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PROBLEM OF REGIOSELECTIVITY IN THE AMINATION OF 2-FLUORO-5-IODOPYRIDINE WITH ADAMANTYLALKYL AMINES

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Abstract – Cu(I)-Catalyzed and catalyst-free amination of 2-fluoro-5-iodopyridine with adamantylalkyl amines possessing different steric hindrances at amino group was investigated to obtain corresponding 5-amino-2-fluoro- and 2-amino-5-iodopyridines. The competition between catalytic substitution of iodine and non-catalytic substitution of fluorine was shown to take place. The catalytic system CuI/2-(isobutyryl)cyclohexanone in DMF provided yields of 5-amino-2-fluoropyridines up to 58% with stoichiometric ratio of the reagents and up to 98% with two equiv. of amines. The non-catalytic amination of 2-fluoro-5-iodopyridine provided the yields of 2-amino-5-iodopyridines up to 97%.

Well-known versatile biological activity of adamantane derivatives implies the need to develop modern synthetic routes to fluoropyridines containing the adamantane backbone in view of further search for their properties. The catalytic amination of dihalopyridines seems to be a logical approach to such compounds. It is to be noted that 2-bromopyridine and 2,6-dibromopyridine were successfully aminated by Buchwald at the beginning of his studies on the Pd-catalyzed amination in 1996.[1] Catalytic amination of dihalopyridines has been studied mostly using Pd-containing catalysts to synthesize various bromo- or chlorosubstituted aminopyridines.[2-4] Recently an example of Pd-catalyzed synthesis of bromo-substituted 2-aminopyridines from 2-chloro-3-bromo- and 2-chloro-5-bromopyridines has been reported.[5] Pd-Catalyzed amination of 2-fluoro-4-iodopyridine was shown as a synthetic way to 4-amino-2-fluoropyridines.[6] At the same time numerous examples of Cu-catalyzed amination of

halopyridines were published.[7-11] There are only three single examples of the catalytic amination of 5-iodo-2-fluoropyridines with cyclic amides[12,13] and amine[14] with humble yields (21-35%).

Previously we investigated Pd-catalyzed amination of 2- and 3-bromopyridines and dihalopyridines with some adamantane-containing amines and diamines.[15-17] We have also found the conditions for effective Cu(I)-catalyzed amination of iodopyridines with adamantylalkyl amines[18] and polyamines.[19]

In this work we studied the Cu(I)-catalyzed amination using 11 different adamantylalkyl amines **1a-k** (Figure 1) which differ by the steric hindrances of the substituents at the amino group and by the presence of additional oxygen (**1c**) or nitrogen (**1j,k**) atoms in the side chains. Amines **1f-i** were used in racemic form.

