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Arylation of Adamantanamines: VII.* Copper(I)-Catalyzed N-Heteroarylation of Adamantane-Containing Amines with Halopyridines

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Abstract—Copper(I)-catalyzed N-heteroarylation of a wide series of adamantane-containing amines with 2-bromo- and 2- and 3-iodopyridines was studied. The corresponding *N*-pyridyl derivatives were formed in all cases, but iodopyridines were considerably more reactive. The best results were obtained with the catalytic system CuI–2-(2-methyl-1-oxopropyl)cyclohexanone–DMF which ensured up to 90% yield of the target products. The yield of *N*-pyridyl derivatives also depended on the steric environment of the amino group in the initial adamantane-containing amine. The yield of the heteroarylation products can be considerably increased using excess iodopyridine. The reaction of 2-(adamantan-1-yl)ethanamine with 2,6-dibromopyridine successfully afforded the corresponding diamine, and *N*,*N*′-dipyridyl derivatives were obtained in high yields from 2,2′-(adamantane-1,3-diyl)diethanamine.

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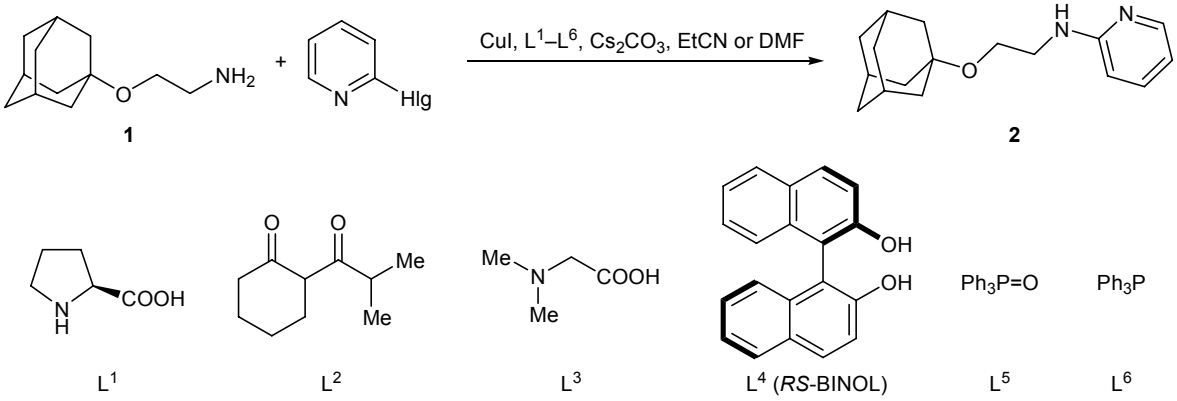
Reactions of amines with aryl halides, catalyzed by zero-valent palladium complexes, provide a convenient general procedure for the synthesis of *N*-aryl and *N*-heteroaryl amines and polyamines [2, 3]. An important trend in the modern stage of development of catalytic methods is replacement of expensive palladium by considerably cheaper copper [4]; however, Cu(I)-catalyzed amination requires more thorough selection of the catalytic system for each particular amine–aryl halide couple [5]. We have initiated a comprehensive study of the arylation [6] and heteroarylation [7, 8] of polyamines under catalysis by copper(I) complexes and shown that the most efficient catalytic systems are CuI–L-proline, CuI–*N*,*N*-dimethylglycine and CuI–2-(2-methyl-1-oxopropyl)cyclohexanone. The choice of the solvent (DMF, acetonitrile, propionitrile) is also determined by the nature of particular reactants. Taking into account high and diverse physiological activity of heteroaryl derivatives of adamantanamines [9–11], development of procedures for their synthesis seems to be an important task. We previously studied Pd(0)-catalyzed heteroarylation of adamantane-containing amines with 2-bromopyridine [12], 3-bromopyridine [1] and mono- and dichloroquinolines [13–15] and showed that diaminoadamantane fragments can be introduced into macroheterocycles [16]. It was also noted that success of these reactions is largely determined by the structure of initial amines containing a bulky adamantane moiety. Continuing these studies, in the present work we examined copper(I)-catalyzed N-heteroarylation of a wide series of adamantane-containing amines with 2-bromo- and 2- and 3-iodopyridines.

The reaction conditions were optimized using the least sterically hindered 2-(adamantan-1-yloxy)ethanamine (**1**) and an equimolar amount of halopyridine at a concentration of 0.5 M (Scheme 1). According to our previous data, 2-bromopyridine is fairly reactive in Cu(I)-catalyzed aminations [7]. Therefore, we initially tried 2-bromopyridine as heteroarylating agent. When

* For communication VI, see [1].

Scheme 1.



