Efficient synthesis of aminomethylated azaindoles and corresponding pyrrole-fused derivatives by copper-catalyzed domino multicomponent coupling and cyclization

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ABSTRACT

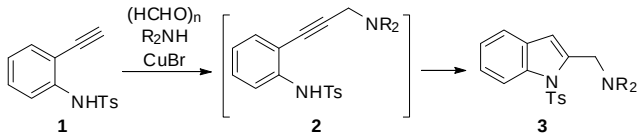
Efficient methods for the synthesis of aminomethylated azaindole derivatives via domino copper-catalyzed multicomponent coupling and cyclization have been developed. Using various secondary amines and aldehydes, *N*-substituted 3-ethynyl-4-aminopyridine was converted to substituted azaindoles in moderate to excellent yields. By use of a 3,4-diaminopyridine derivative bearing two alkynyl groups, the corresponding pyrrole-fused azaindoles were synthesized by controlled stepwise cyclization.

1. Introduction

Azaindoles and related heteroaromatic ring systems are common scaffolds in biologically active natural and synthetic compounds. Their widespread application as pharmaceutical agents[1–7] makes them attractive synthetic targets. Several synthetic routes to access azaindoles are described in the literature, most of which rely on linear synthesis utilizing the conventional cyclization of *ortho*-amino-alkynyl pyridines promoted by bases or transition metals.[8–13] However, few methods have been reported for azaindole synthesis based on multiple component reactions, which provide a divergent approach to functionalized azaindoles in a single step.[14–17]

We recently reported the direct synthesis of 2-(aminomethyl)indoles **3** via copper-catalyzed domino three-component coupling and cyclization reactions of ethynylaniline **1** (Scheme 1).[18–20] The mechanism of this reaction involves the formation of the propargylamine intermediate **2** by Mannich-type three-component coupling of **1** with paraformaldehyde and a secondary amine, and subsequent copper-catalyzed intramolecular cyclization. Using a modified protocol, we developed an efficient synthesis of a series of aminomethylated dipyrroloarenes by direct biscyclization.[21]

As a part of our ongoing project directed toward development of novel CK2 inhibitors,[22,23] we designed aminomethylated azaindole derivatives **4** and more complicated pyrrole-fused azaindole derivatives **5** as potential drug-like templates (Figure 1). They are considered to be synthesized by a copper-catalyzed three-component coupling and cyclization reaction. Here, we report our research on the synthesis of aminomethylated azaindole derivatives **4** using various aldehydes and secondary amines. The synthesis of corresponding pyrrole-fused derivatives **5** by a controlled stepwise cyclization is also depicted.[24,25]



Scheme 1. Copper-catalyzed domino three-component coupling and cyclization

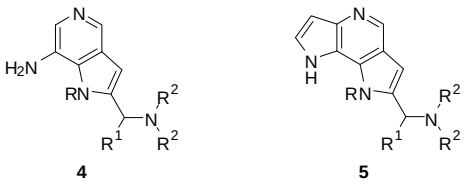


Figure 1. Synthetic targets **4** and **5** as potential drug-like templates

2. Results and discussion

We initially designed a synthetic route to **4** and **5** through a common starting material **6** (Scheme 2). The azaindoles **4** bearing an aminomethyl group can be directed from their nitro congener **7** by reduction. The nitroazaindole **7** is considered to be synthesized by the copper-catalyzed three-component coupling and cyclization reaction of **6** with various aldehydes and secondary amines. The amino group of **4** is envisioned to facilitate a regioselective *ortho*-bromination, permitting introduction of an alkynyl group by Sonogashira coupling. Finally, the subsequent intramolecular cyclization would afford the pyrrole-fused azaindoles **5**.

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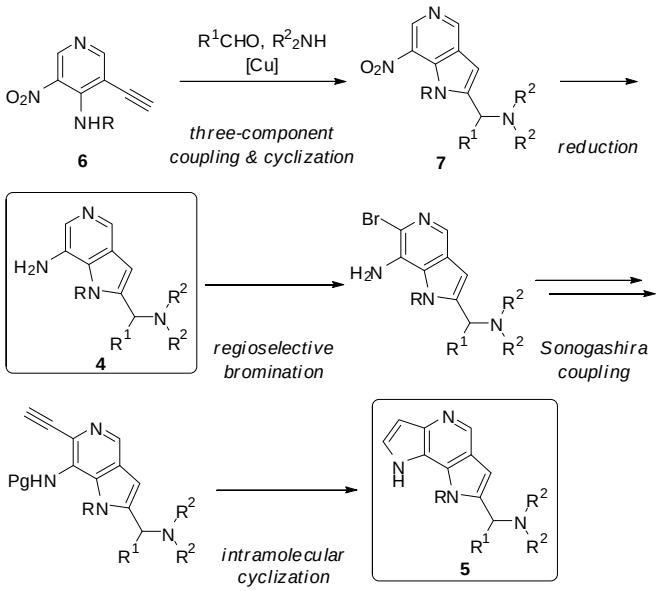
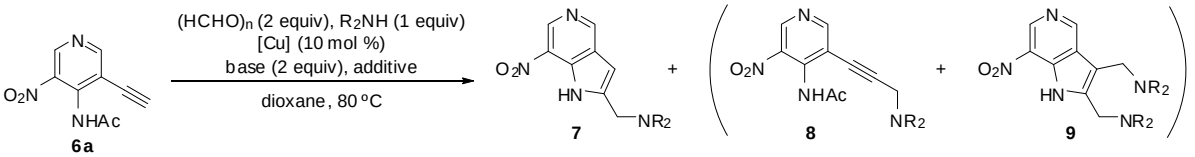


Scheme 2. Initial strategy for the synthesis of **4** and **5**

In our previous study on three-component indole formation, the intramolecular hydroamination required *N*-substituted ethynylanilines.[18,21] Therefore, 3-ethynyl-4-aminopyridine **6a** having an acetyl group was synthesized (see Experimental 4.2) and applied to optimize the reaction conditions for the domino three-component coupling-cyclization (Table 1). We started our investigation by treating **6a** with paraformaldehyde and dipropylamine in dioxane at 80 °C in the presence of 10 mol % of CuI (entry 1). The initial Mannich-type three-component coupling was found to proceed readily to afford **8a** by TLC. However, the subsequent intramolecular hydroamination was rather slow to yield the desired cyclization product **7a** as the deacetylated form in low yield (40%),[26] accompanied by the formation of undesired bis-aminomethylated side product **9a** in 10% yield. Addition of K_3PO_4 resulted in decomposition of the substrate (entry 2), whereas Et_3N slightly improved the yield of **7a** (49%, entry 3). According to the previous study, the counteranion of copper catalysts considerably affects the reactivity of the alkyne toward intramolecular hydroamination.[18,21] Among the copper salts investigated (CuI, CuBr, CuCl, entries 3–5), CuCl afforded the highest yield of **7a** (61%, entry 5). Considering that AcOH (resulted *in situ* from **6a** by the deacetylation with water formed in the step of Mannich reaction) might hinder intramolecular hydroamination, we applied MS4A as an additive to remove water and/or AcOH. As hoped, addition of MS4A dramatically accelerated the cyclization rate to yield **7a** in 85% yield without formation of the side product **9a** (entry 6). Next, we examined the scope of the 2-(aminomethyl)azaindole formation using several secondary amines (entries 7–10). All the secondary amines tested here proved to be acceptable as amine components to yield desired products **7b**–**7e** in high yields (71–86%).

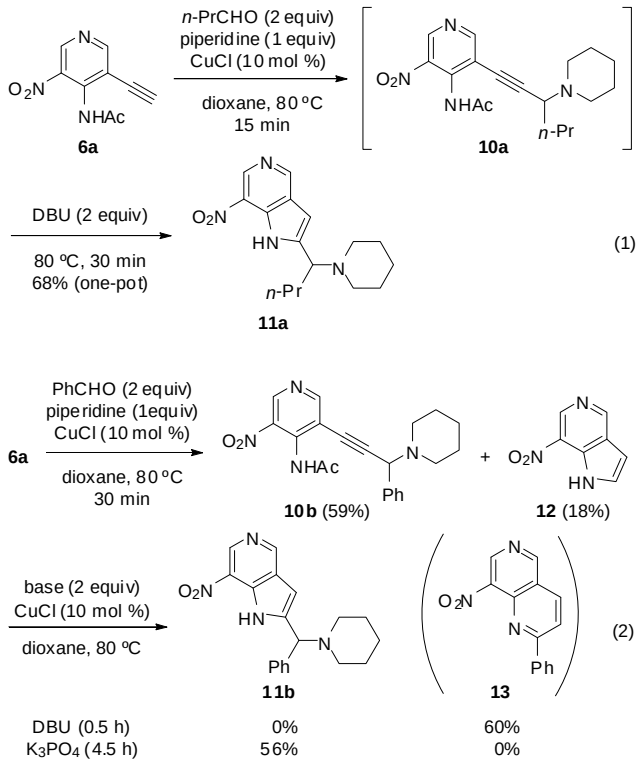
We also investigated the three-component synthesis of 2-(aminomethyl)azaindoles using alkyl or aryl aldehydes (Scheme 3). Treating **6a** with butanal and piperidine under optimized conditions afforded the three-component coupling intermediate **10a** without formation of the desired cyclization product **11a**. Instead of Et_3N, use of the relatively strong base DBU was effective in promoting the intramolecular hydroamination of **10a**. After complete formation of **10a** (monitored by TLC), DBU (2 equiv) was added to the reaction mixture to give the desired azaindole **11a** in 68% yield in a one-pot manner (eq 1). Meanwhile, treatment of **6a** with benzaldehyde and piperidine under standard conditions afforded the three-component coupling intermediate **10b** in 59% yield, mixed with an inseparable co-product **12** in 18% yield. Although treatment of this mixture even after isolation with DBU was ineffective (leading to formation of undesired 1,6-naphthyridine **13** in 60% yield), replacement of DBU with K_3PO_4 as a base afforded the desired azaindole **11b** in a moderate yield (56%, eq 2). Formation of the naphthyridine **13** is attributable to isomerization of the alkyne **10b** to the corresponding allene by the action of DBU followed by 6-*endo* cyclization and elimination of piperidine.