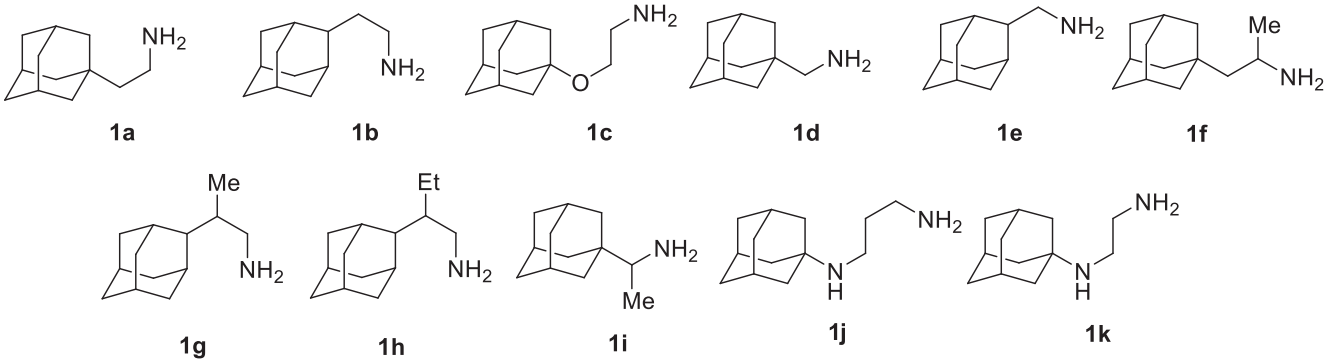
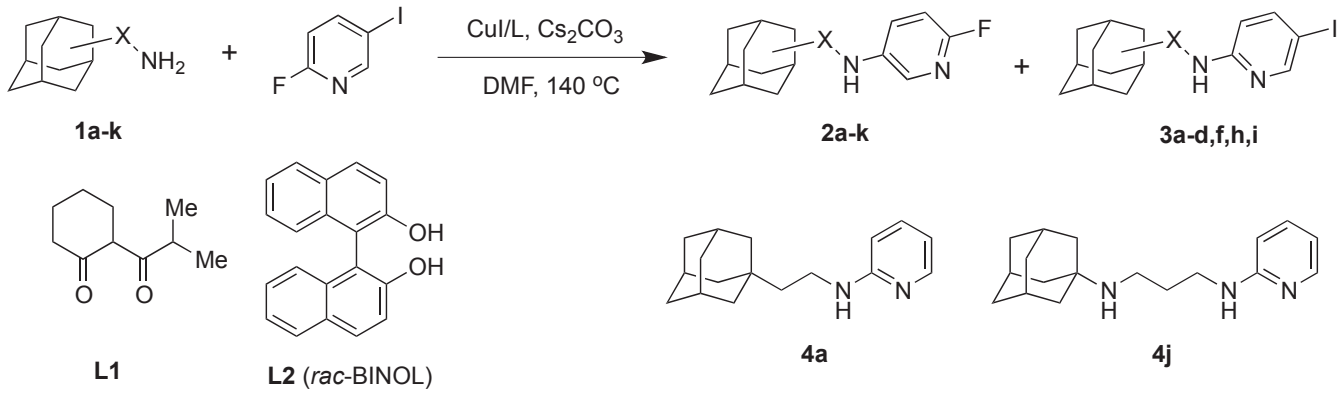


Figure 1. Adamantylalkyl amines under investigation

The reaction was carried out with 2-fluoro-5-iodopyridine in order to obtain valuable 2-fluoropyridinyl substituted amines and to reveal the regularities of the catalytic substitution of the iodine in position 5 of the pyridine ring in the presence of an active fluorine atom in position 2. The competing non-catalytic substitution reaction was thus to be controlled and suppressed as much as possible. Our previous investigations[37] revealed that the best catalytic systems for the copper-catalyzed amination with adamantane-containing amines were CuI/2-(isobutyryl)cyclohexanone (**L1**) and CuI/*rac*-BINOL (**L2**) with a standard catalyst loading 10 mol%. Various ligands suitable in Cu(I)-catalyzed couplings like proline and other amino acids, *N,N'*-dimethylethylenediamine, 1,10-phenanthroline, etc. were found to be inefficient in the amination with adamantane-containing amines.[20,21] DMF was used as a solvent and cesium carbonate (2 equiv.) was taken as base (Scheme 1), the ratio iodopyridine/amine 1:1 was employed with concentration 0.5 M of the starting compounds. The reaction was run under inert atmosphere at 140 ºC, the reaction time was not optimized and was taken as 24 h to ensure full conversion of the starting 2-fluoro-5-iodopyridine. The reaction products were isolated by the column chromatography on silica gel, yields are given in the Table 1.



Scheme 1. Cu(I)-Catalyzed amination with amines **1a-k**

The reaction with the amine **1a** which does not possess steric hindrances at the amino group produced the product of the catalytic amination **2a** (33%) and the compound **4a** (23%) in the result of the nucleophilic substitution of the fluorine together with a simultaneous catalytic reduction of the C-I bond (Table 1, entry 1). Running the reaction at lower temperature (100 °C) led to a lower yield of the desired product **2a** (27%) while the product of the fluorine substitution **3a** was isolated in a comparable yield (entry 2). This substitution is essentially non-catalytic as fluorine is fully inactive in the catalytic amination reactions. Microwave irradiation, though reported to be helpful for conducting catalytic amination,[6] was not efficient in our case leading to a predominance of the product of the non-catalytic substitution **3a** (entry 3).