Hlg = Br, I.

a mixture of amine **1** with 2-bromopyridine and cesium carbonate was heated in DMF for 24 h at 140°C in the absence of a catalyst, the yield of product **2** was as low as 11% (Table 1, run no. 1). No reaction was observed in boiling propionitrile in the presence of CuI–L^1 (5/10 mol %, L^1 = L-proline; run no. 2). Replacement of the catalytic system by CuI–L^2 [5/10 mol %, L^2 = 2-(2-methyl-1-oxopropyl)cyclohexanone] and of the solvent by DMF (110°C) increased the yield of **2** to 28% (run no. 3). Furthermore, the yield of **2** was improved to 57% by raising the amount of the catalyst and ligand to 10/20 mol % and the temperature to 140°C (run no. 4). The yield of **2** was considerably lower (34%) in the presence of CuI–L^1 (10/20 mol %; DMF, 140°C; run no. 5).

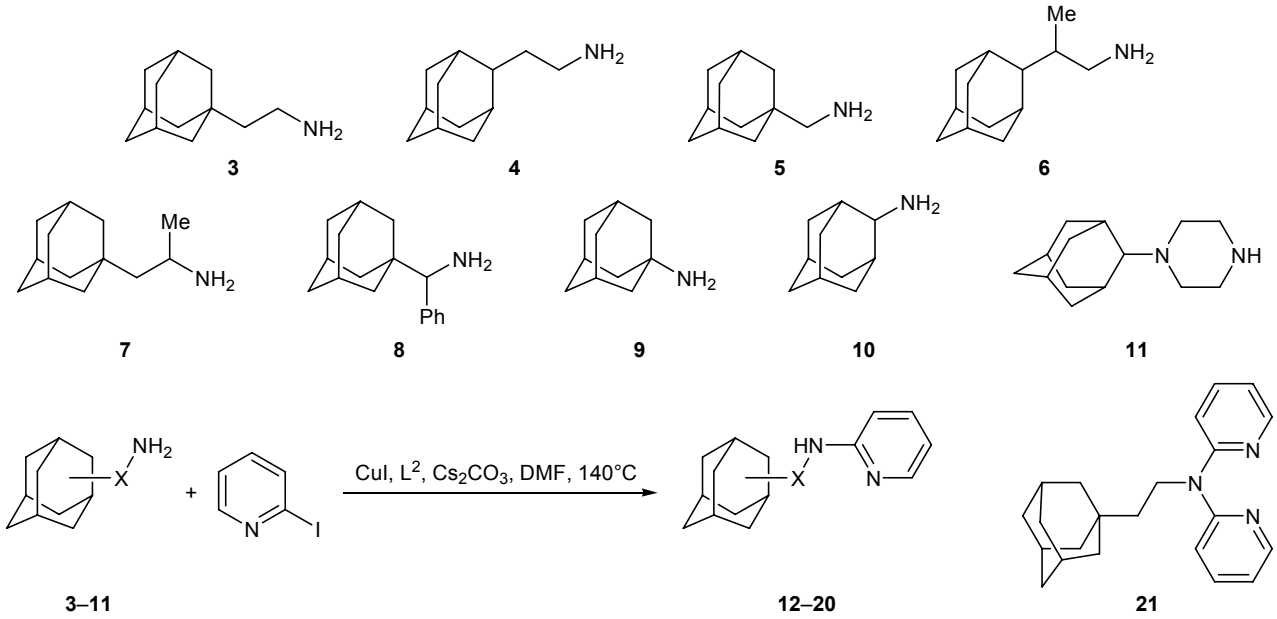
In the reaction of **1** with more reactive 2-iodopyridine in boiling propionitrile catalyzed by CuI–L^1 (5/10 mol %) the yield of **2** was 11% (run no. 6). The system CuI–L^2 (5/10 mol %) in DMF at 110°C ensured 40% yield of **2** (run no. 8). The yield of **2** also increased to an appreciable extent when the catalytic system CuI–L^1 was used in an amount of 10/20 mol % (run no. 7). Compound **2** was formed in 72% yield in the reaction carried out in DMF at 140°C under catalysis by CuI–L^2 (10/20 mol %; run no. 9).