Table 1. Synthesis of azaindole derivatives **7** using paraformaldehyde



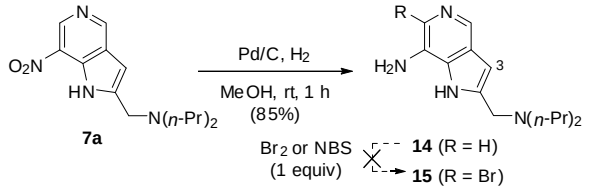
Entry	[Cu]	Base	Additive	R_2NH	Time (h)	Yield % (product)[a]		
						7	**8**	**9**
1	CuI	–	–	$(n\text{-Pr})_2NH$	10	40 (**7a**)	20 (**8a**)	10 (**9a**)
2	CuI	K_3PO_4	–	$(n\text{-Pr})_2NH$	2		decomp.	
3	CuI	Et_3N	–	$(n\text{-Pr})_2NH$	10	49 (**7a**)	17 (**8a**)	4 (**9a**)
4	CuBr	Et_3N	–	$(n\text{-Pr})_2NH$	10	42 (**7a**)	10 (**8a**)	trace (**9a**)
5	CuCl	Et_3N	–	$(n\text{-Pr})_2NH$	10	61 (**7a**)	13 (**8a**)	5 (**9a**)
6	CuCl	Et_3N	MS4A	$(n\text{-Pr})_2NH$	2	85 (**7a**)	trace (**8a**)	
7	CuCl	Et_3N	MS4A	piperidine	2	71 (**7b**)		
8	CuCl	Et_3N	MS4A	$(i\text{-Pr})_2NH$	1.5	81 (**7c**)		
9	CuCl	Et_3N	MS4A	Et_2NH	2	73 (**7d**)		
10	CuCl	Et_3N	MS4A	diallylamine	1	86 (**7e**)		

[a]Isolated yields.



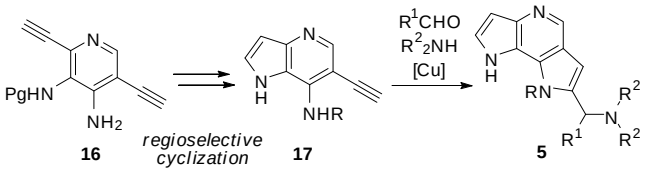
Scheme 3. Synthesis of azaindole derivatives **11** using *n*-PrCHO or PhCHO

With a series of azaindole derivatives **7** and **11** bearing a nitro group in hand, we tested the reduction of the nitro group and subsequent regioselective *ortho*-bromination (Scheme 4). Treatment of **7a** with Pd/C under a H_2 atmosphere enabled the reduction to afford **14** bearing an amino group. However, bromination of **14** with 1.0 equiv Br_2 or NBS failed to yield the desired product **15**, resulting in a mixture of mono- and bis-brominated products with simultaneous decomposition of the substrate **14**. ^{1}H NMR indicated that the 3 position of the azaindole **14** prefers to undergo bromination rather than the position *ortho* to the amino group. Protection of the indole with a Ts or Boc group was unsuccessful. Faced with the difficulty of regioselective bromination and the instability of **14**, we decided to abort this route and seek a new strategy for the synthesis of **5**.



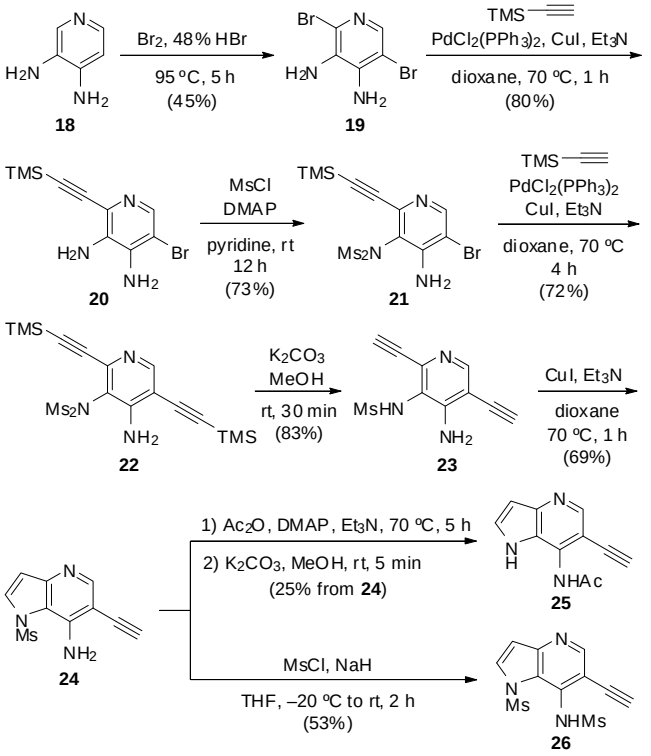
Scheme 4. Unsuccessful *ortho*-bromination of aminoazaindole **14**

Considering the difficulty in introduction of an alkynyl group after formation of an azaindole framework, we designed a new route to access **5** from a 3,4-diaminopyridine derivative **16** bearing two alkynyl groups (Scheme 5). We expected that regioselective introduction of an electron-withdrawing protecting group (Pg) would facilitate controlled monocyclization of **16** to produce azaindole **17**. The three-component coupling-cyclization of **17** would afford the desired pyrroloazaindoles **5**.



Scheme 5. Revised strategy for the synthesis of pyrroloazaindole **5**

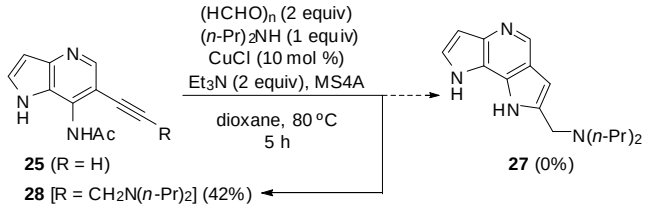
We started our synthesis from commercially available 3,4-diaminopyridine **18** (Scheme 6). Treating **18** with bromine in 48% aqueous HBr afforded the desired bis-brominated product **19**.[27] Sonogashira coupling of **19** with an excessive amount of trimethylsilylacetylene failed to introduce two alkynyl groups, instead yielding a mono-alkynylated product **20** in 80% yield. We expected that the nucleophilicity of the amino group of **20** at the 4 position would be lower than that on the 3 position owing to delocalization of the nitrogen non-bonding electron into the pyridine ring. As hoped, by treating **20** with 2 equiv of MsCl in pyridine in the presence of DMAP, regioselective bis-mesylation of the amino group at the 3 position proceeded readily to produce **21** in 73% yield. Sonogashira coupling of **21** with trimethylsilylacetylene afforded the desired aminopyridine derivative **22** with two alkynyl groups. Introduction of electron-withdrawing Ms groups would result in a decrease of electron density of the pyridine ring, facilitating a second Sonogashira coupling at the 5 position. Subsequent deprotection of TMS groups and one of the Ms groups produced **23**, which underwent regioselective monocyclization in the presence of Et_3N and CuI to yield **24** in 57% yield in two steps. Then, by use of standard methods for acetylation or mesylation, *N*-substituted amino azaindoles **25** and **26** with Ac or Ms group, respectively, were synthesized.