Table 1. Cu(I)-Catalyzed amination with amines **1a-k**

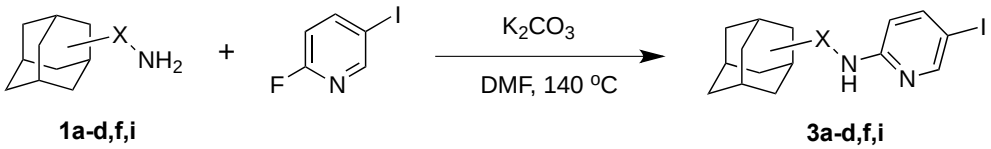
Entry	Amine	Ligand	CuI/L, mol%	Products and yields, %
1	**1a**, X = 1-CH_2CH_2-	**L1**	10/20	**2a**, 33; **4a**, 23
2[a]	**1a**, X = 1-CH_2CH_2-	**L1**	10/20	**2a**, 27; **3a**, 30
3[b]	**1a**, X = 1-CH_2CH_2-	**L1**	10/20	**2a**, 14; **3a**, 48
4	**1a**, X = 1-CH_2CH_2-	**L2**	10/20	**2a**, 42
5	**1a**, X = 1-CH_2CH_2-	**L1**	20/40	**2a**, 45
6[c]	**1a**, X = 1-CH_2CH_2-	**L1**	20/40	**2a**, 47; **3a**, 11
7[d]	**1a**, X = 1-CH_2CH_2-	**L1**	20/40	**2a**, 55; **3a**, 14
8	**1b**, X = 2-CH_2CH_2-	**L1**	10/20	**2b**, 34
9	**1b**, X = 2-CH_2CH_2-	**L2**	10/20	**2b**, 30; **3b**,8
10	**1b**, X = 2-CH_2CH_2-	**L1**	20/40	**2b**, 46; **3b**,9
11[d]	**1b**, X = 2-CH_2CH_2-	**L1**	20/40	**2b**, 65
12	**1c**, X = 1-O-CH_2CH_2-	**L1**	10/20	**2c**, 16; **3c**, 28
13	**1c**, X = 1-O-CH_2CH_2-	**L2**	10/20	**2c**, 24; **3c**, 6
14	**1c**, X = 1-O-CH_2CH_2-	**L1**	20/40	**2c**, 27; **3c**, 21
15[d]	**1c**, X = 1-O-CH_2CH_2-	**L1**	20/40	**2c**, 92
16	**1d**, X = 1-CH_2-	**L1**	10/20	**2d**, 33; **3d**, 7
17[d]	**1d**, X = 1-CH_2-	**L1**	20/40	**2d**, 95
18	**1e**, X = 2-CH_2-	**L1**	10/20	**2e**, 42

19[d]	**1e**, X = 2-CH_2-	**L1**	20/40	**2e**, 75
20	**1f**, X = 1-CH_2-CH(Me)-	**L1**	10/20	**2f**, 18; **3f**, 14
21	**1f**, X = 1-CH_2-CH(Me)-	**L2**	10/20	**2f**, 20; **3f**, 16
22[d]	**1f**, X = 1-CH_2-CH(Me)-	**L1**	20/40	**2f**, 66
23	**1g**, X = 2-CH(Me)-CH_2-	**L1**	10/20	**2g**, 27
24	**1g**, X = 2-CH(Me)-CH_2-	**L2**	10/20	**2g**, 29
25[d]	**1g**, X = 2-CH(Me)-CH_2-	**L1**	20/40	**2g**, 76
26	**1h**, X = 2-CH(Et)-CH_2-	**L1**	10/20	**2h**, 19; **3h**, 63
27[d]	**1h**, X = 2-CH(Et)-CH_2-	**L1**	20/40	**2h**, 82
28	**1i**, X = 1-CH(Me)-	**L1**	10/20	**2i**, 14; **3i**, 9
29[d]	**1i**, X = 1-CH(Me)-	**L1**	20/40	**2i**, 54
30	**1j**, X = 1-NH-CH_2-CH_2-CH_2-	**L1**	10/20	**2j**, 58; **4j**, 21
31[d]	**1j**, X = 1-NH-CH_2-CH_2-CH_2-	**L1**	20/40	**2j**, 95
32	**1k**, X = 1-NH-CH_2-CH_2-	**L1**	10/20	**2k**, 31
33[d]	**1k**, X = 1-NH-CH_2-CH_2-	**L1**	20/40	**2k**, 98

[a] The reaction was conducted at 100 °C. [b] The reaction was conducted under microwave irradiation (Monowave-300) at 140 °C for 4 h. [c] 2 equiv. of 2-fluoro-5-iodopyridine was introduced into the reaction. [d] 2 equiv. of amine was introduced in the reaction.

