t), 28.3 (q, 3C), 28.8 (t), 32.6 (t), 40.7 (t), 44.2 (t, 2C), 52.2 (q), 53.0 (d), 66.8 (t, 2C), 79.9 (s), 94.2 (d), 155.3 (d), 161.6 (s), 162.7 (s), 173.1 (s), 175.5 (s); HRMS (ESI) *m*/*z*: calculated for $C_{20}H_{34}N_5O_5$ $[M+H]^+$ 424.2554, found 424.2571.

***tert*-Butyl (*S*)-1-(methoxylcarbonyl)-2-(1-(2-morpholinopyrimidin-*N*-ly)-1,3-dihydroind-3-yl)ethylcarbamate (12d).** By the general procedure method **B**, N^{α}-Boc-(*S*)-tryptophan methyl ester **9d** (157 mg, 0.49 mmol), K_2CO_3 (96 mg, 0.67 mmol) and OBt-adduct **17b** (100 mg, 0.33 mmol) at 50 °C for 24 h provided **12d** (35 mg, 22%) as a colorless solid: TLC: *Rf* (n-hexane/ethyl acetate, 1 : 1): 0.35; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.41 (s, 9H, C(CH_3)$_3$), 3.23 (dd, *J* = 14.8 Hz, *J′* = 5.8 Hz, 1H, C$H_{2\beta}$), 3.31 (dd, *J* = 14.8, *J′* = 5.5 Hz, 1H, C$H_{2\beta}$), 3.69 (s, 3H, OCH_3), 3.81–3.91 (m, 8H, CH_{2morph}), 4.68 (m, 1H, CH_{α}), 5.11 (d, *J* = 7.9 Hz, 1H, N*H*), 6.62 (d, *J* = 5.5 Hz, *H*(5)$_{pyrim}$), 7.24–7.26 (m, 1H, *H*(5)$_{indol}$), 7.30–7.43 (m, 1H, *H*(6)$_{indol}$), 7.54–7.56 (m, 2H, *H*(4)$_{indol}$ and *H*(7)$_{indol}$), 8.30 (d, *J* = 0.7 Hz, 1H, *H*(2)$_{indol}$), 8.32 (d, *J* = 5.5 Hz, 1H, *H*(6)$_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 27.9 (q), 28.3 (q), 29.6 (t), 44.4 (t, 2C), 52.3 (q), 53.6 (d), 66.8 (t, 2C), 80.0 (s), 98.5 (d), 114.7 (d), 114.9 (s), 119.1 (d), 121.9 (d), 123.3 (s), 123.9 (d), 130.9 (s), 135.2 (d), 155.1 (s),158.4 (s), 158.9 (d), 161,7 (s), 172.4 (s); HRMS (ESI) *m*/*z*: calculated for $C_{25}H_{31}N_5O_5$ $[M+H]^+$ 482.2430, found 482.2421; calculated for $[M+Na]^+$ 504.2217, found 504.2214.

(*S*)-Methyl 1-(2-morpholinopyrimidin-4-yl)pyrrolidine-2-carboxylate (12e). By the general procedure method **A**, (*S*)-methyl pyrrolidinate **9e** (89 mg, 0.69 mmol) at 60 °C for 24 h provided **12e** (119 mg, 89%) as a colorless oil: TLC: *Rf* (ethyl acetate/n-hexane, 1 : 4): 0.29; $[\alpha]_D^{25}$ −160.7 (*c* 1.0, MeOH); IR (neat) 2955 (CH), 2851 (CH), 1738 (CO), 1578 (CC), 1553, 1466, 1435, (CC, CN), 1385, 1238, 1113 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 1.98–2.29 (m, 4H, 2 × CH_2), 3.44–3.63 (m, 2H, NCH_2), 3.66–3.76 (m, 11H, CH_{2morph} and OCH_3), 4.50 (br, 1H, CH_{α}), 5.75 (br, 1H, *H*(5)$_{pyrim}$), 7.93 (d, *J* = 5.6 Hz, 1H, *H*(6)$_{pyrim}$); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 24.3 (t), 29.6 (t), 44.1 (t, 2C), 46.5 (t), 51.8 (d), 59.2 (q), 66.8 (t, 2C), 94.0 (d), 156.0 (d), 159.9 (s), 161.1 (s), 174.0 (s); HRMS (ESI) *m*/*z*: calculated for $C_{14}H_{21}N_4O_3$ $[M+H]^+$ 293.1608, found: 293.1618.