Scheme 6. Synthesis of azaindole derivatives **25** and **26**

Three-component coupling and cyclization of **25** with paraformaldehyde and dipropylamine was first investigated under the condition optimized in Table 1 (Scheme 7). The Mannich-type coupling product **28** was isolated without formation of the

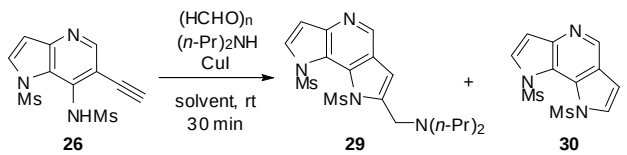
desired cyclization product **27** even with a prolonged reaction time. In our previous study on three-component indole formation, the rate of hydroamination was significantly dependent upon the acidity of the proton on the nitrogen atom.[18,21] In case of substrate **6a** (Scheme 3), a highly electron-withdrawing nitro group *ortho* to the amino group would contribute to an increase in the acidity of the acetamide proton, thereby facilitating hydroamination. The acidity of acetamide proton of **25** (Scheme 7) was considered to be insufficient to promote cyclization.



Scheme 7. Attempted synthesis of pyrroloazaindole derivative **27**

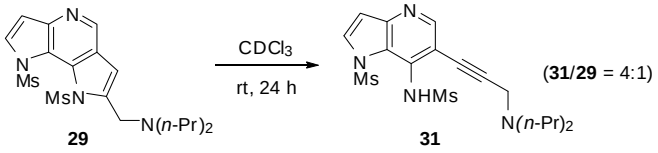
We therefore tested three-component coupling and cyclization with more acidic methanesulfonamide **26** (Table 2). Treating **26** with paraformaldehyde and dipropylamine at room temperature in the presence of 5 mol % of CuI afforded the desired pyrroloazaindole **29** in a low yield (30%) accompanied by generation of a considerable amount of the 2-unsubstituted pyrroloazaindole **30** (entry 1). Use of a mixed solvent of toluene and dioxane partially suppressed the undesired cyclization at the terminal alkyne before the Mannich-type reaction, resulting in a slightly improved yield of **29** (45%, entry 2). For accelerating the rate of the Mannich-type reaction, a mixture of paraformaldehyde and dipropylamine in toluene was heated at 80 °C for 5 min, then added to the mixture of **26** in dioxane. As hoped, the desired product **29** was isolated in an improved yield (70%) with only a trace amount of the undesired product **30** (entry 3). The pyrroloazaindole **29** is stable in a solid state, whereas it was found to readily undergo a ring cleavage reaction in $CDCl_3$. After 24 hours at room temperature, formation of a ring-cleavage product **31** (**31**/**29** = 4:1) was detected by ^{1}H NMR analysis (Scheme 8).

Table 2. Synthesis of pyrroloazaindole derivative **29**[a]



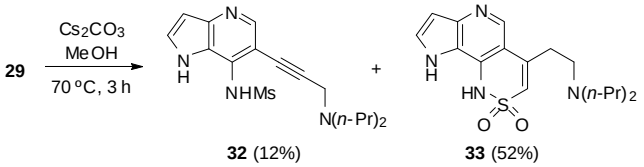
Entry	Solvent	Yield %[b]	
		29	**30**
1	dioxane	30	29
2	toluene/dioxane (1:1)	45	15
3[c]	toluene/dioxane (1:1)	70	trace

[a] Reactions were carried out with $(HCHO)_n$ (2 equiv) and $(n\text{-Pr})_2NH$ (1 equiv) using CuI (5 mol %) in toluene at rt. [b] Isolated yields. [c] A solution of $(HCHO)_n$ and $(n\text{-Pr})_2NH$ in toluene (heated at 80 °C for 5 min) was added to the reaction mixture.

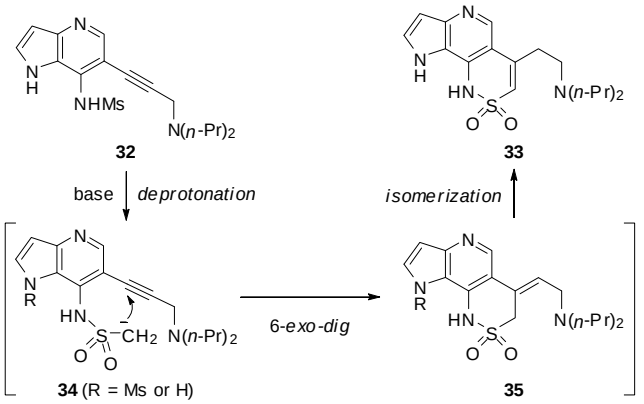


Scheme 8. Ring-cleavage reaction of **29** in $CDCl_3$

For suppressing this undesired ring-cleavage reaction and undertaking further functionalization of the *N*-protected pyrroloazaindole **29**, we tested the deprotection of Ms groups (Scheme 9). To our surprise, treating **29** with Cs_2CO_3 in MeOH at 70 °C afforded a mono-deprotected ring-cleavage product **32** in 12% yield, together with the major product **33**, which was considered to be generated from **32** by its recyclization. A plausible mechanism for the formation of **33** is shown in Scheme 10. First, the carbanion **34** would be formed by deprotonation of the sulfonamide **32** derived from the ring cleavage reaction of **29**. The subsequent 6-*exo* cyclization of **34** followed by an isomerization of alkene would afford **33**.

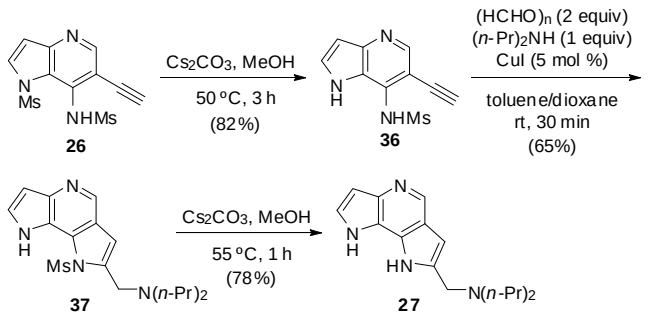


Scheme 9. Attempted removal of the Ms groups of **29**



Scheme 10. Plausible mechanism for the formation of **33**

Faced with the difficulty of the deprotection of Ms groups from **29**, we decided to remove the Ms group of **26** on the pyrrole ring first (Scheme 11). The deprotection of **26** proceeded readily to give **36**, which underwent three-component coupling and cyclization with paraformaldehyde and dipropylamine under the condition optimized in Table 2 to furnish the mono-deprotected pyrroloazaindole **37** in a slightly decreased yield (65%). To our delight, fully deprotected pyrroloazaindole **27** could be derived from **37** in 78% yield by treating with Cs_2CO_3 in MeOH. The azaindoles **37** and **27** can be applied to further functional-group modifications, including *N*-alkylation or *N*-acylation for identification of novel CK2 inhibitors.



Scheme 11. Synthesis of deprotected pyrroloazaindole derivatives **37** and **27**

3. Conclusion

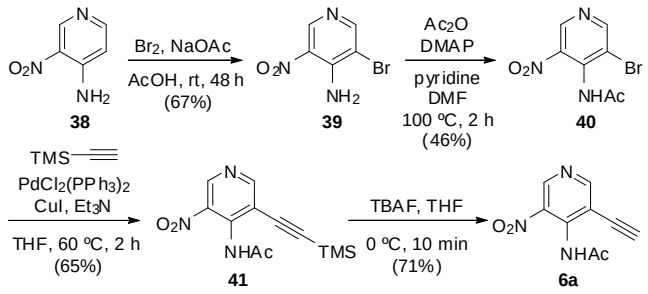
We have developed efficient methodologies for the synthesis of aminomethylated azaindoles using copper-catalyzed three-component coupling and cyclization. A series of secondary amines and aldehydes can be used in this reaction, indicating this reaction to be synthetically useful for the diversity-oriented synthesis of azaindoles and related compounds. Furthermore, the more complicated pyrrole-fused azaindoles were also synthesized by controlled stepwise cyclization. Further studies for the development of CK2 inhibitors utilizing these drug-like templates are in progress.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded using a JEOL AL-500 spectrometer at 500 MHz frequency. Chemical shifts are reported in δ (ppm) relative to Me_4Si (in $CDCl_3$ or DMSO-d_6) as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-500 and referenced to the residual $CDCl_3$ or DMSO-d_6 signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, number of protons, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br s = broad singlet) and coupling constant(s). Melting points were measured by a hot stage melting points apparatus (uncorrected). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. All reagents and solvents were of commercial quality and used without further purification.