Other potential catalytic systems were also tested to optimize the yield. *N*,*N*-Dimethylglycine (L^3) [17] was less efficient than L-proline (L^1): under comparable conditions, the conversion was as low as 9% (run no. 10). Racemic BINOL (L^4) [18] afforded 50% of **2** (run no. 11). The use of some phosphine ligands has been reported [19]. We tried triphenylphosphine (L^6) and triphenylphosphine oxide (L^5) as components of the catalytic system. The catalytic system CuI–L^2–L^5

Table 1. N-Heteroarylation of 2-(adamantan-1-yloxy)ethanamine (**1**) with 2-bromo- and 2-iodopyridines

Run no.	Halopyridine	Ligand	Cu–L, mol %	Solvent	Temperature, °C	Yield of **2**, %
1	2-Bromopyridine	–	–	DMF	140	11
2	2-Bromopyridine	L^1	5/10	EtCN	97	0
3	2-Bromopyridine	L^2	5/10	DMF	110	28
4	2-Bromopyridine	L^2	10/20	DMF	140	57
5	2-Bromopyridine	L^1	10/20	DMF	140	34
6	2-Iodopyridine	L^1	5/10	EtCN	97	11
7	2-Iodopyridine	L^1	10/20	DMF	140	50
8	2-Iodopyridine	L^2	5/10	DMF	110	40
9	2-Iodopyridine	L^2	10/20	DMF	140	72
10	2-Iodopyridine	L^3	5/10	EtCN	97	9
11	2-Iodopyridine	L^4	10/20	DMF	140	50
12	2-Iodopyridine	L^2/L^5	10/10/10	DMF	140	62
13	2-Iodopyridine	L^2/L^6	10/10/10	DMF	140	72

Scheme 2.



(10/10/10 mol %) ensured 62% of **2** (run no. 12), and the yield attained 72% in the presence of CuI–L^2–L^6 (10/10/10 mol %; run no. 13). Thus, the best catalytic system for the arylation of amine **1** with 2-bromo- and 2-iodopyridines is CuI–L^2 (10/20 mol %) in DMF at 140°C. In our further study, the reactions of 2-iodopyridine with all other adamantane-containing amines were carried out under these conditions.

Next, we examined the Cu(I)-catalyzed heteroarylation of a representative series of adamantane-containing amines **3**–**11** characterized by different steric hindrances at the amino group. The reactions with sterically unhindered amines **3** and **4** afforded even higher yields (up to 90%) of heteroarylation products **12** and **13** (Scheme 2; Table 2, run nos. 1, 4); the reaction with amine **3** was accompanied by side formation of *N*,*N*-disubstituted product **21** (9%, run no. 1). It should be noted that the formation of *N*,*N*-diheteroaryl derivatives was observed by us previously in reactions of some polyamines with 2-iodopyridine [7].

Interestingly, the same yields of **12** and **21** (90 and 9%, respectively) were obtained in special experiment with 3 equiv of 2-iodopyridine (run no. 3). Thus, an important advantage of Cu(I)-catalyzed amination compared to analogous Pd(0)-catalyzed reactions is almost complete absence of side *N*,*N*-diarylation of monoamines, which could strongly complicate the synthesis of some adamantanamine derivatives [12]. The reactions with amines **3** and **4** were also carried out in the presence of triphenylphosphine oxide as ligand; however, as with amine **1**, the yields of **12** and **13** were lower, 78 and 53%, respectively (run nos. 2, 5). As might be expected, more sterically loaded amines **5**–**7** reacted with 2-iodopyridine to give the corresponding arylation products in lower yields (50–63%; run nos. 6, 7, 9). In the reaction of amine **6** with 3 equiv of 2-iodopyridine, the conversion of **6** increased from 55 to 90%, whereas the yield of **16** in the reaction with amine **7** increased insignificantly, from 50 to 57% (run nos. 8, 10). Further increase of steric hindrances in going to amine **8** resulted in the reduction of the yield of **17** to 15% (run no. 11). Adamantan-1-amine (**9**) showed the lowest reactivity in Pd(0)-catalyzed amination, which was appreciably lower than the reactivity of amine **8**. However, Cu(I)-catalyzed heteroarylation of **9** gave 36% of **18** (run no. 12). As expected, adamantan-2-amine **10** was more reactive, and the yield of

Scheme 3.

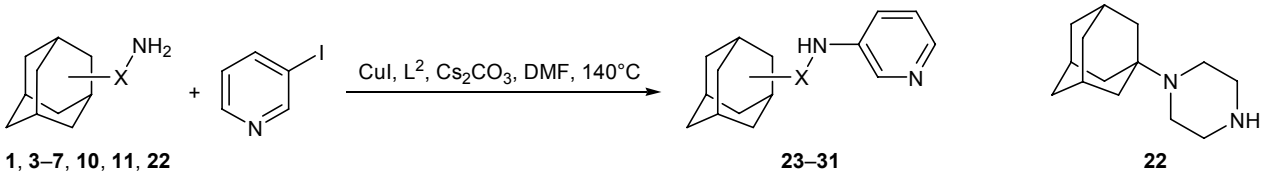


Table 2. N-Heteroarylation of amines **3**–**11** with 2-iodopyridine under optimized conditions (CuI–L^2, 10/20 mol %; DMF, 140°C)