General procedure for the synthesis of N^{α}-Fmoc pyrimidin-4-yl amino acids 18

LiOH monohydrate (2.5 equiv.) was added to a solution of appropriate pyrimidin-4-yl methyl esters **12** (1 equiv.) in THF/MeOH/H_2O (1 : 2 : 2) (8 mL $mmol^{-1}$), and the reaction mixture was stirred at room temperature for 3–4 h. Upon completion of the reaction (TLC monitoring), the organic solvents were removed under reduced pressure. The pH of the resulting aqueous solution was then adjusted to 4 with glacial acetic acid, and the solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Then, the free N^{α}-Boc-amino acid was dissolved in CH_2Cl_2 (1.5 mL $mmol^{-1}$) and the solution was cooled in an ice bath. TFA (1.5 mL $mmol^{-1}$) was added dropwise and the resulting mixture was stirred at 0 °C for 1–2 h. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure. Next, the crude material was dissolved in 1,4-dioxane (3 mL $mmol^{-1}$) and the resulting solution was adjusted to pH 7 with aqueous $NaHCO_3$ (5%). Fmoc-Osu (1.02–1.05 equiv.) was added slowly. During Fmoc-OSu addition, pH was readjusting to 7 with aqueous $NaHCO_3$ (5%). The resulting mixture was stirred at room temperature for 8–12 h. Upon completion of the reaction (TLC monitoring), the solvent was removed under reduced pressure. The resulting residue was dissolved in water (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were back extracted with saturated $NaHCO_3$ solution (3 × 5 mL). Then the combined basic aqueous layers were acidified to pH 1–2 with aqueous HCl (1%), and extracted with ethyl acetate (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography with a gradient elution n-hexane/ethyl acetate/acetic acid from (4 : 1 : 0) to (0 : 20 : 1) to afford N^{α}-Fmoc pyrimidin-4-yl amino acids **18**.

(*S*)-N^{α}-Fmoc-3-(4-(4-(2-morpholinopyrimidin-*N*-yloxy)phenyl)-2-aminopropanoic acid (18a). By the general procedure, from N^{α}-Boc-pyrimidin-4-yl amino ester **12a** (100 mg, 0.22 mmol) provided **18a** (68 mg, 55%) as a colorless solid: mp 88–89 °C; TLC: *Rf* (ethyl acetate/methanol/acetic acid, 10 : 2 : 0.1): 0.49; $[\alpha]_D^{25}$ +5.02 (*c* 0.22, MeOH); IR (neat) 2956 (CH), 2918br (OH), 1714 (CO), 1586 (CC), 1549, 1502, 1437, (CC, CN), 1337, 1235, 1200, 1105 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.89 (dd, *J* = 13.6 Hz, *J′* = 10.2 Hz, 1H, C$H_{2\beta}$), 3.12 (dd, *J* = 13.6 Hz, *J′* = 3.9 Hz, 1H, C$H_{2\beta}$), 3.51–3.53 (m, 8H, CH_{2morph}), 4.17–4.22 (m, 4H, CH_{Fmoc}, OCH_2 and CH_{α}), 6.06 (d, *J* = 5.7 Hz, 1H, *H*(5)$_{pyrim}$), 7.07 (d, *J* = 8.2 Hz, 2H, CH_{aryl}), 7.26–7.32 (m, 4H, CH_{aryl}), 7.37–7.42 (m, 2H, CH_{aryl}), 7.51 (br, 1H, N*H*), 7.64 (t, *J* = 6.5 Hz, 2H, CH_{aryl}), 7.87 (d, *J* = 7.4 Hz, 2H, CH_{aryl}), 8.17 (d, *J* = 5.7 Hz, 1H, *H*(6)$_{pyrim}$), 12.86 (br, 1H, O*H*); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 25.6 (t), 44.2 (t, 2C), 47.1 (d), 55.3 (d), 65.7 (t), 66.3 (t, 2C), 96.3 (d), 120.4 (d, 2C), 121.8 (d, 2C), 127.7 (d, 2C), 128.0 (d, 2C), 129.3 (d, 2C), 130.8 (d), 131.0 (d), 137.8 (s, 2C), 139.8 (s, 2C), 141.1 (s), 143.0 (s), 144.2 (s), 160.3 (d), 161.7 (s), 169.9 (s), 173.4 (s); HRMS (ESI) *m*/*z*: calculated for $C_{32}H_{31}N_4O_6$ $[M+H]^+$ 567.2254, found 567.2238.