4.2. Preparation of 6a



*4.2.1. 3-Bromo-5-nitropyridin-4-amine (**39**).* To a stirred mixture of **38** (3.0 g, 21.6 mmol) and NaOAc (2.7 g, 32.4 mmol) in glacial AcOH (72 mL) was added dropwise a mixture of Br_2 (3.8 g, 23.8 mmol) in glacial AcOH (24 mL), then the mixture was stirred for 48 h at room temperature. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (10 mL), then the solvent was removed under reduced pressure. The resulting yellow solid was collected by filtration and washed by water (50 mL), then dried under vacuum. The crude product was recrystallized from *n*-hexane–EtOAc (3:1) to give **39** (3.2 g, 67% yield) as yellow crystals. ^{1}H and ^{13}C NMR data were in agreement with those previously reported.[28]

*4.2.2. N-(3-Bromo-5-nitropyridin-4-yl)acetamide (**40**).* To a stirred mixture of **39** (2.0 g, 9.2 mmol) and DMAP (113 mg, 0.92 mmol) in DMF (10 mL) were added pyridine (3.7 mL, 46 mmol) and acetic anhydride (4.3 mL, 46 mmol), and the mixture was stirred for 2 h at 100 °C. After being cooled to room temperature, the resulting black mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (2:1), then recrystallized from *n*-hexane–EtOAc (3:1) to give **40** (1.1 g, 46% yield) as colorless crystals: R_f = 0.50 (silica gel, *n*-hexane/EtOAc = 1/1); mp 197 °C; IR (neat) cm^{-1} 1681 (C=O), 1487 (NO_2); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.15 (3H, s), 9.02 (1H, s), 9.09 (1H, s), 10.64 (1H, br s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 22.8 (q), 117.5 (s), 136.7 (s), 142.0 (s), 144.7 (d), 155.9 (d), 168.8 (s). Anal. Calcd for $C_7H_6N_3BrO_3$: C, 32.33; H, 2.33; N, 16.16; O, 18.46. Found: C, 32.30; H, 2.22; N, 16.12; O, 18.56.

*4.2.3. N-{3-Nitro-5-[(trimethylsilyl)ethynyl]pyridin-4-yl}acetamide (**41**).* A mixture of **40** (500 mg, 1.9 mmol), trimethylsilylacetylene (0.4 mL, 2.8 mmol), CuI (19 mg, 0.1 mmol), $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol), and Et_3N (1 mL) in THF (10 mL) was stirred at 60 °C for 2 h under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (3:1), then recrystallized from *n*-hexane–EtOAc (5:1) to give **41** (348 mg, 65% yield) as brown crystals: R_f = 0.65 (silica gel, *n*-hexane/EtOAc = 2/1); mp 135 °C; IR (neat) cm^{-1} 2157 (C≡C), 1726 (C=O), 1492 (NO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.32 (9H, s), 2.27 (3H, s), 8.21 (1H, br s), 8.76 (1H, s), 8.97 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C, q), 24.2 (q), 95.7 (s), 108.8 (s), 115.0 (s), 138.6 (s), 139.4 (s), 145.7 (d), 156.2 (d), 167.7 (s). Anal. Calcd for $C_{12}H_{15}N_3O_3Si$: C, 51.97; H, 5.45; N, 15.15. Found: C, 51.77; H, 5.48; N, 15.14.

*4.2.4. N-(3-Ethynyl-5-nitropyridin-4-yl)acetamide (**6a**).* To a stirred mixture of **41** (300 mg, 1.1 mmol) in THF (5 mL) was added TBAF (1.0 M in THF, 1.2 mL, 1.2 mmol) under argon, and the mixture was stirred for 10 min at 0 °C. The mixture was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with EtOAc. The organic layer was washed with water and brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (2:1), then recrystallized from *n*-hexane–EtOAc (3:1) to give **6a** (158 mg, 71% yield) as brown crystals: R_f = 0.25 (silica gel, *n*-hexane/EtOAc = 2/1); mp 190 °C (decomp.); IR (neat) cm^{-1} 3271 (C≡C), 1694 (C=O), 1484 (NO_2); ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.14 (3H, s), 4.94 (1H, s), 8.94 (1H, s), 9.01 (1H, s), 10.71 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 22.8 (q), 75.5 (s), 91.1 (d), 115.0 (s), 138.8 (s), 140.7 (s), 145.3 (d), 156.9 (d), 168.9 (s). Anal. Calcd for $C_9H_7N_3O_3$: C, 52.69; H, 3.44; N, 20.48; O, 23.39. Found: C, 52.65; H, 3.27; N, 20.43; O, 23.59.

4.3. Copper-catalyzed three-component coupling and cyclization of 6a with various aldehydes and secondary amines

*4.3.1. General procedure for the synthesis of **7** using paraformaldehyde: synthesis of N-[(7-nitro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]-N-propylpropan-1-amine (**7a**) (Table 1, entry 6).* To a stirred mixture of **6a** (30 mg, 0.15 mmol), paraformaldehyde (9 mg, 0.29 mmol), CuCl (1.5 mg, 0.015

mmol), Et_3N (0.04 mL, 0.29 mmol) and MS4A (73 mg) in dioxane (1.5 mL) was added dipropylamine (0.02 mL, 0.15 mmol), and the mixture was stirred for 2.5 h at 80 °C under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (5:1) to give **7a** (34 mg, 85% yield) as a yellow solid: R_f = 0.60 (alumina, *n*-hexane/EtOAc = 3/1); mp 123 °C; IR (neat) cm^{-1} 1510 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.91 (6H, t, *J* = 7.4 Hz), 1.48-1.55 (4H, m), 2.45-2.48 (4H, m), 3.81 (2H, s), 6.56 (1H, s), 8.99 (1H, s), 9.16 (1H, s), 10.19 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8 (2C, q), 20.1 (2C, t), 51.6 (t), 56.2 (2C, t), 100.0 (d), 128.8 (s), 130.2 (s), 132.4 (s), 137.8 (d), 142.8 (s), 147.5 (d); HRMS (FAB) calcd for $C_{14}H_{21}N_4O_2$ [*M*+H^+]: 277.1664, found: 277.1660.

*4.3.2. 7-Nitro-2-(piperidin-1-ylmethyl)-1H-pyrrolo[3,2-c]pyridine (**7b**) (Table 1, entry 7).* By a procedure identical with that described for the preparation of **7a**, **6a** (30 mg, 0.15 mmol) was converted into **7b** (27 mg, 71%) by the reaction with paraformaldehyde (9 mg, 0.29 mmol), CuCl (1.5 mg, 0.015 mmol), Et_3N (0.04 mL, 0.29 mmol) and piperidine (0.015 mL, 0.15 mmol): yellow solid; R_f = 0.70 (alumina, *n*-hexane/EtOAc = 3/1); mp 174 °C; IR (neat) cm^{-1} 1514 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.48-1.49 (2H, m), 1.60-1.64 (4H, m), 2.42-2.46 (4H, m), 3.68 (2H, s), 6.58 (1H, s), 9.00 (1H, s), 9.18 (1H, s), 10.29 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.1 (t), 25.9 (2C, t), 54.8 (2C, t), 55.9 (t), 101.3 (d), 128.5 (s), 130.3 (s), 132.9 (s), 138.1 (d), 141.2 (s), 147.6 (d); HRMS (FAB) calcd for $C_{13}H_{17}N_4O_2$ [*M*+H^+]: 261.1351, found: 261.1343.

*4.3.3. N-Isopropyl-N-[(7-nitro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]propan-2-amine (**7c**) (Table 1, entry 8).* By a procedure identical with that described for the preparation of **7a**, **6a** (30 mg, 0.15 mmol) was converted into **7c** (33 mg, 81%) by the reaction with paraformaldehyde (9 mg, 0.29 mmol), CuCl (1.5 mg, 0.015 mmol), Et_3N (0.04 mL, 0.29 mmol) and diisopropylamine (0.021 mL, 0.15 mmol): yellow solid; R_f = 0.65 (alumina, *n*-hexane/EtOAc = 3/1); mp 141 °C; IR (neat) cm^{-1} 1523 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.09 (12H, d, *J* = 6.3 Hz), 3.05-3.13 (2H, m), 3.89 (2H, s), 6.53 (1H, s), 8.97 (1H, s), 9.14 (1H, s), 10.20 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 20.7 (4C, q), 42.3 (t), 49.0 (2C, d), 98.6 (d), 129.3 (s), 132.0 (s), 137.5 (d), 139.1 (s), 145.1 (s), 147.2 (d); HRMS (FAB) calcd for $C_{14}H_{21}N_4O_2$ [*M*+H^+]: 277.1664, found: 277.1666.

*4.3.4. N-Ethyl-N-[(7-nitro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]ethan-1-amine (**7d**) (Table 1, entry 9).* By a procedure identical with that described for the preparation of **7a**, **6a** (30 mg, 0.15 mmol) was converted into **7d** (27 mg, 73%) by the reaction with paraformaldehyde (9 mg, 0.29 mmol), CuCl (1.5 mg, 0.015 mmol), Et_3N (0.04 mL, 0.29 mmol) and diethylamine (0.017 mL, 0.15 mmol): yellow solid; R_f = 0.70 (alumina, *n*-hexane/EtOAc = 3/1); mp 98 °C; IR (neat) cm^{-1} 1523 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.08 (6H, t, *J* = 7.2 Hz), 2.60 (4H, q, *J* = 7.2 Hz), 3.81 (2H, s), 6.57 (1H, s), 8.99 (1H, s), 9.17 (1H, s), 10.22 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.7 (2C, q), 47.2 (t), 50.5 (2C, t), 100.4 (d), 128.7 (s), 130.9 (s), 132.6 (s), 138.0 (d), 142.5 (s), 147.5 (d); HRMS (FAB) calcd for $C_{12}H_{17}N_4O_2$ [*M*+H^+]: 249.1352, found: 249.1353.

