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Pd-catalyzed reactions on pyridinium *N*-heteroarylaminides. Step-by-step synthesis of 3,5-unsymmetrically disubstituted 2-aminopyridines

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Dedicated to Professor Manuel Bernabé on the occasion of his 74th birthday

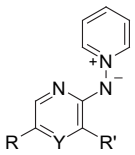
ABSTRACT

Suzuki–Miyaura cross-coupling processes on *N*-pyridinium bromoazinyl aminides allow access to 3,5-disubstituted *N*-alkyl-2-aminopyridines. The synthetic pathway involves a regioselective bromination of pyridinium *N*-(pyridin-2-yl)aminide and a subsequent reaction with boronic acids to afford mono-substituted aminides in good yields. An additional bromination in the 5-position of the pyridine ring followed by a coupling reaction gives pyridinium *N*-(3,5-diarylpyridin-2-yl)aminides. Finally, a regioselective alkylation on the *exo*-nitrogen and reduction of the N–N bond yields highly substituted 2-aminopyridines.

1. Introduction

Palladium-catalyzed Suzuki–Miyaura coupling reactions[1] are amongst the most powerful C–C bond forming reactions from haloarenes. Since the initial development of the reaction numerous authors have contributed to the improvement of the process[2] through the use of new catalytic systems,[3] the preparation of more reactive or stable boron reagents such as alkyltrifluoroborates[4] or boronate esters[5] and the development of greener methods such as the recent use of water[6] or solvent free processes[7] among other relevant examples.

As part of our research programme we became focused on the preparation of different heterobiaryls from *N*-heteroaryl pyridinium aminides **1** (Fig. 1), which are valuable precursors of alkylaminoheterocycles and can thus be easily obtained through a regioselective N-alkylation and a reduction process.[8] In previous communications we reported the success of the Suzuki cross-coupling reaction on mono- and dibrominated aminides **2**, which resulted in the corresponding arylated *N*-azinyl pyridinium aminides **3**–**6** under standard conditions (Fig. 1).[9]



1a Y = CH, R = R' = H
1b Y = N, R = R' = H
2a Y = CH, R' = H, R = Br
2b Y = N, R' = H, R = Br
2c Y = CH, R' = R = Br
2d Y = N, R' = R = Br
3 Y = CH, R' = H, R = Ar
4 Y = N, R' = H, R = Ar
5 Y = CH, R' = R = Ar
6 Y = N, R' = R = Ar
7 Y = CH, R' = Ar, R = Br
8 Y = N, R' = Ar, R = Br

Figure 1. *N*-Pyridinium azinyl aminides.

The reaction on *N*-3,5-dibromopyrazinyl pyridinium aminide **2d** showed a surprising preference towards position 3 in the oxidative addition of palladium.[9b] Further studies demonstrated that although this observed selectivity also appears in the dibrominated aminide **2c**,[9c] it is much lower in the compound stabilized by a pyridine ring. This behaviour allowed us to prepare disubstituted 2-alkylaminopyrazines with different substituents in the 3- and 5-positions. The key step in this process is selective coupling of the dibrominated aminide **2d** to give **8**.[9c] Unfortunately, however, this methodology could not be applied to the *N*-dibromopyridinyl pyridinium aminide **2c** to obtain **7**, as an intermediate in a regioselective synthesis of 2-aminopyridines, due to the lower selectivity found for compound **2c** towards the monocoupling in the 3-position (Fig. 1).[9b]

A continuous effort has been applied to the synthesis and functionalisation of 2-aminopyridines[10] since they are useful building blocks in the synthesis of fused nitrogen heterocycles.[11] Furthermore, some 2-aminopyridine compounds have been used as ligands in the preparation of metal complexes,[12] while other similar derivatives have shown interesting biological activities.[13] In this paper a step-by-step synthesis of 3,5-disubstituted 2-aminopyridines is reported. In this approach it is possible to take advantage of the selectivity found in the monohalogenation of *N*-azinyl pyridinium aminides **1**[14] to introduce an aryl group in the 5-position. A subsequent halogenation/arylation sequence on the electronically activated 3-position of compounds **3** gives the desired products (Scheme 1).

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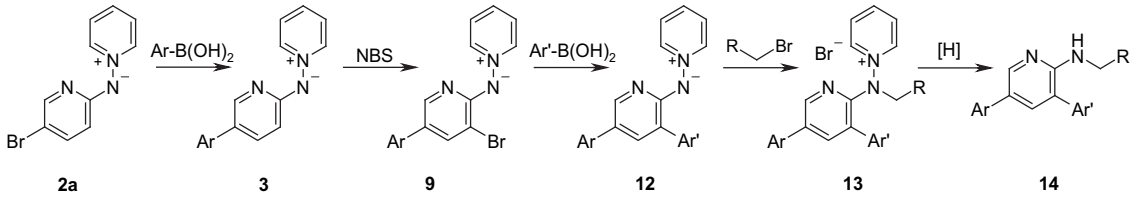


Scheme 1. Synthetic sequence to 3,5-disubstituted 2-aminopyridines.

2. Results and discussion

The *N*-(5-bromopyridin-2-yl)pyridinium aminide **2a**[14] –obtained by selective halogenation of *N*-(pyridin-2-yl)pyridinium aminide **1a**[8a]– was satisfactorily coupled with different boronic acids under previously reported standard conditions: i.e., aminide (1 mmol), boronic acid (1.5 mmol), $Pd(PPh_3)_4$ (5 mmol %) and K_2CO_3 (10 mmol) in refluxing toluene–ethanol (4:1, v/v)[9c] to afford the 5-arylated (or heteroarylated) products **3** in good yields (Scheme 1, Table 1). These compounds are suitable substrates to undergo a new bromination process in the 3-position of the pyridine ring to afford the corresponding aminides **9**. The halogenation was accomplished for **3a** and **3c** under previously reported conditions,[15] which involved the use of NBS in dichloromethane at room temperature. However, when these conditions were applied to **3b**, two compounds were isolated in a 1:1 ratio from the reaction mixture—the desired monobrominated aminide **9b** and the dibrominated product **10** (Fig. 2). In compound **10** an additional bromo-substituent has been incorporated in the *para*-position of the activated benzene ring, flanked by the two methyl groups. Similar behaviour was observed in the bromination of **3e**, where aminide **9e** and compound **11** (Fig. 2) were identified. This drawback was overcome by slow addition of NBS at low temperature (−30 or −40 °C) to the corresponding aminide **3**; the same conditions were used in the synthesis of **9d** (Scheme 1, Table 1).

The cross-coupling between compounds **9** and aryl or heteroaryl boronic acids, to obtain the corresponding 3,5-disubstituted aminides **12**, was performed under the same conditions

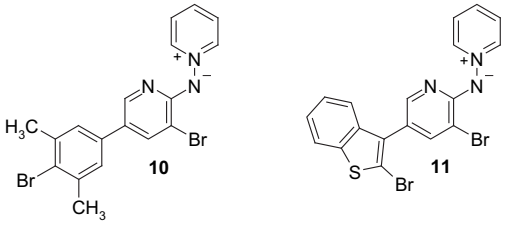
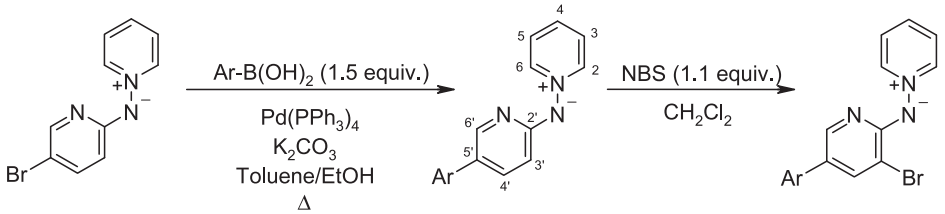
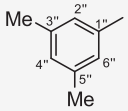
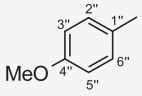
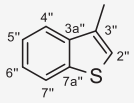


Figure 2. Side products obtained from **3b** and **3e**.

Table 1
Arylation of aminide **2a** and bromination of compounds **3**



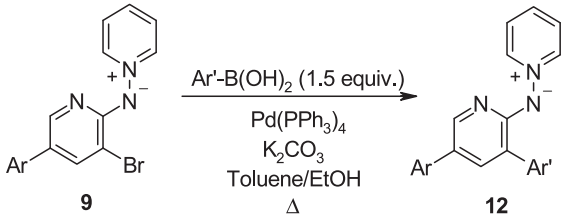
Ar	Compound	Time (h)	Yield (%)	Compound	Time (h)	Yield (%)
	**3a**[9a]	8	91	**9a**[15]	12	74
	**3b**	48	71	**9b**	12	87
	**3c**[9c]	8	85	**9c**[15]	12	78
	**3d**	8	88	**9d**	12	65
	**3e**	24	82	**9e**	4	73

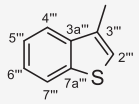
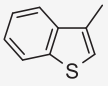
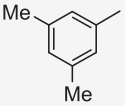
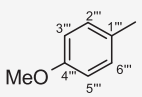
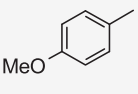
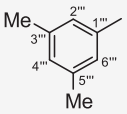
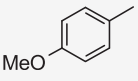
described to transform the *N*-(5-bromopyridin-2-yl)pyridinium aminide **2a** into compounds **3**. The reactions were complete in around 24 h and the coupled products were obtained, after purification by chromatography, in moderate to good yields (Scheme 1, Table 2).