Run no.	Amine no.	2-Iodopyridine, equiv	Product	Yield, %
1	**3**	1	**12** **21**	90[a] 9[a]
2[b]	**3**	1	**12**	78
3	**3**	3	**12** **21**	90 9
4	**4**	1	**13**	90[a]
5[b]	**4**	1	**13**	53
6	**5**	1	**14**	63
7	**6**	1	**15**	55 (46)[a]
8	**6**	3	**15**	90
9	**7**	1	**16**	50
10	**7**	3	**16**	57
11	**8**	1	**17**	15
12	**9**	1	**18**	36
13	**10**	1	**19**	55 (42)[a]
14	**11**	1	**20**	55 (34)[a]

[a] Isolated by chromatography.
[b] Catalytic system CuI–L^2–L^5 (10/10/10 mol %).

Table 3. N-Heteroarylation of amines **1**, **3**–**7**, **10**, **11**, and **22** with 3-iodopyridine under optimized conditions (CuI–L^2, 10/20 mol %; DMF, 140°C)

Run no.	Amine no.	3-Iodopyridine, equiv	Product	Yield, %
1[a]	**1**	1	**23**	47
2	**1**	1	**23**	74
3	**3**	1	**24**	83 (50)[b]
4	**4**	1	**25**	85 (43)[b]
5	**5**	1	**26**	49
6	**5**	3	**26**	75
7	**6**	1	**27**	73 (41)[b]
8	**7**	1	**28**	59
9	**7**	3	**28**	75
10	**10**	1	**29**	67
11	**11**	1	**30**	51 (27)[b]
12	**11**	3	**30**	65
13	**22**	1	**31**	35 (20)[b]

[a] Catalytic system CuI–L^1.
[b] Isolated by chromatography.

19 was 55% (run no. 13). The reaction with cyclic secondary amine, 4-(adamantan-2-yl)piperazine (**11**), was also fairly efficient, and compound **20** was formed in 55% yield (run no. 14).

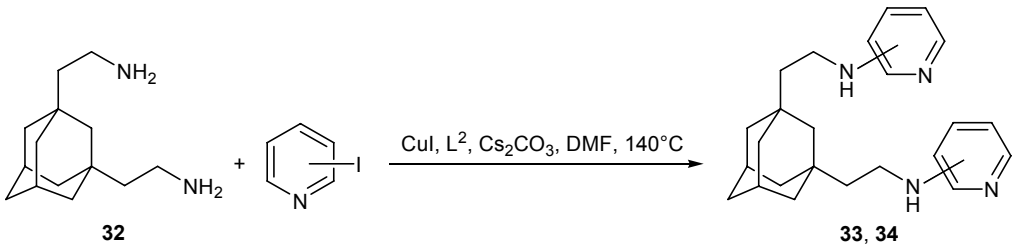
Having studied the amination of 2-halopyridines, we examined Cu(I)-catalyzed amination of less active 3-iodopyridine with adamantane-containing amines **1**, **3**–**7**, **10**, **11**, and **22** (Scheme 3). 3-Bromopyridine was not tested in these reactions, taking into account its inactivity in analogous copper-catalyzed reactions with polyamines. The reaction of 3-iodopyridine with amine **1** in the presence of CuI–L^1 and CuI–L^2 in DMF gave compound **23** in 43 and 74% yield, respectively (Table 3; run nos. 1, 2); therefore, the reactions with the other amines were carried out using only CuI–L^2 as catalytic system.

Sterically unhindered amines **3** and **4** reacted with 3-iodopyridine to afford the corresponding heteroarylation products **24** and **25** in high yields (run nos. 3, 4). In the reactions with more sterically hindered amines **5**–**7**, the yields of the heteroarylation products were lower, 40 to 59% (run nos. 5, 7, 8). The use of 3-equiv of 3-iodopyridine in the reactions with amines **5**, **7** allowed us to increase the yields to 75% (run nos. 6, 9). Reactions of 3-iodopyridine with strongly hindered amines **8** and **9** were not studied. A good yield (67%) was obtained in the reaction with adamantan-2-amine **10** (run no. 10); the reaction of secondary amine **11** with 1 equiv of 3-iodopyridine gave 51% (in the reaction mixture) of heteroarylation product **30**, and the yield of **30** was 65% in the reaction with 3 equiv of 3-iodopyridine (run nos. 11, 12). However, the yield of **31** in the reaction with isomeric amines **22** did not exceed 35% (run no. 13), indicating specific dependence of the reaction outcome on the initial amine nature.