(*S*)-N^{α}-Fmoc-3-(4-(1-(2-morpholinopyrimidin-*N*-yl)-1,4-dihydroimidaz-4-yl)-2-aminopropanoic acid (18b). By the general procedure, N^{α}-Boc-pyrimidin-4-yl amino ester **12b** (100 mg, 0.23 mmol) provided **18b** (110 mg, 88%) as a colorless solid: mp 139–140 °C; TLC: *Rf* (ethyl acetate/methanol/acetic acid, 10 : 3 : 0.2): 0.62; $[\alpha]_D^{25}$ +7.06 (*c* 0.32, MeOH); IR (neat) 3369br (OH), 1682 (CO), 1598 (CC), 1553, 1443, (CC, CN), 1205, 1179, 1132 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) δ 2.94 (dd, *J* = 14.6 Hz, *J′* = 9.7 Hz, 1H, C$H_{2\beta}$), 3.03 (dd, *J* = 14.6 Hz,

J' = 4.1 Hz, 1H, C$H_{2\beta}$), 3.61–3.63 (m, 4H, NCH_{2morph}), 3.70–3.72 (m, 4H, OCH_{2morph}), 4.19–4.23 (m, 3H, CH_{Fmoc} and OCH_2), 4.32–4.37 (m, 1H, CH_α), 6.97 (d, J = 5.4 Hz, 1H, $H(5)_{pyrim}$), 7.21–7.27 (m, 2H, CH_{aryl}), 7.34–7.39 (m, 2H, CH_{aryl}), 7.61–7.64 (t, J = 6.9 Hz, 2H, CH_{aryl}), 7.70 (d, J = 8.2 Hz, 1H, NH), 7.77 (s, 1H, $H(4)_{imid}$), 7.83 (d, J = 6.8 Hz, 2H, CH_{aryl}), 8.43 (d, J = 5.4 Hz, 1H, $H(6)_{pyrim}$), 8.64 (s, 1H, $H(2)_{imid}$), 12.79 (br, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ 29.6 (t), 43.8 (t, 2C), 46.5 (d), 53.5 (d), 65.6 (t), 65.8 (t, 2C), 97.1 (d), 113.5 (d), 120.1 (d, 2C), 125.16 (d), 125.22 (d), 126.98 (d), 127.0 (d), 127.6 (d, 2C), 135.2 (d), 139.3 (s), 140.64 (s), 140.67 (s), 143.7 (s, 2C), 154.8 (s), 155.9 (s), 160.6 (d), 160.9 (s), 173.2 (s); HRMS (ESI) m/z: calculated for $C_{29}H_{29}N_6O_5$ $[M+H]^+$ 541.2194, found 541.2183.