As occurs with other similar compounds,[9c] when aminides **12** were stirred with benzyl bromides in anhydrous acetone at room temperature for the times shown in Table 3, a regioselective N-alkylation process occurred on the *exo*cyclic nitrogen and the corresponding pyridinium salts **13** were obtained in good to excellent yields after removal of the solvent under vacuum, trituration of the crude product with ethyl acetate and removal of the excess alkylating agent by filtration. When this reaction was applied to **12g** the dibromide **13g** was obtained as a consequence of an additional alkylation process on the pyridine nitrogen in the 3-pyridyl substituent (Scheme 1, Table 3).

Finally, amines **14** were obtained by reduction of the corresponding pyridinium salts with zinc (powder) in glacial acetic acid as a metal/acid system (Scheme 1, Table 3). Acceptable yields were obtained after purification by column chromatography and crystallization from a suitable solvent.

Table 2
Arylation of aminides **9a–e**



Ar	Ar′	Compound	Time (h)	Yield (%)
		**12a**	24	77
		**12b**	22	93
		**12c**	23	54
		**12d**	24	86
		**12e**	24	71
		**12f**	19	78
		**12g**	24	78

3. Conclusions

In conclusion, a selective and efficient scheme to prepare a series of 3,5-unsymmetrically disubstituted 2-aminopyridines **14** is described. The sequence starts from *N*-(5-bromopyridin-2-yl)pyridinium aminide **2a** and involves a Suzuki arylation to produce **3**, a second bromination to produce **9**, and a second Suzuki arylation to produce **12**. A final regioselective alkylation on the *exo*cyclic nitrogen produces the salts **13** and a subsequent reduction of the N–N bond completes the synthesis of the 2-aminopyridines **14**.

4. Experimental

4.1. General remarks

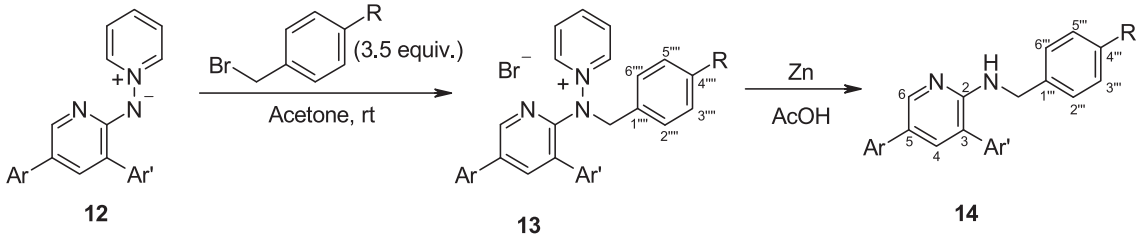
All melting points were determined in open capillary tubes on a Stuart Scientific SMP3 melting point apparatus and are uncorrected. IR spectra were obtained on a Perkin–Elmer FTIR spectrum 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity 300 or 500 MHz spectrometer or on a Varian Mercury VX-300 system at room temperature. Chemical shifts are given in parts per million (δ) downfield from TMS. Coupling constants (J) are in Hertz (Hz) and signals are described as follows: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad; ap, apparent. The tentative assignment of proton and carbon resonances was made on the basis of double resonance, NOESY and TOCSY experiments, two-dimensional H,H- and H,C-correlation experiments, COSY, HSQC, HMBC or related spectra. In order to identify the signals in the description of each product, positions of the pyridinium ring are not labelled, positions of the pyridine ring are labelled (′), positions of the 5-aryl substituent are labelled (″), positions of the 3-aryl substituent are labelled (‴) and positions of the aryl ring belonging to the *N*-benzyl substituent, when present, are labelled (⁗). For reduced compounds **14**, the labelling has one fewer prime label than the precursor (due to the absence of the pyridinium ring). Elemental analyses were carried out on a Heraeus Rapid CHN analyzer and were within 0.4% of the theoretical values for all the new compounds described. Hydration in the solid state was confirmed by Karl Fischer titration. Low-resolution mass spectra (MS) were recorded on a Hewlett–Packard 5988A (70 eV) spectrometer using electron impact (EI) or electrospray (ESI) ionization and high-resolution analysis (TOF) was performed on an Agilent 6210 time-of-flight LC/MS. All reagents were obtained from commercial sources and used without further purification. Solvents were purified and dried by standard procedures. TLC analyses were performed on silica gel (Kieselgel 60 F_{254}, Macherey-Nagel) and spots were visualized under UV light. Column chromatography was carried out with silica gel 60 (40–63 μm, Merck) columns, using the eluent reported in each case.

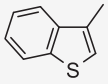
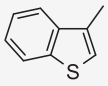
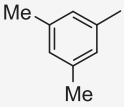
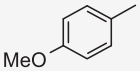
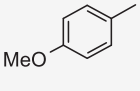
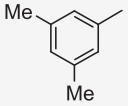
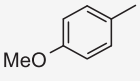
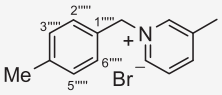
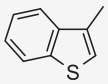
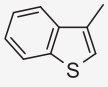
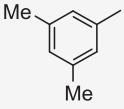
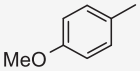
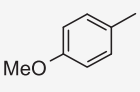
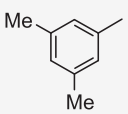
4.2. Preparation of 5-substituted *N*-(pyridin-2-yl)pyridinium aminides (3)

General method: Aminide **2a** (1 mmol), the corresponding boronic acid (1.5 mmol) and K_2CO_3 (10 mmol) were dissolved in a toluene–ethanol mixture (4:1, 15 mL). $Pd(PPh_3)_4$ (5 mmol %) was added and the mixture was stirred under argon and heated under reflux for the reaction time indicated in Table 1.

The course of the reaction was followed by TLC. Once the starting material had been consumed, the system was allowed to reach room temperature, the mixture was filtered through Celite and washed with acetonitrile until colour was no longer observed in the filtrate. The combined filtrates were evaporated to dryness. The crude product was purified by flash chromatography on a silica gel column, with ethanol as the mobile phase, and recrystallized from a suitable solvent.

Table 3
Synthesis of 3,5-disubstituted aminopyridines **14**



Ar	Ar′	R	Compound	Time (h)	Yield (%)
		H	**13a**	48	77
		H	**13b**	24	60
		H	**13c**	24	72
		H	**13d**	96	71
		Me	**13e**	28	76
		Me	**13f**	28	94
		Me	**13g**	24	96
		H	**14a**	24	63
		H	**14b**	44	48
		H	**14c**	24	60
		H	**14d**	24	70
		Me	**14e**	24	74
		Me	**14f**	27	71

*4.2.1. N-(5-Phenylpyridin-2-yl)pyridinium aminide (**3a**).* See Ref. 9a.

*4.2.2. N-[5-(3,5-Dimethylphenyl)pyridin-2-yl]pyridinium aminide (**3b**).* Orange solid (195 mg, 71%, ethanol–ethyl acetate), mp 86–88 °C; IR (KBr) ν_{max} (cm^{-1}): 1595, 1488, 1379, 1147, 1005, 758, 665; ^1H NMR (300 MHz, CD_3OD): δ 8.77 (2H, dd, *J*=7.0 and 1.3 Hz, *H*2(6)), 7.99 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 7.94 (1H, dd, *J*=2.4 and 0.6 Hz, *H*6′), 7.78 (2H, dd, *J*=7.7 and 7.0 Hz, *H*3(5)), 7.66 (1H, dd, *J*=8.8 and 2.4 Hz, *H*4′), 7.10 (2H, br s, *H*2″(6″)), 6.90 (1H, br s, *H*4″), 6.60 (1H, d, J=8.8 Hz, *H*3′), 2.33 (6H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 164.8, 144.8, 144.3, 139.9, 139.3, 137.3, 137.1, 128.8, 128.4, 125.8, 124.3, 112.3, 21.5. MS (EI, *m*/*z*): 275 (55, M^+), 274 (100), 154 (12), 127 (12), 79 (75), 52 (54); HRMS (ESI-TOF, CH_3OH): calcd for $C_{18}H_{18}N_3$: $[M+H]^+$ 276.1501, found 276.1490. Anal. Calcd for $C_{18}H_{17}N_3\cdot 3/2H_2O$: C, 71.50; H, 6.67; N, 13.90. Found: C, 71.64; H, 6.30; N, 13.53.

*4.2.3. N-[5-(4-Methoxyphenyl)pyridin-2-yl]pyridinium aminide (**3c**).* See Ref. 9c.

*4.2.4. N-[5-(Thiophen-3-yl)pyridin-2-yl]pyridinium aminide (**3d**).* Orange solid (223 mg, 88%, ethyl acetate), mp 95–97 °C; IR (KBr) ν_{max} (cm^{-1}): 1597, 1467, 1408, 1390, 1368, 1344, 1150, 767, 666; ^1H NMR (300 MHz, CD_3OD): δ 8.79 (2H, dd, *J*=7.0 and 1.3 Hz, *H*2(6)), 8.04 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 8.02 (1H, d, *J*=2.6 Hz, *H*6′), 7.82 (2H, dd, *J*=7.7 and 7.0 Hz, *H*3(5)), 7.73 (1H, dd, *J*=8.9 and 2.6 Hz, *H*4′), 7.45 (1H, dd, *J*=4.9 and 2.9 Hz, *H*5″), 7.40 (1H, dd, *J*=2.9 and 1.5 Hz, *H*2″), 7.35 (1H, dd, *J*=4.9 and 1.5 Hz, *H*4″), 6.59 (1H, d, J=8.9 Hz, *H*3′); ^{13}C NMR (75 MHz, CD_3OD): δ 164.1, 144.7, 144.1, 140.9, 138.3, 136.9, 128.6, 127.2, 126.2, 121.8, 118.5, 112.2. MS (EI, *m*/*z*): 253 (57, M^+), 252 (100), 176 (14), 146 (37), 126 (22), 103 (17), 79 (25), 52 (23); HRMS (ESI-TOF, CH_3OH): calcd for $C_{14}H_{12}N_3S$: $[M+H]^+$ 254.07464, found 254.07431. Anal. Calcd for $C_{14}H_{11}N_3S\cdot 1/3H_2O$: C, 64.84; H, 4.53; N, 16.20; S, 12.36. Found: C, 64.58; H, 4.64; N, 16.11; S, 12.37.