Successful *N*,*N*′-diheteroarylation of adamantane-containing diamine **32** was accomplished using 2 equiv of 2- and 3-iodopyridine (Scheme 4). The reaction with 2-iodopyridine gave 70% of **33**, and compound **34** was obtained in 75% yield from 3-iodopyridine. In these cases, the amount of the catalytic system was also doubled (CuI–L^2 (20/40 mol %).

The possibility of Cu(I)-catalyzed diamination in the pyridine series was demonstrated by the reaction of 2,6-dibromopyridine with 4 equiv of amine **3** (Scheme 5) in the presence of two catalytic systems CuI–L^1 and CuI–L^2 (20/40 mol %; DMF, 140°C). In the first case, the yield of diamination product **35** was 70%, and in the second case, it was nearly quantitative.

Scheme 4.



33, pyridin-2-yl; **34**, pyridin-3-yl.

Scheme 5.

In summary, copper(I)-catalyzed heteroarylation of adamantane-containing amines with 2- and 3-iodopyridines has been successfully accomplished. The most efficient catalytic system is CuI–L^2 in DMF at 140°C, and *N*,*N*′-diheteroarylation of adamantane-containing diamine, as well as diamination of 2,6-dibromopyridine, is also possible. Strong steric hindrances at the amino group, e.g., as in amines **8** and **9**, considerably reduce the yield of the target products, which is also typical of Pd(0)-catalyzed arylation of the same amines studied previously.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400 and 100.6 MHz, respectively, using $CDCl_3$ as solvent and reference ($CHCl_3$, δ 7.25 ppm; $CDCl_3$, δ_C 77.00 ppm). The mass spectra (MALDI TOF, positive ion detection) were taken on a Bruker Daltonics Autoflex II instrument using 1,8,9-trihydroxyanthracene as matrix and poly(ethylene glycols) as standards. Silica gel (40–60 μm; Merck) was used for preparative column chromatography. Commercial 2-bromopyridine, 2- and 3-iodopyridines, copper(I) iodide, cesium carbonate, L-proline, *N*,*N*-dimethylglycine, 2-(2-methyl-1-oxopropyl)cyclohexanone, (*RS*)-BINOL, triphenylphosphine, and triphenylphosphine oxide were used without additional purification. Amines **1** [20], **5**, **7**, **8**, **32** [12, 21], **9**, **10** [22, 23], **3**, **4**, **6** [24–26], and **11**, **22** [27] were synthesized according to known methods. Dimethylformamide was purified by vacuum distillation over calcium hydride; propionitrile, methanol, petroleum ether, and methylene chloride were distilled prior to use.

***N*-Pyridyl-substituted adamantane-containing amines 2, 12–20, and 23–31 (*general procedure*).** A two-necked flask equipped with a reflux condenser and a magnetic stirrer was charged under argon with 0.5 mmol (103 mg) of 2- or 3-iodopyridine, 0.5 mmol of the corresponding adamantane-containing amine, 0.05 mmol (9.5 mg) of copper(I) iodide, 0.1 mmol (17 mg) of 2-(2-methyl-1-oxopropyl)cyclohexanone, 1 mmol (326 mg) of cesium carbonate, and 1 mL of DMF. The mixture was heated for 24 h at 140°C under stirring, cooled, and diluted with 5 mL of methylene chloride, and the precipitate was filtered off and washed with methylene chloride (5 mL). The filtrate was combined with the washings and evaporated under reduced pressure, the residue was dissolved in methylene chloride (5 mL), the solution was treated with water (5 mL), and the organic layer was separated, dried over anhydrous sodium sulfate, and evaporated under reduced pressure. If necessary, the residue was subjected to silica gel chromatography using methylene chloride–petroleum ether (1:4 to 4:1), methylene chloride, or methylene chloride–methanol (100:1 to 3:1) as eluent. The products were isolated as slightly colored solids or oily substances. The spectral parameters of compounds **14**, **16**–**18**, and **33** were given in [12], and of **23**, **26**, **28**, **29**, and **34**, in [1].

***N*-[2-(Adamantan-1-yloxy)ethyl]pyridin-2-amine (2)** was synthesized from 98 mg of amine **1**. The product was isolated by chromatography (CH_2Cl_2–MeOH, 200:1); yield 68 mg (50%). ^{1}H NMR spectrum, δ, ppm: 1.51–1.61 m (6H), 1.68–1.70 m (6H), 2.09 br.s (3H), 3.37 q (2H, ^3J = 5.3 Hz), 3.56 t (2H, ^3J = 5.1 Hz), 4.90 br.s (1H), 6.35 d (1H, ^3J = 8.3 Hz), 6.46–6.52 m (1H), 7.31–7.36 m (1H), 8.03 d (1H, ^3J =

4.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 30.3 (3C), 36.3 (3C), 41.1 (3C), 42.3 (1C), 58.4 (1C), 72.2 (1C), 107.1 (1C), 112.5 (1C), 137.1 (1C), 147.8 (1C), 158.7 (1C). Mass spectrum: *m*/*z* 273.188 $[M + H]^+$. $C_{17}H_{25}N_2O$. Calculated: *M* + H 273.197.