*4.3.5. N-Allyl-N-[(7-nitro-1H-pyrrolo[3,2-c]pyridin-2-yl)methyl]prop-2-en-1-amine (**7e**) (Table 1, entry 10).* By a procedure identical with that described for the preparation of **7a**, **6a** (30 mg, 0.15 mmol) was converted into **7e** (34 mg, 86%) by the reaction with paraformaldehyde (9 mg, 0.29 mmol), CuCl (1.5 mg, 0.015 mmol), Et_3N (0.04 mL, 0.29 mmol) and diallylamine (0.018 mL, 0.15 mmol): yellow solid; R_f = 0.65 (alumina, *n*-hexane/EtOAc = 3/1); mp 131 °C; IR (neat) cm^{-1} 1522 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 3.16 (4H, d, *J* = 6.3 Hz), 3.83 (2H, s), 5.21-5.26 (4H, m), 5.85-5.94 (2H, m), 6.58 (1H, s), 9.00 (1H, s), 9.17 (1H, s), 10.15 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 49.9 (t), 56.7 (2C, t), 101.1 (d), 118.5 (2C, t), 128.5 (s), 130.2 (s), 132.7 (s), 134.7 (2C, d), 138.0 (d), 141.5 (s), 147.6 (d); HRMS (FAB) calcd for $C_{14}H_{17}N_4O_2$ [*M*+H^+]: 273.1352, found: 273.1348.

*4.3.6. N-{3-[3-(Dipropylamino)prop-1-ynyl]-5-nitropyridin-4-yl}acetamide (**8a**) and N,N'-(7-nitro-1H-pyrrolo[3,2-c]pyridine-2,3-diyl)bis(methylene)bis(N-propylpropan-1-amine) (**9a**) (Table 1, entry 1).* To a stirred mixture of **6a** (50 mg, 0.24 mmol), paraformaldehyde (15 mg, 0.48 mmol) and CuI (4.6 mg, 0.024 mmol) in dioxane (2.0 mL) was added dipropylamine (0.033 mL, 0.24 mmol), then the mixture was stirred for 10 h at 80 °C under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (10:1) to give **7a** (26 mg, 40% yield), **8a** (15 mg, 20% yield) and **9a** (9 mg, 10% yield).

Compound **8a**: light yellow solid; R_f = 0.25 (alumina, *n*-hexane/EtOAc = 3/1); mp 151 °C; IR (neat) cm^{-1} 2217 (C≡C), 1683 (C=O), 1496 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.94 (6H, t, *J* = 7.2 Hz), 1.50-1.57 (4H, m), 2.27 (3H, s), 2.50 (4H, t, *J* = 7.4 Hz), 3.72 (2H, s), 8.24 (1H, br s), 8.76 (1H, s), 8.97 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8 (2C, q), 20.7 (2C, t), 23.9 (q), 42.9 (t), 56.0 (2C, t), 76.2 (s), 97.6 (s), 114.9 (s), 137.8 (s), 139.2 (s), 144.9 (d), 156.1 (d), 167.4 (s); HRMS (FAB) calcd for $C_{16}H_{23}N_4O_3$ [*M*+H^+]: 319.1770, found: 319.1771.

Compound **9a**: yellow oil; R_f = 0.75 (alumina, *n*-hexane/EtOAc = 3/1); IR (neat) cm^{-1} 1520 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.83 (6H, t, *J* = 7.4 Hz), 0.91 (6H, t, *J* = 7.4 Hz), 1.46-1.55 (8H, m), 2.35 (4H, t, *J* = 7.4 Hz), 2.45 (4H, t, *J* = 7.4 Hz), 3.68 (2H, s), 3.77 (2H, s), 9.16 (1H, s), 9.24 (1H, s), 10.09 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8 (2C, q), 12.0 (2C, q), 20.18 (2C, t), 20.20 (2C, t), 48.5 (t), 49.9 (t), 55.9 (2C, t), 56.4 (2C, t), 112.0 (s), 129.3 (s), 130.0 (s), 132.0 (s), 137.9 (d), 139.3 (s), 147.8 (d); HRMS (FAB) calcd for $C_{21}H_{36}N_5O_2$ [*M*+H^+]: 390.2869, found: 390.2863.

*4.3.7. 7-Nitro-2-[1-(piperidin-1-yl)butyl]-1H-pyrrolo[3,2-c]pyridine (**11a**).* A mixture of **6a** (60 mg, 0.29 mmol), butanal (0.055 mL, 0.58 mmol), piperidine (0.035 mL, 0.35 mmol) and CuCl (3 mg, 0.03 mmol) in dioxane (2 mL) was stirred at 80 °C for 15 min under argon. After Mannich-type three-component coupling was completed (monitored by TLC), DBU (0.09 mL, 0.58 mmol) was added. The resulting mixture was stirred for additional 30 min at 80 °C under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (4:1) to give **11a** (58 mg, 68% yield) as an orange oil; R_f = 0.75 (alumina, *n*-hexane/EtOAc = 3/2); IR (neat) cm^{-1} 1523 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.94 (3H, t, *J* = 7.4 Hz), 1.28-1.44 (4H, m), 1.54-1.59 (4H, m), 1.70-1.78 (1H, m), 1.90-1.97 (1H, m), 2.42-2.49 (4H, m), 3.66 (1H, dd, *J* = 8.9, 4.9 Hz), 6.54 (1H, s), 8.99 (1H, s), 9.15 (1H, s), 10.15 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.1 (q), 20.4 (t), 24.5 (t), 26.3 (2C, t), 31.9 (t), 51.0 (2C, t), 63.1 (d), 100.8 (d), 128.4 (s), 130.2 (s), 132.4 (s), 137.9 (d), 144.9 (s), 147.5 (d); HRMS (FAB) calcd for $C_{16}H_{23}N_4O_2$ [*M*+H^+]: 303.1821, found: 303.1818.

*4.3.8. 7-Nitro-2-[phenyl(piperidin-1-yl)methyl]-1H-pyrrolo[3,2-c]pyridine (**11b**).* A mixture of **6a** (50 mg, 0.24 mmol), benzaldehyde (0.05 mL, 0.49 mmol), piperidine (0.025 mL, 0.24 mmol) and CuCl (2.4 mg, 0.024 mmol) in dioxane (2 mL) was stirred at 80 °C for 30 min under argon. After being cooled to room temperature, solvent was removed under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (3:1) to give a mixture of **10b** (54 mg, 59% yield) and **12** (7 mg, 18% yield). To this mixture were added CuCl (1.5 mg, 0.015 mmol), K_3PO_4 (62 mg, 0.29 mmol) and dioxane (2 mL), then the mixture was stirred at 80 °C for 4.5 h under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (5:1) to give **11b** (28 mg, 56% yield from **10b**) as a brown oil; R_f = 0.80 (alumina, *n*-hexane/EtOAc = 1/1); IR (neat) cm^{-1} 1522 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.43-1.45 (2H, m), 1.63-1.64 (4H, m), 2.36-2.42 (4H, m), 4.77 (1H, s), 6.51 (1H, s), 7.33-7.40 (5H, m), 8.95 (1H, s), 9.17 (1H, s), 10.26 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.3 (t), 26.2 (2C, t), 52.1 (2C, t), 69.2 (d), 101.5 (d), 128.2 (d), 128.5 (s), 128.6 (2C, d), 128.8 (2C, d), 130.3 (s), 132.7 (s), 136.9 (s), 138.1 (d), 144.4 (s), 147.7 (d); HRMS (FAB) calcd for $C_{19}H_{21}N_4O_2$ [*M*+H^+]: 337.1665, found: 337.1663.

*4.3.9. 8-Nitro-2-phenyl-1,6-naphthyridine (**13**).* By a procedure identical with that described for the preparation of **11b**, **6a** (50 mg, 0.24 mmol) was converted into **10b** (54 mg, 59%) mixed with **12** (7 mg, 18% yield) by the reaction with benzaldehyde (0.05 mL, 0.49 mmol), CuCl (2.4 mg, 0.024 mmol) and piperidine (0.025 mL, 0.24 mmol). To this mixture were added CuCl (1.5 mg, 0.015 mmol), DBU (0.043 mL, 0.29 mmol) and dioxane (2 mL), then the mixture was stirred at 80 °C for 30 min under argon. After being cooled to room temperature, solvent was removed and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (5:1) to give **13** (21 mg, 60% yield from **10b**) as a brown solid; R_f = 0.60 (alumina, *n*-hexane/EtOAc = 1/1); mp 186 °C (decomp.); IR (neat) cm^{-1} 1521 (NO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 7.53-7.56 (3H, m), 8.18 (1H, d, *J* = 8.7 Hz), 8.26-8.27 (2H, m), 8.45 (1H, d, *J* = 8.7 Hz), 9.13 (1H, s), 9.39 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 121.4 (d), 123.2 (s), 128.3 (2C, d), 129.2 (2C, d), 131.5 (d), 136.3 (d), 137.1 (s), 138.5 (s), 141.7 (d), 142.2 (s), 155.8 (d), 163.2 (s); HRMS (FAB) calcd for $C_{14}H_{10}N_3O_2$ [*M*+H^+]: 252.0773, found: 252.0772.