*4.2.5. N-[5-(Benzo[b]thiophen-3-yl)pyridin-2-yl]pyridinium aminide (**3e**).* Orange solid (248 mg, 82%, ethyl acetate–hexane), mp 145–147 °C; IR (KBr) ν_{max} (cm^{-1}): 1654, 1647, 1521, 1474, 1381, 1139, 762, 734; ^1H NMR (300 MHz, CD_3OD): δ 8.83 (2H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 8.10 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 7.90 (5H, m, *H*3(5), *H*6′, *H*4″ and *H*7″), 7.67 (1H, dd, *J*=8.8 and 2.6 Hz, *H*4′), 7.43 (1H, s, *H*2″), 7.40 (2H, m, *H*5″ and *H*6″), 6.69 (1H, d, J=8.8 Hz, *H*3′); ^{13}C NMR (75 MHz, CD_3OD): δ 165.0, 146.3, 144.8, 142.1, 139.2, 138.8, 138.1, 136.6, 128.6, 125.4, 125.3, 123.9, 123.5, 122.8, 120.7, 112.1. MS (EI, *m*/*z*): 303 (69, M^+), 302 (100), 226 (59), 224 (27), 196 (86), 171 (22), 151 (37), 79 (81), 52 (64); HRMS (ESI-TOF, CH_3OH): calcd for $C_{18}H_{14}N_3S$: $[M+H]^+$ 304.09029, found 304.09209. Anal. Calcd for $C_{18}H_{13}N_3S\cdot 2/3H_2O$: C, 68.55; H, 4.58; N, 13.32; S, 10.17. Found: C, 68.54; H, 4.35; N, 13.41; S, 9.92.

4.3. Synthesis of 3-bromo-5-substituted *N*-(pyridin-2-yl)pyridinium aminides (9)

General method: To a stirred solution of the corresponding aminide **3** (1 mmol) in dichloromethane (8 mL) at room temperature, a solution of NBS (1.1 mmol) in the same solvent (15 mL) was added. The mixture was stirred until starting material was no longer detected by TLC. The solvent was evaporated in vacuo and the product was purified by chromatography on silica gel, using ethanol as eluent and then crystallized from a suitable solvent and identified.

The procedure was used with dropwise addition of the described NBS solution over 30 min, and low temperature in the case of compounds **9b** (−40 °C) and **9d** and **9e** (−30 °C), in order to avoid bromination of the aromatic substituent at the 5-position of the pyridine ring.

Compounds **10** and **11** were obtained together with the corresponding monobrominated aminide **9b** and **9e**, when the addition of NBS to **3b** and **3e** was carried out in 3 min, and at room temperature. The compounds obtained in each case were separated by column chromatography and crystallized from the appropriate solvent.

*4.3.1. N-(3-Bromo-5-phenylpyridin-2-yl)pyridinium aminide (**9a**).* See Ref. 15.

*4.3.2. N-[3-Bromo-5-(3,5-dimethylphenyl)pyridin-2-yl]pyridinium aminide (**9b**).* Orange solid (308 mg, 87%, ethyl acetate), mp 176–178 °C; IR (KBr) ν_{max} (cm^{-1}): 1588, 1469, 1449, 1380, 847, 766, 672; ^1H NMR (300 MHz, CD_3OD): δ 8.72 (2H, dd, *J*=7.0 and 1.3 Hz, *H*2(6)), 8.17 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 7.92 (1H, d, *J*=2.0 Hz *H*6′), 7.90 (2H, m, *H*3(5)), 7.87 (1H, d, *J*=2.0 Hz, *H*4′), 7.08 (2H, ap s, *H*2″(6″)), 6.92 (1H, ap s, *H*4″), 2.34 (6H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 162.0, 146.0, 144.0, 139.9, 139.5, 139.3, 138.7, 129.1, 128.7, 126.3, 124.3, 106.7, 21.5. MS (EI, *m*/*z*): 355/353 (63/64, M^+), 354/352 (100/91), 195 (33), 179 (24), 168 (77), 153 (45), 140 (24), 128 (20), 115 (32), 79 (81), 52 (61); HRMS (ESI-TOF, CH_3OH): calcd for $C_{18}H_{17}{}^{79}BrN_3$: $[M+H]^+$ 354.0606, found 354.0602. Anal. Calcd for $C_{18}H_{16}BrN_3\cdot 3/4H_2O$ (%): C, 58.79; H, 4.80; N, 11.43. Found: C, 58.81; H, 4.64; N, 11.20.

*4.3.3. N-[3-Bromo-5-(4-methoxyphenyl)pyridin-2-yl]pyridinium aminide (**9c**).* See Ref. 15.

*4.3.4. N-[3-Bromo-5-(thiophen-3-yl)pyridin-2-yl]pyridinium aminide (**9d**).* Orange solid (216 mg, 65%, ethyl acetate–hexane), mp 148–150 °C; IR (KBr) ν_{max} (cm^{-1}): 1584, 1472, 1445, 1387, 1165, 1155, 1030, 1015, 777, 764, 742, 676; ^1H NMR (300 MHz, CD_3OD): δ 8.74 (2H, dd, *J*=6.9 and 1.4 Hz, *H*2(6)), 8.19 (1H, tt, *J*=7.7 and 1.4 Hz, *H*4), 8.02 (1H, d, *J*=2.2 Hz, *H*6′), 7.97 (1H, d, *J*=2.2 Hz, *H*4′), 7.92 (2H, dd, *J*=7.7 and 6.9 Hz, *H*3(5)), 7.47 (1H, dd, *J*=4.9 and 3.0 Hz, *H*5″), 7.44 (1H, dd, *J*=3.0 and 1.8 Hz, *H*2″), 7.34 (1H, dd, *J*=4.9 and 1.8 Hz, *H*4″); ^{13}C NMR (75 MHz, CD_3OD): δ 161.6, 146.0, 143.7, 139.9, 139.5, 139.4, 128.6, 127.3, 126.2, 122.0, 118.7, 106.7. MS (EI, *m*/*z*): 333/331 (22/21, M^+), 332/330 (31/27), 173 (34), 146 (100), 79 (32), 52 (26); HRMS (ESI-TOF, CH_3OH): calcd for $C_{14}H_{11}{}^{79}BrN_3S$: $[M+H]^+$ 331.9857, found 331.9835. Anal. Calcd for $C_{14}H_{10}BrN_3S\cdot H_2O$ (%): C, 48.01; H, 3.45; N, 12.00; S, 9.15. Found: C, 48.27; H, 3.25; N, 12.17; S, 9.34.

*4.3.5. N-[5-(Benzo[b]thiophen-3-yl)-3-bromopyridin-2-yl]pyridinium aminide (**9e**).* Orange solid (279 mg, 73%, ethyl acetate), mp 81–83 °C; IR (KBr) ν_{max} (cm^{-1}): 1588, 1470, 1439, 1419, 1387, 1145, 760, 734; ^1H NMR (300 MHz, CD_3OD): δ 8.77 (2H, dd, *J*=7.0 and 1.4 Hz, *H*2(6)), 8.21 (1H, tt, *J*=7.7 and 1.4 Hz, *H*4), 7.92 (5H, m, *H*3(5), *H*6′, *H*4′, *H*7″ or *H*4″), 7.83 (1H, m, *H*7″ or *H*4″), 7.46 (1H, s, *H*2″), 7.41 (2H, m, *H*5″ and *H*6″); ^{13}C NMR (75 MHz, CD_3OD): δ 162.0, 146.0, 145.6, 142.0, 141.3, 139.4, 139.0, 135.2, 128.6, 125.5, 125.4, 123.9, 123.3 (two overlapped signals), 121.0, 106.3. MS (EI, *m*/*z*): 383/381 (33/16, M^+), 382/380 (13/14), 303 (14), 223 (15), 196 (54), 129 (18), 111 (21), 97 (36), 95 (27), 83 (50), 71 (50), 69 (77), 57 (99), 55 (100); HRMS (ESI-TOF, CH_3OH): calcd for $C_{18}H_{13}{}^{79}BrN_3S$: $[M+H]^+$ 381.99929, found 382.00081. Anal. Calcd for $C_{18}H_{12}BrN_3S\cdot 1/2H_2O$ (%): C, 55.25; H, 3.35; N, 10.74; S, 8.19. Found: C, 55.24; H, 3.65; N, 10.81; S, 7.95.