***N*-[2-(Adamantan-1-yl)ethyl]pyridin-2-amine (12)** was synthesized from 90 mg of amine **3**. The product was isolated by chromatography (CH_2Cl_2); yield 115 mg (90%). ^{1}H NMR spectrum, δ, ppm: 1.36–1.42 m (2H), 1.55 br.s (6H), 1.60–1.72 m (6H), 1.95 br.s (3H), 3.20–3.26 m (2H), 4.41 br.s (1H), 6.35 d (1H, ^3J = 8.5 Hz), 6.51–6.55 m (1H), 7.37–7.43 m (1H), 8.05 d (1H, ^3J = 4.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.6 (3C), 32.0 (1C), 37.1 (4C), 42.3 (3C), 43.9 (1C), 106.3 (1C), 112.5 (1C), 137.5 (1C), 148.0 (1C), 158.8 (1C). Mass spectrum: *m*/*z* 257.209 $[M + H]^+$. $C_{17}H_{25}N_2$. Calculated: *M* + H 257.202.

***N*-[2-(Adamantan-1yl)ethyl]-*N*-(pyridin-2-yl)-pyridin-2-amine (21)** was isolated by chromatography (CH_2Cl_2–MeOH, 100:1) as by-product in the synthesis of **12**. Yield 14 mg (9%). ^{1}H NMR spectrum, δ, ppm: 1.20–1.26 m (2H), 1.46 br.s (6H), 1.52–1.68 m (6H), 1.92 br.s (3H), 3.60–3.65 m (2H), 7.01–7.08 m (4H), 7.69–7.75 m (2H), 8.23–8.26 m (2H). Mass spectrum: *m*/*z* 334.24 $[M + H]^+$. $C_{22}H_{28}N_3$. Calculated: *M* + H 334.23.

***N*-[2-(Adamantan-2-yl)ethyl]pyridin-2-amine (13)** was synthesized from 90 mg of amine **4**. The product was isolated by chromatography (petroleum ether–CH_2Cl_2, 2:1); yield 115 mg (90%). ^{1}H NMR spectrum, δ, ppm: 1.51 d (2H, ^3J = 12.3 Hz), 1.68–1.89 m (15H), 3.19–3.24 m (2H), 4.55 br.s (1H), 6.35 d (1H, ^3J = 8.5 Hz), 6.52 d.d.d (1H, ^3J = 7.0, 5.1, ^4J = 0.8 Hz), 7.39 d.d.d (1H, ^3J = 8.5, 7.0, ^4J = 1.9 Hz), 8.05 d.d.d (1H, ^3J = 5.1, ^4J = 1.9, 0.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.0 (1C), 28.2 (1C), 31.6 (2C), 31.9 (2C), 32.4 (1C), 38.3 (1C), 39.1 (2C), 40.7 (1C), 41.9 (1C), 106.2 (1C), 112.5 (1C), 137.4 (1C), 148.1 (1C), 158.9 (1C). Mass spectrum: *m*/*z* 257.198 $[M + H]^+$. $C_{17}H_{25}N_2$. Calculated: *M* + H 257.202.

***N*-[2-(Adamantan-2-ylpropy]pyridin-2-amine (15)** was synthesized from 6 mg of amine **6**. The product was isolated by chromatography (CH_2Cl_2); yield 62 mg (46%). ^{1}H NMR spectrum, δ, ppm: 0.96 d (3H, ^3J = 6.7 Hz), 1.39 d (1H, ^3J = 10.7 Hz), 1.48–1.57 m (2H), 1.65–1.98 m (12H), 1.99–2.07 m (1H), 2.95 d.d.d (1H, ^2J = 12.5, ^3J = 7.8, 5.7 Hz), 3.37 d.d.d (1H, ^2J = 12.5, ^3J = 5.7, 3.3 Hz), 4.59 br.s (1H), 6.35 d (1H, ^3J = 8.5 Hz), 6.52 d.d.d (1H, ^3J = 7.2, 5.1, ^4J = 0.9 Hz), 7.39 d.d.d (1H, ^3J = 8.5, 7.2, ^4J = 1.9 Hz), 8.04 d.d (1H, ^3J = 5.1, ^4J = 1.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 16.0, 27.7, 27.9, 29.0, 29.2, 31.6, 32.1, 32.2, 38.1, 39.1, 39.3, 46.1, 47.2, 106.1, 112.4, 137.4, 148.1, 159.2. Mass spectrum: *m*/*z* 271.213 $[M + H]^+$. $C_{18}H_{27}N_2$. Calculated: *M* + H 271.217.