*4.3.10. 2-[(Dipropylamino)methyl]-1H-pyrrolo[3,2-c]pyridin-7-amine (**14**).* A mixture of **7a** (50 mg, 0.18 mmol) and 10% Pd/C (5 mg) in MeOH (2 mL) was stirred at room temperature for 1 h under H_2 atmosphere. Then, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with $CHCl_3$–MeOH (30:1) to give **14** (38 mg, 85% yield) as a brown oil: R_f = 0.50 (alumina, $CHCl_3$/MeOH = 10/1); IR (neat) cm^{-1} 3400, 3190 (NH × 2); ^1H NMR (500 MHz, DMSO-d_6) δ: 0.83 (6H, t, *J* = 7.2 Hz), 1.41-1.49 (4H, m), 2.38 (4H, t, *J* = 7.4 Hz), 3.67 (2H, s), 5.16 (2H, br s), 6.26 (1H, s), 7.51 (1H, s), 8.04 (1H, s), 10.71 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 11.8 (2C, q), 19.5 (2C, t), 51.3 (t), 55.4 (2C, t), 99.4 (d), 124.6 (d), 125.2 (s), 128.9 (s), 129.8 (s), 131.4 (d), 137.5 (s); HRMS (FAB) calcd for $C_{14}H_{23}N_4$ [*M*+H^+]: 247.1923, found: 247.1922.

4.4. Synthesis of pyrrole-fused azaindoles

The compound **19** was prepared from commercially available 3,4-diaminopyridine **18** according to a reported literature.[27]

*4.4.1. 5-Bromo-2-[(trimethylsilyl)ethynyl]pyridine-3,4-diamine (**20**).* A mixture of **19** (3 g, 11.3 mmol), trimethylsilylacetylene (1.76 mL, 12.5 mmol), CuI (108 mg, 0.57 mmol), $PdCl_2(PPh_3)_2$ (398 mg, 0.57 mmol), and Et_3N (8 mL) in dioxane (30 mL) was stirred at 70 °C for 1 h under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (5:1), then recrystallized from *n*-hexane–EtOAc (10:1) to give **20** (2.56 g, 80% yield) as light yellow crystals: R_f = 0.55 (silica gel, *n*-hexane/EtOAc = 1/1); mp 185 °C; IR (neat) cm^{-1} 3446, 3355, 3272, 3204 (NH × 4), 2144 (C≡C); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.27 (9H, s), 3.93 (2H, br s), 4.46 (2H, br s), 8.00 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C, q), 100.3 (s), 101.1 (s), 106.9 (s), 127.8 (s), 133.2 (s), 139.9 (s), 143.0 (d). Anal. Calcd for $C_{10}H_{14}N_3BrSi$: C, 42.26; H, 4.96; N, 14.78; Br, 28.11. Found: C, 42.04; H, 4.92; N, 14.81; Br, 28.02.

*4.4.2. N-{4-Amino-5-bromo-2-[(trimethylsilyl)ethynyl]pyridin-3-yl}-N-(methylsulfonyl)methanesulfonamide (**21**).* To a stirred mixture of **20** (2.24 g, 7.9 mmol) and DMAP (98 mg, 0.8 mmol) in pyridine (10 mL) was added MsCl (3 mL, 40 mmol) at 0 °C, then the mixture was stirred at room temperature for 12 h under argon. To the resulting mixture was added water (20 mL) and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (3:1), then recrystallized from *n*-hexane–EtOAc (5:1) to give **21** (2.53 g, 73% yield) as yellow crystals: R_f = 0.60 (silica gel, *n*-hexane/EtOAc = 1/1); mp 208 °C (decomp.); IR (neat) cm^{-1} 3477, 3385 (NH × 2), 2164 (C≡C), 1366, 1156 (SO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.26 (9H, s), 3.56 (6H, s), 5.04 (2H, br s), 8.39 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 0.0 (3C, q), 45.8 (2C, q), 101.5 (s), 102.2 (s), 108.4 (s), 119.5 (s), 144.3 (s), 151.2 (s), 152.4 (d); HRMS (FAB) calcd for $C_{12}H_{19}N_3BrO_2S_2Si$ [*M*+H^+]: 439.9770, found: 439.9764.

*4.4.3. N-{4-Amino-2,5-bis[(trimethylsilyl)ethynyl]pyridin-3-yl}-N-(methylsulfonyl)methanesulfonamide (**22**).* A mixture of **21** (1 g, 2.3 mmol), trimethylsilylacetylene (0.5 mL, 3.5 mmol), CuI (44 mg, 0.23 mmol), $PdCl_2(PPh_3)_2$ (161 mg, 0.23 mmol), and Et_3N (4 mL) in dioxane (15 mL) was stirred at 70 °C for 4 h under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (5:1), then recrystallized from *n*-hexane–EtOAc (10:1) to give **22** (758 mg, 72% yield) as a white solid: R_f = 0.70 (silica gel, *n*-hexane/EtOAc = 2/1); mp 193 °C; IR (neat) cm^{-1} 3467, 3312 (NH × 2), 2141 (C≡C), 1369, 1164 (SO_2); ^1H NMR (500 MHz, DMSO-d_6) δ: 0.21 (9H, s), 0.26 (9H, s), 3.60 (6H, s), 6.21 (2H, s), 8.18 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 0.0 (3C, q), 0.5 (3C, q), 46.2 (2C, q), 98.1 (s), 101.3 (s), 102.9 (s), 105.8 (s), 106.0 (s), 118.1 (s), 144.1 (s), 153.2 (d), 154.2 (s). Anal. Calcd for $C_{17}H_{27}N_3O_4S_2Si_2$: C, 44.61; H, 5.95. Found: C, 44.21; H, 5.70.

*4.4.4. N-(4-Amino-2,5-diethynylpyridin-3-yl)methanesulfonamide (**23**).* To a stirred mixture of **22** (500 mg, 1.1 mmol) in MeOH (10 mL) was added K_2CO_3 (453 mg, 3.3 mmol) at 0 °C, then the mixture was stirred at room temperature for 30 min under argon. The mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over silica gel with $CHCl_3$–MeOH (9:1) to give **23** (215 mg, 83% yield) as a white solid: R_f = 0.30 (silica gel, $CHCl_3$/MeOH = 9/1); mp 172 °C; IR (neat) cm^{-1} 3488, 3387, 3165 (NH × 3), 2100 (C≡C), 1318, 1152 (SO_2); ^1H NMR (500 MHz, DMSO-d_6) δ: 3.10 (3H, s), 4.47 (1H, s), 4.69 (1H, s),

6.16 (2H, s), 8.11 (1H, s), 9.21 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 42.2 (q), 77.0 (d), 81.5 (d), 84.7 (s), 89.6 (s), 103.6 (s), 119.2 (s), 141.2 (s), 151.0 (d), 153.3 (s); HRMS (FAB) calcd for $C_{10}H_{10}N_3O_2S$ [M+H$^+$]: 236.0494, found: 236.0500.

*4.4.5. 6-Ethynyl-1-(methylsulfonyl)-1H-pyrrolo[3,2-b]pyridin-7-amine (**24**)*. A mixture of **23** (1 g, 4.3 mmol), CuI (43 mg, 0.22 mmol) and Et_3N (0.6 mL, 4.3 mmol) in dioxane (10 mL) was stirred at 60 °C for 1 h under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (2:1), then recrystallized from *n*-hexane–EtOAc (5:1) to give **24** (690 mg, 69% yield) as colorless crystals: R_f = 0.55 (alumina, *n*-hexane/EtOAc = 1/1); mp 147 °C; IR (neat) cm^{-1} 3377, 3336 (NH × 2), 2094 (C≡C), 1352, 1113 (SO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.21 (3H, s), 3.57 (1H, s), 6.10 (2H, s), 6.82 (1H, d, J = 4.6 Hz), 7.66 (1H, d, J = 4.6 Hz), 8.41 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.7 (q), 78.0 (s), 85.5 (d), 100.5 (s), 111.0 (d), 115.2 (s), 131.1 (d), 142.8 (s), 150.5 (s), 150.6 (d); HRMS (FAB) calcd for $C_{10}H_{10}N_3O_2S$ [M+H$^+$]: 236.0494, found: 236.0500.