*4.3.6. N-[3-Bromo-5-(4-bromo-3,5-dimethylphenyl)pyridin-2-yl]-pyridinium aminide (**10**).* This compound was obtained together with **9b** by addition of NBS to **3b** at room temperature. Orange solid (ethyl acetate), mp 74–76 °C; IR (KBr) ν_{max} (cm^{-1}): 1590, 1474, 1443, 1406, 1372, 1326, 1147, 1025, 669; ^1H NMR (300 MHz, CD_3OD): δ 8.74 (2H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 8.20 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 7.96 (1H, d, *J*=2.3 Hz *H*6′), 7.92 (2H, dd, *J*=7.7 and 6.9 Hz,

*H*3(5)), 7.91 (1H, d, *J*=2.3 Hz, *H*4′), 7.25 (2H, s, *H*2″(6″)), 2.45 (6H, s, C*H*$_3$); ^{13}C NMR (75 MHz, CD_3OD): δ 162.0, 146.2, 144.2, 139.8 (two overlapped signals), 139.6, 137.5, 128.7, 126.4, 126.3, 125.3, 106.7, 24.0. MS (EI, *m*/*z*): 435/433/431 (7/14/7, M^+), 434/432/430 (12/20/10, M−1), 358/356/354 (50/100/52), 196 (50); HRMS (ESI-TOF, CH_3OH): calcd for $C_{18}H_{16}{}^{79}Br_2N_3$: $[M+H]^+$ 431.9711, found 431.9697.

*4.3.7. N-[5-(Benzo[b]-2-bromothiophen-3-yl)-3-bromopyridin-2-yl]-pyridinium aminide (**11**).* This compound was obtained together with **9e** by addition of NBS to **3e** at room temperature. Orange solid (ethyl acetate–hexane), mp 189–191 °C; IR (KBr) ν_{max} (cm^{-1}): 1591, 1472, 1439, 1420, 1388, 1331, 1145, 761, 676; ^{1}H NMR (300 MHz, CD_3OD): δ 8.76 (2H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 8.21 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 7.93 (2H, dd, *J*=7.7 and 6.9 Hz, *H*3(5)), 7.83 (1H, m, *H*7″), 7.75 (1H, d, *J*=2.0, *H*6′), 7.73 (1H, d, *J*=2.0 Hz, *H*4′), 7.56 (1H, m, *H*4″), 7.38 (2H, m, *H*5″ and *H*6″); ^{13}C NMR (75 MHz, CD_3OD): δ 162.4, 147.4, 146.2, 142.2, 141.1, 139.9, 139.8, 135.0, 128.8, 126.2, 126.1, 123.5, 123.0, 118.0, 114.0, 105.8. MS (EI, *m*/*z*): 463/461/459 (18/34/17, M^+), 462/460/458 (33/56/27, M−1), 386/384/382 (4/9/5), 276/274 (32/32), 230 (21), 222 (47), 221 (30), 196 (18), 195 (40), 194 (29), 151 (23), 79 (100), 52 (74); HRMS (ESI-TOF, CH_3OH): calcd for $C_{18}H_{12}{}^{79}Br_2N_3S$: $[M+H]^+$ 459.9119, found 459.9116. Anal. Calcd for $C_{18}H_{11}Br_2N_3S\cdot 2H_2O$(%): C, 43.48; H, 3.04; N, 8.45; S, 6.45. Found: C, 43.78; H, 2.64; N, 8.58; S, 6.19.

4.4. Synthesis of unsymmetrical 3,5-disubstituted aminides 12

General method: $Pd(PPh_3)_4$ (5 mmol %), the corresponding boronic acid (1.5 mmol), the corresponding aminide **9** (1 mmol) and K_2CO_3 (10 mmol) were suspended in a mixture of toluene–ethanol (4:1, 15 mL). The mixture was stirred and heated under reflux under argon until the starting material was no longer detected by TLC (see Table 2). The system was then allowed to reach room temperature, the mixture was filtered through Celite and the residue was washed well with acetonitrile. The filtrates were combined and evaporated to dryness. The aminide **12** was purified by flash chromatography on a silica gel column, using ethanol as eluent, and recrystallized from the appropriate solvent.

*4.4.1. N-[5-Phenyl-3-(thiophen-3-yl)pyridin-2-yl]pyridinium aminide (**12a**).* Orange solid (253 mg, 77%, ethanol), mp 165–167 °C; IR (KBr) ν_{max} (cm^{-1}): 1591, 1472, 1433, 1381, 1302, 1145, 797, 765, 757, 696, 643, 501; ^{1}H NMR (300 MHz, CD_3OD): δ 8.74 (2H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 8.06 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 7.98 (1H, dd, *J*=3.2 and 1.3 Hz, *H*2‴), 7.91 (1H, d, *J*=2.3 Hz, *H*6′), 7.83 (3H, m, *H*3(5) and *H*4′), 7.67 (1H, dd, *J*=5.3 and 1.3 Hz, *H*4‴), 7.55 (2H, ap dd, *J*=8.2 and 1.3 Hz, *H*2″(6″)), 7.45 (1H, dd, *J*=5.3 and 3.2 Hz, *H*5‴), 7.41 (2H, ap dd, *J*=8.2 and 7.3 Hz, *H*3″(5″)), 7.26 (1H, tt, *J*=7.3 and 1.3 Hz, *H*4″); ^{13}C NMR (75 MHz, CD_3OD): δ 163.0, 145.2, 143.7, 140.7, 140.1, 137.7, 136.3, 129.9, 129.5, 128.4, 127.2, 126.5, 125.3, 125.2, 124.2, 119.4. MS (EI, *m*/*z*): 329 (10, M^+), 251 (25), 250 (100), 222 (16), 125 (12), 79 (52), 52 (36); HRMS (ESI-TOF, CH_3OH): calcd for $C_{20}H_{16}N_3S$: $[M+H]^+$ 330.1065, found 330.1029. Anal. Calcd for $C_{20}H_{15}N_3S\cdot 2/5H_2O$: C, 71.36; H, 4.73; N, 12.48; S, 9.52. Found: C, 71.10; H, 4.62; N, 12.27; S, 9.23.

*4.4.2. N-[3-Phenyl-5-(thiophen-3-yl)pyridin-2-yl]pyridinium aminide (**12b**).* Red solid (306 mg, 93%, ethanol–diethyl ether), mp 63–65 °C; IR (KBr) ν_{max} (cm^{-1}): 1594, 1472, 1456, 1430, 1387, 1145, 778, 699; ^{1}H NMR (300 MHz, CD_3OD): δ 8.75 (2H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 8.11 (1H, tt, *J*=7.6 and 1.3 Hz, *H*4), 8.03 (1H, d, *J*=2.3 Hz, *H*6′), 7.85 (2H, dd, *J*=7.6 and 6.9 Hz, *H*3(5)), 7.73 (2H, dd, *J*=8.1 and 1.2 Hz, *H*2‴(6‴)), 7.68 (1H, d, *J*=2.3 Hz, *H*4′), 7.46 (4H, m, *H*3‴(5‴), *H*2″ and *H*5″), 7.39 (1H, m, *H*4″), 7.36 (1H, tt, *J*=7.4 and 1.2 Hz, *H*4‴). ^{13}C NMR (75 MHz, CD_3OD): δ 162.6, 145.1, 143.6, 141.0, 140.9, 137.6, 137.2, 130.5, 129.2, 128.4, 128.0, 127.2, 126.2, 125.0, 121.5, 118.2. MS (EI, *m*/*z*): 329 (71, M^+), 328 (72), 252 (39), 251 (58), 250 (100), 222 (33), 205 (16), 79 (29), 52 (16); HRMS (ESI-TOF, CH_3OH): calcd for $C_{20}H_{16}N_3S$: $[M+H]^+$ 330.1065, found 330.1071. Anal. Calcd for $C_{20}H_{15}N_3S\cdot 1/3H_2O$: C, 71.62; H, 4.71; N, 12.53; S, 9.56. Found: C, 71.37; H, 5.02; N, 12.75; S, 9.21.

*4.4.3. N-[3-(Benzo[b]thiophen-3-yl)-5-phenylpyridin-2-yl]pyridinium aminide (**12c**).* Orange solid (205 mg, 54%, ethanol), mp 94–96 °C; IR (KBr) ν_{max} (cm^{-1}): 1593, 1425, 1382, 1296, 1145, 761; ^{1}H NMR (300 MHz, CD_3OD): δ 8.76 (2H, dd, *J*=7.0 and 1.3 Hz, *H*2(6)), 8.14 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 8.10 (1H, d, *J*=2.3 Hz, *H*6′), 7.96 (1H, m, *H*7‴ or *H*4‴), 7.87 (2H, dd, *J*=7.7 and 7.0 Hz, *H*3(5)), 7.86 (1H, m, and *H*4‴ or *H*7‴), 7.79 (1H, d, *J*=2.3 Hz, *H*4′), 7.74 (1H, s, *H*2‴), 7.57 (2H, dd, *J*=8.3 and 1.3 Hz, *H*2″(6″)), 7.41 (4H, m, *H*3″(5″), *H*5‴ and *H*6‴), 7.28 (1H, tt, *J*=7.3 and 1.3 Hz, *H*4″). ^{13}C NMR (75 MHz, CD_3OD): δ 161.6, 145.9, 144.9, 141.7, 139.8, 139.4, 138.7, 138.4, 135.6, 130.0, 128.7, 127.6, 126.7, 126.5, 125.6, 125.4, 125.1, 124.6, 123.7, 119.1. MS (EI, *m*/*z*): 379 (3, M^+), 301 (36), 300 (100), 198 (49), 181 (25), 152 (26), 150 (31), 79 (77), 52 (55); HRMS (ESI-TOF, CH_3OH): calcd for $C_{24}H_{18}N_3S$: $[M+H]^+$ 380.1221, found 380.1299. Anal. Calcd for $C_{24}H_{17}N_3S\cdot 3/2H_2O$ (%): C, 70.91; H, 4.96; N, 10.34; S, 7.89. Found: C, 70.51; H, 4.63; N, 10.09; S, 7.72.