***N*-(Adamantan-2-yl)pyridin-2-amine (19)** was synthesized from 103 mg of amine **10**. The product was isolated by chromatography (CH_2Cl_2); yield 52 mg (42%). ^{1}H NMR spectrum, δ, ppm: 1.61 d (2H, ^3J = 12.6 Hz), 1.74 br.s (4H), 1.81–1.98 m (6H), 2.01 br.s (2H), 3.73 br.s (1H), 4.96 br.s (1H), 6.35 d (1H, ^3J = 8.1 Hz), 6.49–6.53 m (1H), 7.39 t (1H, ^3J = 7.8 Hz), 8.05 br.s (1H). ^{13}C NMR spectrum, δ_C, ppm: 27.2 (1C), 27.3 (1C), 31.5 (2C), 31.7 (2C), 37.2 (2C), 37.6 (1C), 55.4 (1C), 106.2 (1C), 112.3 (1C), 137.5 (1C), 147.9 (1C), 158.0 (1C). Mass spectrum: *m*/*z* 229.175 $[M + H]^+$. $C_{15}H_{21}N_2$. Calculated: *M* + H 229.171.

1-(Adamantan-2-yl)-4-(pyridin-2-yl)piperazine (20) was synthesized from 110 mg of amine **11**. The product was isolated by chromatography (CH_2Cl_2–MeOH, 100:1); yield 50 mg (34%). ^{1}H NMR spectrum, δ, ppm: 1.39 d (1H, ^3J = 11.0 Hz), 1.60–1.71 m (4H), 1.74–1.87 m (4H), 1.98–2.14 m (5H), 2.47–2.55 m (4H), 3.45–3.53 m (4H), 6.56 d.d (1H, ^3J = 7.2, 5.1 Hz), 6.61 d (1H, ^3J = 8.6 Hz), 7.43 d.d.d (1H, ^3J = 8.6, 7.2, ^4J = 2.0 Hz), 8.16 d.d (1H, ^3J = 5.1, ^4J = 2.0 Hz). ^{13}C NMR spectrum, δ_C, ppm: 27.3 (1C), 27.5 (1C), 28.9 (2C), 31.2 (1C), 31.3 (2C), 37.2 (2C), 37.7 (1C), 45.6 (2C), 49.3 (2C), 106.9 (1C), 112.9 (1C), 137.2 (1C), 147.9 (1C), 160.4 (1C). Mass spectrum: *m*/*z* 298.231 $[M + H]^+$. $C_{19}H_{28}N_3$. Calculated: *M* + H 298.228.

***N*-[2-(Adamantan-1-yl)ethyl]pyridin-3-amine (24)** was synthesized from 90 mg of amine **3**. The product was isolated by chromatography (CH_2Cl_2–MeOH, 100:1); yield 64 mg (50%). ^{1}H NMR spectrum, δ, ppm: 1.33–1.38 m (2H), 1.51–1.53 m (6H), 1.58–1.71 m (6H), 1.94 br.s (3H), 3.05–3.11 m (2H), 3.68 br.s (1H), 6.82 d (1H, ^3J = 8.1 Hz), 7.06 br.s (1H), 7.91 br.s (2H). ^{13}C NMR spectrum, δ_C, ppm: 28.5 (3C), 31.9 (1C), 36.9 (3C), 38.1 (1C), 42.4 (3C), 43.7 (1C), 118.1 (1C), 123.9 (1C), 135.7 (1C), 138.0 (1C), 144.8 (1C). Mass spectrum: *m*/*z* 257.206 $[M + H]^+$. $C_{17}H_{25}N_2$. Calculated: *M* + H 257.202.

***N*-[2-(Adamantan-2-yl)ethyl]pyridin-3-amine (25)** was synthesized from 90 mg of amine **4**. The product was isolated by chromatography (CH_2Cl_2–MeOH, 100:1); yield 55 mg (43%). ^{1}H NMR spectrum, δ, ppm: 1.52 (2H, ^3J = 12.3 Hz), 1.66–1.75 m

(9H), 1.76–1.89 m (6H), 3.05–3.10 m (2H), 3.80 br.s (1H), 6.84 d (1H, ^3J = 8.2 Hz), 7.06 br.s (1H), 7.94 br.s (2H). ^{13}C NMR spectrum, δ_C, ppm: 27.9 (1C), 28.1 (1C), 31.6 (3C), 31.9 (1C), 32.3 (1C), 38.2 (1C), 39.0 (2C), 42.0 (2C), 118.1 (1C), 123.8 (1C), 135.7 (1C), 138.0 (1C), 144.3 (1C). Mass spectrum: *m*/*z* 257.199 $[M + H]^+$. $C_{17}H_{25}N_2$. Calculated: *M* + H 257.202.