*4.4.6. N-(6-Ethynyl-1H-pyrrolo[3,2-b]pyridin-7-yl)acetamide (**25**)*. To a stirred mixture of **24** (166 mg, 0.7 mmol) and DMAP (10 mg, 0.07 mmol) in dichloroethane (5 mL) were added Et_3N (0.3 mL, 2.1 mmol) and Ac_2O (0.33 mL, 3.5 mmol), then the mixture was stirred at 70 °C for 5 h under argon. After being cooled to room temperature, solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give the corresponding bis-acetylated product (90 mg, 0.32 mmol). Then, a mixture of this compound and K_2CO_3 (45 mg, 0.32 mmol) in MeOH (2 mL) was stirred at room temperature for 5 min. The resulting mixture was purified by column chromatography over alumina with *n*-hexane–EtOAc (3:1) to give **25** (24 mg, 25% yield from **24**) as a white solid: R_f = 0.40 (alumina, = *n*-hexane/EtOAc 2/1); mp 167 °C; IR (neat) cm^{-1} 3303 (NH), 2253 (C≡C), 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.37 (3H, s), 3.64 (1H, s), 6.72 (1H, dd, J = 2.4, 2.4 Hz), 7.49 (1H, dd, J = 2.4, 2.4 Hz), 8.26 (1H, br s), 8.48 (1H, s), 10.70 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.6 (q), 78.2 (s), 86.0 (d), 99.4 (s), 103.9 (d), 117.6 (s), 129.0 (d), 130.9 (s), 146.5 (d), 148.8 (s), 169.0 (s); HRMS (FAB) calcd for $C_{11}H_{10}N_3O$ [M+H$^+$]: 200.0824, found: 200.0821.

*4.4.7. N-[6-Ethynyl-1-(methylsulfonyl)-1H-pyrrolo[3,2-b]pyridin-7-yl]methanesulfonamide (**26**)*. A mixture of **24** (500 mg, 2.1 mmol) and NaH (150 mg, 6.3 mmol) in THF (10 mL) was stirred at –20 °C for 30 min under argon. To the resulting mixture was added MsCl (0.45 mL, 6.3 mmol) and stirred at room temperature for an additional 2 h under argon. The reaction mixture was acidified by aqueous HCl (1 N) until pH < 2, then extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography over silica gel with *n*-hexane–EtOAc (2:1), then recrystallized from *n*-hexane–EtOAc (3:1) to give **26** (348 mg, 53% yield) as colorless crystals: R_f = 0.65 (silica gel, *n*-hexane/EtOAc = 1/2); mp 168 °C; IR (neat) cm^{-1} 3223 (C≡C), 1356, 1330, 1148, 1121 (SO_2 × 2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.49 (1H, s), 3.59 (3H, s), 3.65 (3H, s), 6.94 (1H, d, J = 4.0 Hz), 7.82 (1H, d, J = 4.0 Hz), 8.63 (1H, br s), 8.73 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 44.1 (q), 44.5 (q), 80.6 (s), 84.4 (d), 105.3 (s), 109.7 (d), 112.4 (s), 131.5 (s), 132.4 (d), 150.8 (s), 152.3 (d); HRMS (FAB) calcd for $C_{11}H_{12}N_3O_4S_2$ [M+H$^+$]: 314.0270, found: 314.0266.

*4.4.8. N-{6-[3-(Dipropylamino)prop-1-ynyl]-1H-pyrrolo[3,2-b]pyridin-7-yl}acetamide (**28**)*. To a stirred mixture of **25** (24 mg, 0.12 mmol), paraformaldehyde (8 mg, 0.24 mmol), CuCl (1.3 mg, 0.012 mmol), Et_3N (0.04 mL, 0.24 mmol) and MS4A (70 mg) in dioxane (1.5 mL) was added dipropylamine (0.02 mL, 0.12 mmol), and the mixture was stirred for 5 h at 80 °C under argon. After being cooled to room temperature, the mixture was filtered through a pad of Celite. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (4:1) to give **28** (16 mg, 42% yield) as a yellow solid: R_f = 0.50 (alumina, *n*-hexane/EtOAc = 2/1); mp 168 °C; IR (neat) cm^{-1} 3259 (NH), 2222 (C≡C), 1668 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.94 (6H, t, J = 7.4 Hz), 1.50-1.58 (4H, m), 2.52 (4H, t, J = 7.4 Hz), 2.36 (3H, s), 3.72 (2H, s), 6.79 (1H, d, J = 4.0 Hz), 7.62 (1H, d, J = 4.0 Hz), 8.36 (1H, s), 10.84 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8 (2C, q), 20.6 (2C, t), 24.8 (q), 42.8 (t), 55.7 (2C, t), 78.4 (s), 93.1 (s), 101.8 (s), 110.7 (d), 115.2 (s), 130.6 (d), 141.8 (s), 149.7 (s), 150.0 (d), 170.1 (s); HRMS (FAB) calcd for $C_{18}H_{25}N_4O$ [M+H$^+$]: 313.2028, found: 313.2021.

*4.4.9. N-{[1,8-Bis(methylsulfonyl)-1,8-dihydrodipyrrolo[3,2-b:2',3'-d]pyridin-7-yl]methyl}-N-propylpropan-1-amine (**29**) (Table 2, entry 3)*. To a stirred mixture of **26** (100 mg, 0.32 mmol) and CuI (3 mg, 0.016 mmol) in dioxane (1 mL) was added a preheated solution (80 °C for 5 min) of paraformaldehyde (19 mg, 0.64 mmol) and dipropylamine (0.044 mL, 0.32 mmol) in toluene (1 mL), and then the mixture was stirred at room temperature for 30 min under argon. Solvent was removed under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (2:1) to give **29** (95 mg, 70% yield) as a white solid: R_f = 0.70 (alumina, *n*-hexane/EtOAc = 1/1); mp 102 °C; IR (neat) cm^{-1} 1361, 1296, 1161, 1146 (SO_2 × 2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.91 (6H, t, J = 7.4 Hz), 1.48-1.56 (4H, m), 2.44-2.48 (4H, m), 3.32 (3H, s), δ: 3.44 (1H, dd, J = 15.5, 6.9 Hz), 3.47 (1H, dd, J = 15.5, 6.9 Hz), 3.82 (3H, s), 5.86 (1H, dd, J = 6.9, 6.9 Hz), 6.76 (1H, d, J = 4.0 Hz), 7.81 (1H, d, J = 4.0 Hz), 8.50 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8 (2C, q), 20.3 (2C, t), 40.3 (q), 44.3 (q), 48.3 (t), 56.1 (2C, t), 107.5 (d), 111.7 (d), 120.3 (s), 131.3 (s), 135.4 (s), 142.8 (d), 145.6 (s), 151.2 (d), 152.0 (s); HRMS (FAB) calcd for $C_{18}H_{27}N_4O_4S_2$ [M+H$^+$]: 427.1474, found: 427.1466.

*4.4.10. 1,8-Bis(methylsulfonyl)-1,8-dihydrodipyrrolo[3,2-b:2',3'-d]pyridine (**30**) (Table 2, entry 1)*. To a stirred mixture of **26** (50 mg, 0.16 mmol) and CuI (1.5 mg, 0.008 mmol) in dioxane (1 mL) were added paraformaldehyde (10 mg, 0.32 mmol) and dipropylamine (0.022 mL, 0.16 mmol), then the mixture was stirred at room temperature for 30 min under argon. The solvent was removed under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (3:1) to give **29** (20 mg, 30% yield) and **30** (15 mg, 29% yield).

Compound **30**: white solid; R_f = 0.45 (alumina, *n*-hexane/EtOAc = 1/1); mp 170 °C; IR (neat) cm^{-1} 1363, 1320, 1165, 1108 (SO_2 × 2); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.30 (3H, s), 3.82 (3H, s), 5.11 (1H, d, J = 3.4 Hz), 5.34 (1H, d, J = 3.4 Hz), 6.77 (1H, d, J = 3.9 Hz), 7.83 (1H, d, J = 3.9 Hz), 8.57 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 49.5 (q), 53.8 (q), 105.7 (s), 117.2 (d), 119.4 (s), 129.8 (s), 141.1 (d), 145.2 (s), 152.7 (d), 161.1 (d), 161.3 (s); HRMS (FAB) calcd for $C_{11}H_{12}N_3O_4S_2$ [M+H$^+$]: 314.0269, found: 314.0257.