*4.4.4. N-[5-(Benzo[b]thiophen-3-yl)-3-phenylpyridin-2-yl]pyridinium aminide (**12d**).* Orange solid (326 mg, 86%, ethanol–ethyl acetate), mp 83–85 °C; IR (KBr) ν_{max} (cm^{-1}): 1616, 1594, 1471, 1457, 1430, 1385, 1325, 1144, 760, 699; ^{1}H NMR (500 MHz, CD_3OD): δ 8.76 (2H, dd, *J*=7.0 and 1.2 Hz, *H*2(6)), 8.09 (1H, tt, *J*=7.8 and 1.2 Hz, *H*4), 7.94 (1H, m, *H*4″ or *H*7″), 7.93 (1H, d, *J*=2.3 Hz, *H*6′), 7.91 (1H, m, *H*4″ or *H*7″), 7.85 (2H, dd, *J*=7.8 and 7.0 Hz, *H*3(5)), 7.77 (2H, dd, *J*=8.1 and 1.3 Hz, *H*2‴(6‴)), 7.58 (1H, d, *J*=2.3 Hz, *H*4′), 7.47 (1H, s, *H*2″), 7.45 (2H, dd, *J*=8.1 and 7.4 Hz, *H*3‴(5‴)), 7.41 (2H, m, *H*5″ and *H*6″), 7.34 (1H, tt, *J*=7.4 and 1.3 Hz, *H*4‴). ^{13}C NMR (75 MHz, CD_3OD): δ 163.1, 145.6, 145.4, 142.1, 140.9, 139.3, 139.1, 138.0, 136.5, 130.5, 129.2, 128.5, 128.0, 125.4, 125.3, 124.7, 124.0, 123.5, 122.7, 120.7. MS (EI, *m*/*z*): 379 (66, M^+), 378 (68), 302 (50), 301 (68), 300 (100), 299 (44), 272 (33), 255 (23), 79 (45), 52 (31); HRMS (ESI-TOF, CH_3OH): calcd for $C_{24}H_{18}N_3S$: $[M+H]^+$ 380.1221, found 380.1181. Anal. Calcd for $C_{24}H_{17}N_3S\cdot 1/2H_2O$ (%): C, 73.82; H, 5.16; N, 10.76; S, 8.21. Found: C, 73.59; H, 5.39; N, 10.53; S, 8.10.

*4.4.5. N-[5-(3,5-Dimethylphenyl)-3-(4-methoxyphenyl)pyridin-2-yl]pyridinium aminide (**12e**).* Red solid (271 mg, 71%, ethanol–ethyl acetate), mp 72–74 °C; IR (KBr) ν_{max} (cm^{-1}): 1592, 1509, 1440, 1400, 1375, 1320, 1242, 1143, 831; ^{1}H NMR (300 MHz, CD_3OD): δ 8.67 (2H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 7.98 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 7.88 (1H, d, *J*=2.4 Hz, *H*6′), 7.76 (2H, dd, *J*=7.7 and 6.9 Hz, *H*3(5)), 7.66 (2H, d, *J*=8.9 Hz, *H*2‴(6‴)), 7.54 (1H, d, *J*=2.4 Hz, *H*4′), 7.13 (2H, ap s, *H*2″(6″)), 6.98 (2H, d, *J*=8.9 Hz, *H*3‴(5‴)), 6.91 (1H, ap s, *H*4″), 3.84 (3H, s, OC*H*$_3$), 2.34 (6H, s, C*H*$_3$); ^{13}C NMR (75 MHz, CD_3OD): δ 163.0, 160.2, 144.9, 143.6, 139.9, 139.4, 137.3, 137.2, 133.3, 131.5, 128.8, 128.3, 125.9, 124.6, 124.3, 114.6, 55.7, 21.5. MS (EI, *m*/*z*): 381 (93, M^+), 380 (93), 302 (100), 287 (52), 260 (42), 259 (74), 217 (15), 216 (13), 190 (14), 151 (29), 143 (19), 128 (24), 79 (79), 52 (44); HRMS (ESI-TOF, CH_3OH): calcd for $C_{25}H_{24}N_3O$: $[M+H]^+$ 382.1919, found 382.1909. Anal. Calcd for $C_{25}H_{23}N_3O\cdot 2H_2O$: C, 71.92; H, 6.52; N, 10.06. Found: C, 71.96; H, 6.33; N, 9.66.

*4.4.6. N-[3-(3,5-Dimethylphenyl)-5-(4-methoxyphenyl)pyridin-2-yl]pyridinium aminide (**12f**).* Red solid (297 mg, 78%, ethanol–ethyl acetate), mp 77–79 °C; IR (KBr) ν_{max} (cm^{-1}): 1589, 1442, 1405, 1373, 1327, 1145, 1013; ^{1}H NMR (300 MHz, CD_3OD): δ 8.67 (2H, dd, *J*=6.9 and 1.3 Hz, *H*2(6)), 7.99 (1H, tt, *J*=7.7 and 1.3 Hz, *H*4), 7.87 (1H, d, *J*=2.4 Hz, *H*6′), 7.77 (2H, dd, *J*=7.7 and 6.9 Hz, *H*3(5)), 7.52 (1H, d, *J*=2.4 Hz, *H*4′), 7.44 (2H, d, *J*=8.9 Hz, *H*2″(6″)), 7.30 (2H, s, *H*2‴(6‴)),

6.98 (1H, s, *H4‴*), 6.96 (2H, d, *J*=8.9 Hz, *H3″*(5″)), 3.82 (3H, s, OC*H*$_3$), 2.37 (6H, s, C*H*$_3$); ^{13}C NMR (75 MHz, CD$_3$OD): δ 162.6, 160.0, 145.0, 143.3, 140.9, 138.6, 137.4, 137.3, 132.6, 129.5, 128.3, 128.2, 127.6, 125.7, 125.4, 115.3, 55.7, 21.5. MS (EI, *m*/*z*): 381 (53, M$^+$), 304 (48), 303 (56), 302 (77), 287 (100), 259 (23), 151 (15), 144 (15), 122 (16), 79 (16), 52 (76); HRMS (ESI-TOF, CH$_3$OH): calcd for $C_{25}H_{24}N_3O$: [M+H]$^+$ 382.1919, found 382.1958. Anal. Calcd for $C_{25}H_{23}N_3O$: C, 77.49; H, 6.16; N, 10.84. Found: C, 77.66; H, 6.33; N, 10.56.

*4.4.7. N-[5-(4-Methoxyphenyl)-3-(pyridin-3-yl)pyridin-2-yl]pyridinium aminide (**12g**).* Orange solid (276 mg, 78%, ethanol–ethyl acetate), mp 169–171 °C; IR (KBr) ν_{max} (cm^{-1}): 1598, 1514, 1467, 1442, 1416, 1402, 1382, 1281, 1247, 1143, 826, 768, 708; ^{1}H NMR (300 MHz, CD$_3$OD): δ 8.92 (1H, dd, *J*=2.3 and 0.6 Hz, *H2‴*), 8.74 (2H, dd, *J*=6.9 and 1.3 Hz, *H2*(6)), 8.48 (1H, dd, *J*=4.9 and 1.6 Hz, *H6‴*), 8.24 (1H, ap dt, *J*=7.9 and 2.0 Hz, *H4‴*), 8.05 (1H, tt, *J*=7.7 and 1.3 Hz, *H4*), 7.94 (1H, d, *J*=2.3 Hz, *H6′*), 7.82 (2H, dd, *J*=7.7 and 6.9 Hz, *H3*(5)), 7.62 (1H, d, *J*=2.3 Hz, *H4′*), 7.51 (1H, ddd, *J*=7.9, 4.9 and 1.0 Hz, *H5‴*), 7.47 (2H, d, *J*=8.9 Hz, *H2″*(6″)), 6.98 (2H, d, *J*=8.9 Hz, *H3″*(5″)), 3.83 (3H, s, OC*H*$_3$); ^{13}C NMR (75 MHz, CD$_3$OD): δ 162.7, 160.1, 150.6, 147.9, 145.2, 144.9, 139.2, 137.8, 137.5, 132.3, 128.4 (two overlapped signals), 127.6, 125.5, 124.9, 120.4, 115.4, 55.7. MS (EI, *m*/*z*): 354 (49, M$^+$), 353 (41), 277 (100), 276 (92), 275 (27), 262 (24), 260 (62), 233 (27), 232 (30), 205 (19), 79 (97), 52 (47); HRMS (ESI-TOF, CH$_3$OH): calcd for $C_{22}H_{19}N_4O$: [M+H]$^+$ 355.1559, found 355.1552. Anal. Calcd for $C_{22}H_{18}N_4O\cdot 2/3H_2O$: C, 72.11; H, 5.32; N, 15.29. Found: C, 72.16; H, 5.29; N, 15.06.

4.5. Reaction of 3,5-disubstituted *N*-(pyridin-2-yl)pyridinium aminides (12) with benzyl bromides

General method: In a dry round-bottomed flask, the corresponding aminide (1 mmol) was dissolved in anhydrous acetone (11 mL). After addition of the corresponding benzyl bromide (3.5 mmol) the mixture was stirred at room temperature for the time indicated in Table 3, until the starting aminide was no longer detected by TLC. Once the reaction was complete, the solvent was evaporated in vacuo and the residue was triturated with ethyl acetate in an ultrasonic bath. The resulting suspension was filtered and the solid was washed well with ethyl acetate to remove excess benzyl bromide. The isolated salts **13** were used without further purification in the next step.