***N*-[2-(Adamantan-2-yl)propyl]pyridin-3-amine (27)** was synthesized from 97 mg of amine **6**. The product was isolated by chromatography (CH_2Cl_2–MeOH, 200:1); yield 55 mg (41%). ^{1}H NMR spectrum, δ, ppm: 0.94 d (3H, ^3J = 6.6 Hz), 1.36 d (1H, ^3J = 10.6 Hz), 1.46–1.57 m (2H), 1.65–1.94 m (12H), 1.97–2.08 m (1H), 2.77 d.d (1H, ^2J = 12.1, ^3J = 8.2 Hz), 3.23 d.d (1H, ^2J = 12.1, ^3J = 2.5 Hz), 3.92 br.s (1H), 6.85 d (1H, ^3J = 7.8 Hz), 7.11 br.s (1H), 7.97 br.s (2H). ^{13}C NMR spectrum, δ_C, ppm: 16.0, 27.6, 27.8, 29.0, 29.3, 31.6, 31.9, 32.1, 38.1, 39.0, 39.2, 47.4, 47.5, 118.0, 123.8, 135.5, 137.5, 144.7. Mass spectrum: *m*/*z* 271.221 $[M + H]^+$. $C_{18}H_{27}N_2$. Calculated: *M* + H 271.217.

1-(Adamantan-2-yl)-4-(pyridin-3-yl)piperazine (30) was synthesized from 110 mg of amine **11**. The product was isolated by chromatography (CH_2Cl_2–MeOH, 100:1); yield 40 mg (27%). ^{1}H NMR spectrum, δ, ppm: 1.42 d (2H, ^3J = 12.0 Hz), 1.68 d (2H, ^3J = 12.4 Hz), 1.71 br.s (2H), 1.78–1.90 m (4H), 2.07–2.15 m (5H), 2.62 br.s (4H), 3.24 br.s (4H), 7.17 br.s (2H), 8.10 br.s (1H), 8.32 br.s (1H). ^{13}C NMR spectrum, δ_C, ppm: 27.3 (1C), 27.5 (1C), 28.9 (2C), 31.3 (3C), 37.2 (2C), 37.7 (1C), 48.7 (2C), 49.3 (2C), 122.0 (1C), 123.5 (1C), 138.3 (1C), 140.4 (1C); one quaternary carbon signal was not identified. Mass spectrum: *m*/*z* 298.232 $[M + H]^+$. $C_{19}H_{28}N_3$. Calculated: *M* + H 298.228.

1-(Adamantan-1-yl)-4-(pyridin-3-yl)piperazine (31) was synthesized from 110 mg of amine **22**. The product was isolated by chromatography (CH_2Cl_2–MeOH, 35:1); yield 30 mg (20%). ^{1}H NMR spectrum, δ, ppm: 1.57–1.70 m (12H), 1.78 m (6H), 2.85–2.90 m (4H), 3.25–3.30 m (4H), 7.15 br.s (2H), 8.08 br.s (1H), 8.28 br.s (1H). ^{13}C NMR spectrum, δ_C, ppm: 29.6 (3C), 36.7 (3C), 38.3 (3C), 44.0 (2C), 49.0 (2C), 59.2 (1C), 121.9 (1C), 122.1 (1C), 135.0 (1C), 138.4 (1C), 140.5 (1C). Mass spectrum: *m*/*z* 298.225 $[M + H]^+$. $C_{19}H_{28}N_3$. Calculated: *M* + H 298.228.

***N*,*N*′-Bis[2-(adamantan-1-yl)ethyl]pyridine-2,6-diamine (35)** was synthesized from 358 mg (2 mmol) of amine **3** using 0.2 mmol (34 mg) of 2-(2-methyl-1-oxopropyl)cyclohexanone as ligand. Yield >95% (in the reaction mixture). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.25–1.30 m (4H), 1.42–1.46 m (6H), 1.51 br.s (6H), 1.55–1.69 m (12H), 1.89 br.s (6H), 3.14–3.20 m (4H), 5.50 d (2H, ^3J = 7.8 Hz), 5.71 t (2H, ^3J = 4.9 Hz), 6.92 t (1H, ^3J = 7.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.0 (6C), 32.0 (2C), 36.5 (6C), 41.7 (6C), 42.2 (2C), 43.4 (2C), 93.9 (2C), 137.1 (1C), 158.1 (2C). Mass spectrum: *m*/*z* 434.350 $[M + H]^+$. $C_{29}H_{44}N_3$. Calculated: *M* + H 434.354.

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