*4.4.11. N-{6-[3-(Dipropylamino)prop-1-ynyl]-1-(methylsulfonyl)-1H-pyrrolo[3,2-b]pyridin-7-yl}methanesulfonamide (**31**)*. A solution of **29** (20 mg, 0.05 mmol) in $CDCl_3$ (0.5 mL) was placed in a NMR tube. After 24 h at room temperature, ^{1}H NMR analysis showed that **29** was converted to **31** with a ratio of 4:1

(**31**/**29**). The mixture was purified by column chromatography over silica gel with $CHCl_3$–MeOH (9:1) to give **31** (13 mg, 65% yield) as an orange oil; R_f = 0.50 (silica gel, $CHCl_3$/MeOH = 9/1); IR (neat) cm^{-1} 2228 (C≡C), 1349, 1316, 1158, 1137 (SO_2 × 2); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.94 (6H, t, *J* = 7.2 Hz), 1.52-1.57 (4H, m), 2.59 (4H, t, *J* = 7.4 Hz), 3.51 (3H, s), 3.66 (3H, s), 3.69 (2H, s), 6.88 (1H, d, *J* = 3.4 Hz), 7.78 (1H, d, *J* = 3.4 Hz), 8.63 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.8 (2C, q), 20.3 (2C, t), 43.6 (q), 44.0 (q), 44.2 (t), 55.8 (2C, t), 82.4 (s), 92.0 (s), 109.3 (d), 113.0 (s), 123.2 (s), 131.8 (d), 136.2 (s), 149.9 (s), 152.0 (d); HRMS (FAB) calcd for $C_{18}H_{27}N_4O_4S_2$ [*M*+H^+]: 427.1474, found: 427.1478.

*4.4.12. N-{6-[3-(Dipropylamino)prop-1-ynyl]-1H-pyrrolo[3,2-b]pyridin-7-yl}methanesulfonamide (**32**) and 4-[2-(dipropylamino)ethyl]-1,9-dihydropyrrolo[2',3':5,6]pyrido[4,3-c][1,2]thiazine 2,2-dioxide (**33**).* A mixture of **29** (94 mg, 0.22 mmol) and Cs_2CO_3 (216 mg, 0.66 mmol) in THF (2 mL) and MeOH (1 mL) was stirred at 70 °C for 3 h under argon. After being cooled to room temperature, the solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel with $CHCl_3$–MeOH (9:1) to give **33** (43 mg, 52% yield) and **32** (9 mg, 12% yield).

Compound **32**: orange oil; R_f = 0.45 (silica gel, $CHCl_3$/MeOH = 9/1); IR (neat) cm^{-1} 3440 (NH), 2249 (C≡C), 1342, 1159 (SO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.94 (6H, t, *J* = 7.4 Hz), 1.53-1.58 (4H, m), 2.57-2.61 (4H, m), 3.13 (3H, s), 3.68 (2H, s), 6.48 (1H, dd, *J* = 2.9, 2.9 Hz), 7.38 (1H, dd, *J* = 2.9, 2.9 Hz), 8.07 (1H, s), 10.49 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.9 (2C, q), 20.2 (2C, t), 41.7 (q), 43.1 (t), 55.7 (2C, t), 79.6 (s), 90.6 (s), 100.2 (s), 105.1 (d), 111.5 (s), 120.6 (s), 129.5 (d), 137.4 (s), 141.5 (d); HRMS (FAB) calcd for $C_{17}H_{25}N_4O_2S$ [*M*+H^+]: 349.1698, found: 349.1688.

Compound **33**: light yellow solid; R_f = 0.30 (silica gel, $CHCl_3$/MeOH = 9/1); mp 205 °C; IR (neat) cm^{-1} 3187 (NH), 1409, 1104 (SO_2); ^1H NMR (500 MHz, DMSO-d_6) δ: 0.84 (6H, t, *J* = 7.2 Hz), 1.36-1.44 (4H, m), 2.43 (4H, t, *J* = 7.4 Hz), 2.68 (2H, t, *J* = 7.2 Hz), 2.77 (2H, t, *J* = 7.2 Hz), 6.42 (1H, d, *J* = 2.9 Hz), 6.49 (1H, s), 7.47 (1H, d, *J* = 2.9 Hz), 8.28 (1H, s), 12.26 (1H, br s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 11.7 (2C, q), 19.7 (2C, t), 29.5 (t), 52.9 (t), 55.1 (2C, t), 96.4 (d), 105.7 (s), 117.1 (d), 121.7 (s), 128.0 (d), 131.8 (s), 133.2 (d), 140.3 (s), 145.1 (s); HRMS (FAB) calcd for $C_{17}H_{25}N_4O_2S$ [*M*+H^+]: 349.1698, found: 349.1688.

*4.4.13. N-(6-Ethynyl-1H-pyrrolo[3,2-b]pyridin-7-yl)methanesulfonamide (**36**).* A mixture of **26** (100 mg, 0.32 mmol) and Cs_2CO_3 (214 mg, 0.64 mmol) in THF (2 mL) and MeOH (1 mL) was stirred at 50 °C for 3 h under argon. After being cooled to room temperature, solvent was removed under reduced pressure and the residue was purified by column chromatography over silica gel with $CHCl_3$–MeOH (9:1) to give **36** (61 mg, 82% yield) as a white solid: R_f = 0.40 (silica gel, $CHCl_3$/MeOH = 9/1); mp 147 °C; IR (neat) cm^{-1} 3282 (NH), 3226 (C≡C), 1343, 1115 (SO_2); ^1H NMR (500 MHz, DMSO-d_6) δ: 3.04 (3H, s), 4.13 (1H, s), 6.44 (1H, d, *J* = 3.0 Hz), 7.67 (1H, dd, *J* = 3.0, 3.0 Hz), 8.22 (1H, s), 11.16 (1H, s), 13.15 (1H, br s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 42.1 (q), 79.6 (s), 83.7 (d), 96.7 (s), 103.1 (s), 108.4 (d), 124.3 (s), 127.1 (d), 130.7 (s), 143.4 (d); HRMS (FAB) calcd for $C_{10}H_{10}N_3O_2S$ [*M*+H^+]: 236.0494, found: 236.0500.

*4.4.14. N-{[8-(Methylsulfonyl)-1,8-dihydrodipyrrolo[3,2-b:2',3'-d]pyridin-7-yl]methyl}-N-propylpropan-1-amine (**37**).* To a stirred mixture of **36** (53 mg, 0.23 mmol) and CuI (2.6 mg, 0.012 mmol) in dioxane (1 mL) was added a preheated solution (80 °C, 5 min) of paraformaldehyde (14 mg, 0.46 mmol) and dipropylamine (0.032 mL, 0.23 mmol) in toluene (1 mL), and then the mixture was stirred at room temperature for 30 min under argon. The solvent was removed under reduced pressure and the residue was purified by column chromatography over alumina with *n*-hexane–EtOAc (5:1) to give **37** (50 mg, 65% yield) as a white solid: R_f = 0.65 (alumina, *n*-hexane/EtOAc = 1/1); mp 125 °C; IR (neat) cm^{-1} 3439 (NH), 1337, 1153 (SO_2); ^1H NMR (500 MHz, $CDCl_3$) δ: 0.81 (6H, t, *J* = 7.2 Hz), 1.42-1.48 (4H, m), 2.45-2.48 (4H, m), 3.60 (3H, s), 3.90 (2H, s), 6.71 (1H, s), 6.84-6.86 (1H, m), 7.35-7.37 (1H, m), 8.68 (1H, s), 9.95 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 11.7 (2C, q), 18.7 (2C, t), 42.1 (q), 52.0 (t), 54.8 (2C, t), 104.3 (d), 111.1 (d), 115.0 (s), 119.3 (s), 124.8 (d), 127.4 (s), 136.0 (s), 137.4 (d), 143.9 (s); HRMS (FAB) calcd for $C_{17}H_{25}N_4O_2S$ [*M*+H^+]: 349.1698, found: 349.1696.

*4.4.15. N-[(1,8-Dihydrodipyrrolo[3,2-b:2',3'-d]pyridin-7-yl)methyl]-N-propylpropan-1-amine (**27**).* A mixture of **37** (50 mg, 0.14 mmol) and Cs_2CO_3 (91 mg, 0.28 mmol) in THF (1 mL) and MeOH (0.5 mL) was stirred at 55 °C for 1 h under argon. After being cooled to room temperature, solvent was removed under reduced pressure and the residue was purified by column chromatography over alumina with $CHCl_3$–MeOH (30:1) to give **27** (30 mg, 78% yield) as a yellow solid: R_f = 0.55 (alumina, $CHCl_3$/MeOH = 15/1); IR (neat) cm^{-1} 3431 (NH × 2); mp 155 °C (decomp.); ^1H NMR (500 MHz, DMSO-d_6) δ: 0.84 (6H, t, *J* = 7.4 Hz), 1.43-1.51 (4H, m), 2.40 (4H, t, *J* = 7.4 Hz), 3.73 (2H, s), 6.44 (1H, s), 6.54 (1H, dd, *J* = 2.5, 2.5 Hz), 7.34 (1H, dd, *J* = 2.5, 2.5 Hz), 8.47 (1H, s), 10.50 (1H, s), 10.72 (1H, s); ^{13}C NMR (125 MHz, DMSO-d_6) δ: 11.8 (2C, q), 19.6 (2C, t), 51.3 (t), 55.4 (2C, t), 100.5 (d), 102.7 (d), 115.2 (s), 120.1 (s), 123.1 (d), 126.7 (s), 134.8 (s), 136.7 (d), 139.5 (s); HRMS (FAB) calcd for $C_{16}H_{23}N_4$ [*M*+H^+]: 271.1922, found: 271.1924.

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