*4.5.1. 1-{N-Benzyl-N-[5-phenyl-3-(thiophen-3-yl)pyridin-2-yl]amino}pyridinium bromide (**13a**).* Beige solid (385 mg, 77%, ethanol), mp 182–184 °C; IR (KBr) ν_{max} (cm^{-1}): 1616, 1466, 1435, 1359, 772, 759, 719, 697, 686, 674; ^{1}H NMR (300 MHz, CD$_3$OD): δ 8.88 (2H, dd, *J*=6.9 and 1.4 Hz, *H2*(6)), 8.77 (1H, d, *J*=2.3 Hz, *H6′*), 8.51 (1H, tt, *J*=7.7 and 1.4 Hz, *H4*), 8.10 (1H, d, *J*=2.3 Hz, *H4′*), 7.93 (2H, dd, *J*=7.7 and 6.9 Hz, *H3*(5)), 7.75 (2H, ap dd, *J*=8.2 and 1.3 Hz, *H2″*(6″)), 7.64 (1H, dd, *J*=5.0 and 2.9 Hz, *H5‴*), 7.60 (1H, dd, *J*=2.9 and 1.5 Hz, *H2‴*), 7.53 (3H, m, *H4″* and *H3″*(5″)), 7.46 (1H, dd, *J*=5.0 and 1.5 Hz, *H4‴*), 7.31 (5H, s, *H2⁗*(6⁗), *H4⁗* and *H3⁗*(5⁗)), 5.10 (2H, s, C*H*$_2$); ^{13}C NMR (75 MHz, CD$_3$OD): δ 154.5, 148.0, 147.8, 146.3, 140.4, 137.7, 137.6, 137.5, 134.8, 130.7, 130.4, 130.1, 130.0, 129.7, 129.5 (two overlapped signals), 128.5, 128.2, 127.6, 126.4, 60.8. MS (EI, *m*/*z*): 420 (2, M$^+$−Br), 339 (53), 338 (100), 337 (92), 309 (16), 263 (31), 261 (35) 169 (20), 168 (15), 91 (49); HRMS (ESI-TOF, CH$_3$OH): calcd for $C_{27}H_{22}N_3S$: [M−Br]$^+$ 420.1534, found 420.1528. Anal. Calcd for $C_{27}H_{22}BrN_3S\cdot 3/2H_2O$: C, 61.48; H, 4.78; N, 7.97; S, 6.08. Found: C, 61.60; H, 4.39; N, 7.92; S, 5.70.

*4.5.2. 1-{N-Benzyl-N-[3-phenyl-5-(thiophen-3-yl)pyridin-2-yl]amino}pyridinium bromide (**13b**).* White solid (300 mg, 60%, ethanol–ethyl acetate), mp 193–195 °C; IR (KBr) ν_{max} (cm^{-1}): 1615, 1488, 1466, 1452, 1434, 1413, 1366, 913, 818, 721, 701, 685; ^{1}H NMR (500 MHz, CD$_3$OD): δ 8.86 (1H, d, *J*=2.3 Hz, *H6′*), 8.74 (2H, dd, *J*=6.9 and 1.3 Hz, *H2*(6)), 8.46 (1H, tt, *J*=7.7 and 1.3 Hz, *H4*), 8.09 (1H, d, *J*=2.3 Hz, *H4′*), 7.91 (1H, dd, *J*=4.2 and 1.7 Hz, *H5″*), 7.85 (2H, dd, *J*=7.7 and 6.9 Hz, *H3*(5)), 7.61 (2H, m, *H2″* and *H4″*), 7.48 (5H, m, *H2⁗*(6⁗), *H4⁗* and *H3⁗*(5⁗)), 7.28 (3H, m, *H2‴*(6‴) and *H4‴*), 7.23 (2H, m, *H3‴*(5‴)), 5.07 (2H, s, C*H*$_2$); ^{13}C NMR (75 MHz, CD$_3$OD): δ 154.7, 148.8, 146.6, 140.4, 139.3, 138.7, 135.8, 133.5, 133.3, 131.6, 131.2, 131.0, 130.9 (two overlapped signals), 130.8, 130.7, 130.4, 129.4, 127.7, 124.6, 61.7. MS (EI, *m*/*z*): 420 (2, M$^+$−Br), 340 (45), 339 (42), 264 (19), 263 (100), 237 (30), 236 (70), 170 (13), 106 (16), 79 (40), 52 (15); HRMS (ESI-TOF, CH$_3$OH): calcd for $C_{27}H_{22}N_3S$: [M−Br]$^+$ 420.1534, found 420.1523. Anal. Calcd for $C_{27}H_{22}BrN_3S\cdot 2/3H_2O$: C, 63.28; H, 4.59; N, 8.20; S, 6.26. Found: C, 63.06; H, 4.36; N, 8.04; S, 6.18.

*4.5.3. 1-{N-[3-(Benzo[b]thiophen-3-yl)-5-phenylpyridin-2-yl]-N-benzylamino}pyridinium bromide (**13c**).* Brown solid (396 mg, 72%, ethanol–ethyl acetate), mp 63–65 °C; IR (KBr) ν_{max} (cm^{-1}): 1616, 1430, 766, 700; ^{1}H NMR (300 MHz, CD$_3$OD): δ 8.95 (1H, d, *J*=2.4 Hz, *H6′*), 8.31 (2H, dd, *J*=7.0 and 1.3 Hz, *H2*(6)), 8.27 (1H, tt, *J*=7.7 and 1.3 Hz, *H4*), 8.15 (1H, d, *J*=2.4 Hz, *H4′*), 8.00 (1H, m, *H4‴* or *H7‴*), 7.78 (2H, dd, *J*=8.3 and 1.3 Hz, *H2″*(6″)), 7.68 (2H, dd, *J*=7.7 and 7.0 Hz, *H3*(5)), 7.58 (1H, s, *H2‴*), 7.50 (6H, m, *H5‴*, *H6‴*, *H7‴* or *H4‴*, *H4″* and *H3″*(5″)), 7.24 (3H, m, *H2⁗*(6⁗) and *H4⁗*), 7.13 (2H, m, *H3⁗*(5⁗)); ^{13}C NMR (75 MHz, CD$_3$OD): δ 155.1, 147.5, 147.4, 147.0, 141.3, 141.2, 138.5, 137.4, 137.3, 134.9, 132.9, 130.9, 130.4, 130.0, 129.8, 129.4, 128.2, 128.1, 126.6, 126.0, 125.8, 124.2, 123.7, 116.2, 60.8. MS (EI, *m*/*z*): 470 (<2, M$^+$−Br), 392 (11), 302 (19), 301 (25), 91 (100), 82 (15), 80 (16), 79 (37), 65 (24), 52 (25), 51 (25); HRMS (ESI-TOF, CH$_3$OH): calcd for $C_{31}H_{24}N_3S$: [M−Br]$^+$ 470.1691, found 470.1690. Anal. Calcd for $C_{31}H_{24}BrN_3S$: C, 67.63; H, 4.39; N, 7.63; S, 5.82. Found: C, 67.48; H, 4.39; N, 7.89; S, 5.53.

*4.5.4. 1-{N-[5-(Benzo[b]thiophen-3-yl)-3-phenylpyridin-2-yl]-N-benzylamino}pyridinium bromide (**13d**).* White solid (391 mg, 71%, ethanol–ethyl acetate), mp 181–183 °C; IR (KBr) ν_{max} (cm^{-1}): 1615, 1466, 1432, 1403, 1064, 765, 736, 700, 683, 474; ^{1}H NMR (500 MHz, CD$_3$OD): δ 8.82 (2H, dd, *J*=7.0 and 1.3 Hz, *H2*(6)), 8.79 (1H, d, *J*=2.3 Hz, *H6′*), 8.49 (1H, tt, *J*=7.8 and 1.3 Hz, *H4*), 8.04 (1H, d, *J*=2.3 Hz, *H4′*), 8.03 (1H, m, *H7″* or *H4″*), 7.96 (1H, m, *H4″* or *H7″*), 7.89 (2H, dd, *J*=7.8 and 7.0 Hz, *H3*(5)), 7.86 (1H, s, *H2″*), 7.50 (7H, m, *H2⁗*(6⁗), *H4⁗* and *H3⁗*(5⁗), *H5″* and *H6″*), 7.28 (5H, m, *H2‴*(6‴), *H4‴* and *H3‴*(5‴)); ^{13}C NMR (75 MHz, CD$_3$OD): δ 154.4, 148.1, 148.0, 147.5, 142.2, 141.9, 138.5, 137.7, 134.8, 133.8, 132.7, 132.2, 130.7, 130.4, 130.1, 130.0 (two signals), 129.9, 129.6, 127.2, 126.0, 124.2, 123.0, 116.2, 60.7. MS (EI, *m*/*z*): 470 (<2, M$^+$−Br), 390 (31), 389 (28), 313 (55), 286 (53), 79 (100), 52 (45), 51 (26); HRMS (ESI-TOF, CH$_3$OH): calcd for $C_{31}H_{24}N_3S$: [M−Br]$^+$ 470.1691, found 470.1696. Anal. Calcd for $C_{31}H_{24}BrN_3S$: C, 67.63; H, 4.39; N, 7.63; S, 5.82. Found: C, 67.87; H, 4.58; N, 7.52; S, 5.78.