(*S*)-*N*$^\alpha$-Fmoc-6-(1-(2-morpholinopyrimidin-*N*-ylamino)-2-amino-hexanoic acid (18c). By the general procedure, *N*$^\alpha$-Boc-pyrimidin-4-yl amino ester **12c** (100 mg, 0.24 mmol) provided **18c** (117 mg, 93%) as a colorless solid: mp 96–98 °C; TLC: *Rf* (ethyl acetate/methanol/acetic acid, 2 : 3 : 0.3): 0.57; $[\alpha]_D^{25}$ −2.99 (*c* 0.30, MeOH); IR (neat) 3269br (OH), 1688 (CO), 1656 (CC), 1583 (CN), 1198, 1176, 1125, 1024 (CO) cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d$_6$) δ 1.41–1.47 (m, 2H, CH_2), 1.50–1.52 (m, 2H, CH_2), 1.60–1.64 (m, 1H, CH_2), 1.66–1.74 (m, 1H, C$H_{2\beta}$), 3.22 (m, 2H, NC$H_{2\beta}$), 3.58 (s, 8H, CH_{2morph}), 3.91 (dd, J = 8.8 Hz, J' = 4.8 Hz, 1H, CH_α), 4.20–4.29 (m, 3H, CH_{Fmoc} and OCH_2), 5.76 (d, J = 5.8 Hz, 1H, $H(5)_{pyrim}$), 7.05 (br, 1H, NH), 7.32 (m, 2H, CH_{aryl}), 7.40 (m, 2H, CH_{aryl}), 7.54 (br, 1H, NH), 7.72 (m, 3H, CH_{aryl} and $H(6)_{pyrim}$), 7.88 (d, J = 7.4 Hz, 2H, CH_{aryl}), 12.56 (br, 1H, OH); ^{13}C-NMR (100 MHz, DMSO-d$_6$) δ 23.2 (t), 25.2 (t), 28.4 (t), 30.7 (t), 43.9 (t, 2C), 46.7 (d), 53.9 (d), 65.5 (t), 66.1 (t, 2C), 96.2 (d), 120.1 (d, 2C), 125.26 (d), 125.29 (d), 127.1 (d, 2C), 127.6 (d, 2C), 140.71 (s), 140.73 (s), 143.81 (s), 143.88 (s), 154.2 (d), 156.1 (s), 161.2 (s), 162.4 (s), 174.3 (s); HRMS (ESI) m/z: calculated for $C_{29}H_{34}N_5O_5$ $[M+H]^+$ 532.2554, found 532.2570.

Synthesis of (*S*)-1-(2-morpholinopyrimidin-4-yl)pyrrolidine-2-carboxylic acid (18e). To a solution of methyl ester **12e** (90 mg, 0.31 mmol, 1 equiv.) in THF/MeOH/H_2O (1 : 2 : 2) (8 mL mmol^{-1}) was added LiOH monohydrate (44.7 mg, 0.77 mmol, 2.5 equiv.) and the reaction mixture was stirred at room temperature for 4 h. Upon completion of the reaction (TLC monitoring), the organic solvents were removed under reduced pressure. The pH of the resulting aqueous solution was then adjusted to 4 with glacial acetic acid, and the solution was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography with a gradient elution n-hexane/ethyl acetate/acetic acid from (4 : 1 : 0) to (0 : 20 : 1) to afford 61 mg (70%) of pyrimidin-4-yl amino acids **18e** as a colorless solid: mp 193–106 °C; TLC: *Rf* (ethyl acetate/methanol/acetic acid, 1 : 3 : 0.5): 0.21; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2.07–2.30 (m, 4H, 2 × CH_2), 3.62–3.77 (m, 10H, CH_{2morph} and NCH_{2pro}), 4.50 (br, 1H, CH_α), 5.92 (d, J = 6.6 Hz,1H, $H(5)_{pyrim}$), 8.02 (d, J = 6.6 Hz, 1H, $H(6)_{pyrim}$), 9.98 (br, 1H, COOH); ^{13}C-NMR (50 MHz, DMSO-d$_6$) δ 23.6 (t), 28.8 (t), 42.0 (t, 2C), 46.5 (t), 59.0 (d), 65.5 (t, 2C), 94.6 (d), 151.1 (d), 157.0 (s), 159.0 (s), 173.4 (s); HRMS (ESI) m/z: calculated for $C_{13}H_{19}N_4O_3$ $[M+H]^+$ 279.1379, found: 279.1452.

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