*4.5.5. 1-{N-[5-(3,5-Dimethylphenyl)-3-(4-methoxyphenyl)pyridin-2-yl]-N-[(4-methyl)benzyl]-amino}pyridinium bromide (**13e**).* White solid (430 mg, 76%, ethanol–ethyl acetate), mp 182–184 °C; IR (KBr) ν_{max} (cm^{-1}): 1608, 1514, 1441, 1256, 1181, 1029, 847, 839, 700; ^{1}H NMR (300 MHz, CD$_3$OD): δ 8.76 (2H, dd, *J*=6.9 and 1.3 Hz, *H2*(6)), 8.71 (1H, d, *J*=2.3 Hz, *H6′*), 8.47 (1H, tt, *J*=7.7 and 1.3 Hz, *H4*), 7.96 (1H, d, *J*=2.3 Hz, *H4′*), 7.88 (2H, dd, *J*=7.7 and 6.9 Hz, *H3*(5)), 7.43 (2H, d, *J*=8.9 Hz, *H2‴*(6‴)), 7.33 (2H, br s, *H2″*(6″)), 7.11 (5H, m , *H4″*, *H2⁗*(6⁗) and *H3⁗*(5⁗)), 7.04 (2H, d, *J*=8.9 Hz, *H3‴*(5‴)), 5.03 (2H, s, C*H*$_2$), 3.87 (3H, s, OC*H*$_3$), 2.41 (6H, s, C*H*$_3$), 2.28 (3H, s, C*H*$_3$); ^{13}C NMR (75 MHz, CD$_3$OD): δ 161.6, 154.5, 147.9, 147.8, 145.9, 140.4, 140.1, 137.8, 137.5, 131.9, 131.8, 131.3 (three overlapped signals), 131.2, 130.6, 129.8, 129.4, 125.9, 115.7, 60.4, 55.9, 21.4, 21.1. MS (EI, *m*/*z*): 486 (<2, M$^+$−Br), 406 (17), 405 (15), 315 (34), 82 (31), 81 (16), 80 (54), 79 (100), 52 (51), 51 (27); HRMS (ESI-TOF, CH$_3$OH): calcd for $C_{33}H_{32}N_3O$:

$[M-Br]^+$ 486.2545, found 486.2532. Anal. Calcd for $C_{33}H_{32}BrN_3O$: C, 68.51; H, 5.81; N, 7.26. Found: C, 68.33; H, 5.70; N, 7.20.

*4.5.6. 1-{N-[3-(4-Bromo-3,5-dimethylphenyl)-5-(4-methoxyphenyl)pyridin-2-yl]-N-[(4-methyl)benzyl]-amino}pyridinium bromide (**13f**).* Beige solid (532 mg, 94%, ethanol–ethyl acetate), mp 165–167 °C; IR (KBr) ν_{max} (cm^{-1}): 1609, 1516, 1468, 1247, 1184, 833, 709; ^1H NMR (300 MHz, CD_3OD): δ 8.72 (1H, d, J=2.4 Hz, *H*6′), 8.70 (2H, dd, J=6.9 and 1.3 Hz, *H*2(6)), 8.49 (1H, tt, J=7.9 and 1.3 Hz, *H*4), 7.95 (1H, d, J=2.4 Hz, *H*4′), 7.88 (2H, dd, J=7.9 and 6.9 Hz, *H*3(5)), 7.68 (2H, d, J=8.9 Hz, *H*2″(6″)), 7.10 (9H, m, *H*3″(5″), *H*2‴(6‴), *H*4‴, *H*2⁗(6⁗) and *H*3⁗(5⁗)), 5.03 (2H, s, CH_2), 3.87 (3H, s, OCH_3), 2.37 (6H, s, CH_3), 2.28 (3H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 161.7, 153.9, 148.1, 147.6, 145.6, 140.2, 140.1, 139.6, 137.8, 137.0, 132.2, 131.8, 131.1, 130.6, 130.5, 129.7, 129.4, 129.2, 127.6, 115.8, 60.2, 55.8, 21.3, 21.1. MS (EI, m/z): 486 (<2, M^+-Br), 406 (15), 315 (30), 274 (13), 105 (15), 82 (40), 80 (44), 79 (100), 52 (42); HRMS (ESI-TOF, CH_3OH): calcd for $C_{33}H_{32}N_3O$: $[M-Br]^+$ 486.2545, found 486.2538. Anal. Calcd for $C_{33}H_{32}BrN_3O$: C, 69.96; H, 5.69; N, 7.42. Found: C, 69.86; H, 5.59; N, 7.78.

*4.5.7. 1-(N-{5-(4-Methoxyphenyl)-3-[N-(4-methylbenzyl)pyridin-3-ium]pyridin-2-yl}-N-[(4-methyl)benzyl]amino)pyridinium dibromide (**13g**).* Yellow solid (695 mg, 96%, ethanol), mp 176–178 °C; IR (KBr) ν_{max} (cm^{-1}): 1609, 1517, 1428, 1250, 1183, 1120, 684; ^1H NMR (300 MHz, CD_3OD): δ 9.48 (1H, m, *H*2‴), 9.21 (1H, dt, J=6.4 and 1.3 Hz, *H*6‴), 9.15 (2H, dd, J=6.9 and 1.3 Hz, *H*2(6)), 8.97 (1H, dt, J=8.0 and 1.6 Hz, *H*4‴), 8.92 (1H, d, J=2.4 Hz, *H*6′), 8.57 (1H, tt, J=7.7 and 1.3 Hz, *H*4), 8.33 (1H, d, J=2.4 Hz, *H*4′), 8.32 (1H, dd, J=8.1 and 6.4 Hz, *H*5‴), 8.04 (2H, dd, J=7.7 and 6.9 Hz, *H*3(5)), 7.76 (2H, d, J=8.9 Hz, *H*2″(6″)), 7.53 (2H, d, J=8.1 Hz, *H*2⁗(6⁗)), 7.33 (2H, d, J=8.1 Hz, *H*3⁗(5⁗)), 7.12 (2H, d, J=8.9 Hz, *H*3″(5″)), 7.04 (2H, d, J=7.9 Hz, *H*2⁗⁗(6⁗⁗)), 6.86 (2H, d, J=7.9 Hz, *H*3⁗⁗(5⁗⁗)), 5.94 (2H, s, CH_2), 4.93 (2H, s, CH_2), 3.89 (3H, s, OCH_3), 2.39 (3H, s, CH_3), 2.28 (3H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 162.2, 153.2, 148.6, 148.0, 147.9, 145.7, 145.6, 141.7, 140.4, 140.3, 138.8, 138.4, 131.6, 131.5, 130.9, 130.8, 130.5, 130.4, 129.9, 129.7, 129.6, 128.8, 126.0, 115.9, 115.5, 66.0, 62.2, 55.9, 21.3, 21.1. MS (EI, m/z): 645/643 (<2/<2, M^+-Br), 288 (17), 82 (49), 81 (44), 80 (87), 79 (100), 78 (15), 53 (27), 52 (57), 51 (36), 50 (22); HRMS (ESI-TOF, CH_3OH): calcd for $C_{38}H_{36}{}^{79}BrN_4O$: $[M-Br]^+$ 643.2072, found 643.2035. Anal. Calcd for $C_{38}H_{36}Br_2N_4O\cdot 2/5H_2O$ (%): C, 59.31; H, 5.37; N, 7.28; S, 9.52. Found: C, 59.34; H, 4.98; N, 7.57.

4.6. Preparation of unsymmetrical benzyl (3,5-diarylpyridin-2-yl)amines (14)

General method: Zinc dust (10 mmol) was added to a solution of the corresponding pyridinium salt **13** (1 mmol) in glacial acetic acid (15 mL) and the mixture was stirred at room temperature for the time indicated in Table 3, until the starting pyridinium salt was no longer detected by TLC. Once the reaction had finished, the solvent was evaporated to dryness. The residue was purified by column chromatography on silica gel, using hexane:ethyl acetate as eluent, and the corresponding *N*-benzyl(3,5-diarylpyridin-2-yl)amine **14** was crystallized from a suitable solvent.

*4.6.1. N-Benzyl-N-[5-phenyl-3-(thiophen-3-yl)pyridin-2-yl]amine (**14a**).* White solid (215 mg, 63%, ethyl acetate–hexane), mp 130–132 °C; IR (KBr) ν_{max} (cm^{-1}): 1602, 1485, 1350, 1227, 800, 774, 765, 734, 694, 674; ^1H NMR (500 MHz, $CDCl_3$): δ 8.38 (1H, d, J=2.4 Hz, *H*6), 7.62 (1H, d, J=2.4 Hz, *H*4), 7.53 (2H, dd, J=8.1 and 1.2 Hz, *H*2′(6′)), 7.44 (1H, dd, J=5.0 and 2.9 Hz, *H*5″), 7.40 (3H, m, *H*3′(5′) and *H*2″), 7.31 (5H, m, *H*2‴(6‴), *H*3‴(5‴) and *H*4′), 7.24 (2H, m, *H*4‴ and *H*4″), 5.07 (1H, d, J=5.5 Hz, N*H*), 4.70 (2H, d, J=5.5 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.9, 145.2, 139.8, 138.4, 138.0, 135.8, 128.9, 128.6, 127.8, 127.5, 127.1 (two overlapped signals), 126.7, 126.2 (two overlapped signals), 123.4, 117.2, 45.7. MS (EI, m/z): 342 (72, M^+), 251 (19), 237 (24), 236 (24), 132 (12), 106 (100), 91 (63), 77 (14), 65 (19), 57 (11); HRMS (ESI-TOF, CH_3OH): calcd for $C_{22}H_{19}N_2S$: $[M+H]^+$ 343.1269, found 343.1260. Anal. Calcd for $C_{22}H_{18}N_2S\cdot 1/5H_2O$ (%): C, 76.36; H, 5.36; N, 8.09; S, 9.27. Found: C, 76.58; H, 5.62; N, 7.78; S, 9.18.

*4.6.2. N-Benzyl-N-[3-phenyl-5-(thiophen-3-yl)pyridin-2-yl]amine (**14b**).* White solid (164 mg, 48%, ethyl acetate–hexane), mp 101–103 °C; IR (KBr) ν_{max} (cm^{-1}): 3427, 1606, 1487, 1468, 784, 757, 700; ^1H NMR (300 MHz, CD_3OD): δ 8.41 (1H, d, J=2.3 Hz, *H*6), 7.52 (1H, d, J=2.3 Hz, *H*4), 7.44 (3H, m, *H*2″(6″) and *H*4″), 7.37 (2H, m, *H*3″(5″)), 7.32 (5H, m, *H*2‴(6‴), *H*3‴(5‴) and *H*4‴), 7.24 (3H, m, *H*2′, *H*4′ and *H*5′), 4.94 (1H, d, J=5.5 Hz, N*H*), 4.69 (2H, d, J=5.5 Hz, CH_2); ^{13}C NMR (75 MHz, CD_3OD): δ 155.9, 144.8, 141.4, 140.4, 138.9, 136.8, 130.3, 130.1, 129.4, 129.1, 128.2, 127.8, 127.4, 126.4, 124.4, 122.9, 119.5, 46.1. MS (EI, m/z): 342 (51, M^+), 237 (18), 236 (18), 149 (24), 106 (100), 91 (48), 57 (26); HRMS (ESI-TOF, CH_3OH): calcd for $C_{22}H_{19}N_2S$: $[M+H]^+$ 343.1269, found 343.1260. Anal. Calcd for $C_{22}H_{18}N_2S$: C, 77.16; H, 5.30; N, 8.18; S, 9.36. Found: C, 77.55; H, 5.68; N, 7.93; S, 9.09.

*4.6.3. N-[3-(Benzo[b]thiophen-3-yl)-5-phenylpyridin-2-yl]-N-benzylamine (**14c**).* Beige solid (235 mg, 60%, ethyl acetate–hexane), mp 78–80 °C; IR (KBr) ν_{max} (cm^{-1}): 2919, 1602, 1508, 1486, 1451, 1427, 762, 734, 696; ^1H NMR (500 MHz, $CDCl_3$): δ 8.49 (1H, d, J=2.3 Hz, *H*6), 7.91 (1H, br d, J=7.9 Hz, *H*7″), 7.68 (1H, d, J=2.3 Hz, *H*4), 7.63 (1H, br d, J=7.2 Hz, *H*4″), 7.54 (2H, dd, J=8.1 and 1.2 Hz, *H*2′(6′)), 7.50 (1H, s, *H*2″), 7.38 (4H, m, *H*3′(5′), *H*5″ and *H*6″), 7.29 (1H, tt, J=7.4 and 1.1 Hz, *H*4′), 7.26 (4H, m, *H*2‴(6‴) and *H*3‴(5‴)), 7.21 (1H, m, *H*4‴), 4.80 (1H, t, J=5.6 Hz, N*H*), 4.68 (2H, d, J=5.6 Hz, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.4, 145.9, 140.5, 139.7, 138.2, 137.7, 136.9, 132.8, 128.9, 128.4, 127.4, 127.0, 126.7, 126.1, 125.9, 125.7, 124.9, 124.5, 123.1, 122.9, 115.7, 45.4. MS (EI, m/z): 392 (13, M^+), 91 (100), 77 (22), 65 (27); HRMS (ESI-TOF, CH_3OH): calcd for $C_{26}H_{21}N_2S$: $[M+H]^+$ 393.14200, found 393.14307. Anal. Calcd for $C_{26}H_{20}N_2S\cdot 1/2H_2O$ (%): C, 78.36; H, 5.23; N, 7.03; S, 8.05. Found: C, 78.65; H, 5.18; N, 7.32; S, 8.05.

*4.6.4. N-[5-(Benzo[b]thiophen-3-yl)-3-phenylpyridin-2-yl]-N-benzylamine (**14d**).* Yellow oil (275 mg, 70%); IR (NaCl) ν_{max} (cm^{-1}): 3436, 2922, 1676, 1605, 1524, 1489, 1394, 1346, 1258, 1243, 783, 759, 733, 699; ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (1H, d, J=2.3 Hz, *H*6), 7.90 (2H, m, *H*7′ and *H*4′), 7.56 (1H, d, J=2.3 Hz, *H*4), 7.47 (4H, m, *H*2″(6″) and *H*3″(5″)), 7.37 (3H, m, *H*5′, *H*6′ and *H*4″), 7.35 (1H, s, *H*2′), 7.32 (4H, m, *H*2‴(6‴) and *H*3‴(5‴)), 7.24 (1H, m, *H*4‴), 5.03 (1H, t, J=5.6 Hz, N*H*), 4.72 (2H, d, J=5.6 Hz, CH_2); ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.7, 146.5, 140.6, 139.7, 138.0, 137.5, 137.4, 135.0, 129.3, 128.9, 128.5, 128.0, 127.5, 127.1, 124.4, 124.3, 123.0, 122.7, 122.4, 122.1, 121.3, 45.6. MS (EI, m/z): 392 (65, M^+), 391 (29), 286 (25), 106 (100), 91 (56), 65 (18); HRMS (ESI-TOF, CH_3OH): calcd for $C_{26}H_{21}N_2S$: $[M+H]^+$ 393.1425, found 393.1424.

*4.6.5. N-[5-(3,5-Dimethylphenyl)-3-(4-methoxyphenyl)pyridin-2-yl]-N-[(4-methyl)benzyl]amine (**14e**).* \Colourless oil (302 mg, 74%); IR (NaCl) ν_{max} (cm^{-1}): 3435, 2922, 1602, 1513, 1246, 1176, 1030; ^1H NMR (300 MHz, CD_3OD): δ 8.18 (1H, d, J=2.3 Hz, *H*6), 7.53 (1H, d, J=2.3 Hz, *H*4), 7.38 (2H, d, J=8.6 Hz, *H*2″(6″)), 7.19 (2H, d, J=8.1 Hz, *H*2‴(6‴)), 7.15 (2H, ap s, *H*2′(6′)), 7.11 (2H, d, J=8.1 Hz, *H*3‴(5‴)), 7.04 (2H, d, J=8.6 Hz, *H*3″(5″)), 6.95 (1H, ap s, *H*4′), 4.55 (2H, s, CH_2), 3.83 (3H, s, OCH_3), 2.34 (6H, s, CH_3), 2.30 (3H, s, CH_3); ^{13}C NMR (75 MHz, CD_3OD): δ 161.0, 156.2, 144.6, 139.5, 139.3, 138.1, 137.5, 137.4, 131.2, 130.8, 130.0, 129.4, 128.2, 127.6, 124.8, 124.2, 115.7, 55.7, 46.0, 21.5, 21.1.

MS (EI, *m*/*z*): 408 (76, M^+), 407 (37), 289 (27), 120 (100), 105 (87), 77 (24), 57 (15); HRMS (ESI-TOF, CH_3OH): calcd for $C_{28}H_{29}N_2O$: $[M+H]^+$ 409.2280, found 409.2419.

*4.6.6. N-[3-(3,5-Dimethylphenyl)-5-(4-methoxyphenyl)pyridin-2-yl]-N-[(4-methyl)benzyl]amine (**14f**).* White solid (290 mg, 71%, ethyl acetate–hexane), mp 140–142 °C; IR (KBr) ν_{max} (cm^{-1}): 3408, 1608, 1569, 1493, 1460, 1339, 1280, 1248, 1181, 1130, 827; ^1H NMR (300 MHz, $CDCl_3$): δ 8.32 (1H, d, *J*=2.3 Hz, *H*6), 7.48 (1H, d, *J*=2.3 Hz, *H*4), 7.45 (2H, d, *J*=8.6 Hz, *H*2′(6′)), 7.20 (2H, d, *J*=8.0 Hz, *H*2‴(6‴)), 7.10 (2H, d, *J*=8.0 Hz, *H*3‴(5‴)), 7.04 (2H, s, *H*2″(6″)), 6.98 (1H, s, *H*4″), 6.94 (2H, d, *J*=8.6 Hz, *H*3′(5′)), 4.91 (1H, t, *J*=5.7 Hz, N*H*), 4.62 (2H, d, *J*=5.7 Hz, CH_2), 3.82 (3H, s, OCH_3), 2.32 (6H, s, CH_3), 2.30 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6, 154.4, 144.5, 138.8, 137.7, 136.9, 136.5, 135.5, 131.1, 129.5, 129.1, 127.4, 127.2, 126.6, 125.7, 122.4, 114.3, 55.3, 45.4, 21.3, 21.1. MS (EI, *m*/*z*): 408 (100, M^+), 407 (35), 289 (25), 120 (53), 105 (53), 79 (13), 77 (15); HRMS (ESI-TOF, CH_3OH): calcd for $C_{28}H_{29}N_2O$: $[M+H]^+$ 409.2280, found 409.2269. Anal. Calcd for $C_{28}H_{28}N_2O \cdot 1/2H_2O$ (%): C, 80.37; H, 6.74; N, 6.94. Found: C, 80.24; H, 6.64; N, 6.54.

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