The application of another ligand, i.e. *rac*-BINOL (**L2**) resulted in a better yield of the product of the catalytic amination (42%, entry 4), almost the same outcome of the reaction was observed when taking two-fold amount of the catalyst with **L1** ligand (entry 5). Application of 2 equiv. of 2-fluoro-5-iodopyridine did not improve the result (entry 6) while the use of 2 equiv. of the amine **1a** increased the yield of **2a** to 65%. Similar regularities were noted also for the majority of amines under investigation: the use of both catalytic systems, CuI/**L1** and CuI/**L2** with 10/20 mol% catalyst loadings gave mainly the mixtures of two products **2** and **3** (entries 8, 9, 12, 13, 16, 20, 21, 23, 24, 26, 28) and the yields of the target products **2** did not surpass 34%. In one case (with the amine **1j**) the reaction with 10 mol% catalyst was more successful providing 58% of **2j** (entry 30). A simple increase in the catalyst loading to 20 mol% with 40 mol% ligand **L1** improved the results to some extent (entries 10, 14), and the application of 2 equiv. of amines with 20/40 mol% catalytic system CuI/**L1** allowed significant increase in the compounds yields (entries 11, 15, 17, 19, 22, 25, 27, 29, 31, 33). In the case of compounds **2c,d,j,k** the yields even exceeded 90%. In other reactions they were lower either due to pronounced steric hindrances at the amino group (compounds **2f-i**) or probably due to some other side reactions. It is worth noting that no products of type **3** (non-catalytic substitution) were obtained in the reactions with excess amine. The explanation of this fact is quite difficult, one may assume that the increase in the rate of the catalytic reaction was more pronounced.

To examine the non-catalytic substitution of the fluorine atom in 2-fluoro-5-iodopyridine, a special study has been undertaken with a variety of adamantylalkyl amines **1a-d,f,i**. The reactions of equimolar amounts of starting compounds were run in DMF at 140 °C using potassium carbonate as base (Scheme 2). The results are summarized in the Table 2.



1a-d,f,i **3a-d,f,i**

Scheme 2. Catalyst-free amination with amines **1a-d,f,i**

Table 2. Catalyst-free amination with amines **1a-d,f,i**

Entry	Amine	Product and yield, %
1	**1a**, X = 1-CH_2CH_2-	**3a**, 82
2	**1b**, X = 2-CH_2CH_2-	**3b**, 76
3	**1c**, X = 1-O-CH_2CH_2-	**3c**, 97
4	**1d**, X = 1-CH_2-	**3d**, 74
5	**1f**, X = 1-CH_2-CH(Me)-	**3f**, 56
6	**1i**, X = 1-CH(Me)-	**3i**, 42

Amines **1a-d** which do not possess steric hindrances at the amino group provided good to excellent yields of the products of fluorine substitution **3a-d** (Table 2, entries 1-4). The reaction with amines **1f,i** with more bulky fragments adjacent to amino group afforded lower yields of the corresponding compounds **3f, i** (entries 5, 6). This fact implies that sterically hindered adamantane-containing amines are reluctant in both catalytic and non-catalytic amination reactions leading to quite humble yields of the desired products. Also it is quite expectable that no substitution of the iodine under non-catalytic conditions was observed as it is much less active in the conventional aromatic nucleophilic substitution and fluorine occupies the position much more inclined to substitution. In the Cu(I)-catalyzed reactions considered in this investigation the full consumption of 2-fluoro-5-iodopyridine was due not only to the amination (both in catalytic and non-catalytic versions) but also to other catalytic transformations giving rise to a variety of by-products which were not isolated in pure state.

In conclusion, we have synthesized a series of *N*-adamantylalkyl-substituted aminohalopyridines in yields from moderate to excellent *via* 2-fluro-5-iodopyridine amination reactions. In Cu(I)-catalyzed amination reactions run with 10 mol% catalyst the yields of the products of the catalytic substitution of iodine were mainly humble and the products of competing non-catalytic substitution of fluorine were always obtained. The increase of the catalyst loading to 20 mol% together with the application of 2 equiv. of amines allowed a substantial increase in the yields of the target 5-amino-2-fluoropyridines which reached 98%. The dependence of the amination products yields on steric hindrances at the amino groups was noted both in catalytic and non-catalytic processes.

EXPERIMENTAL

Unless otherwise stated, all chemicals and starting materials were obtained commercially from Sigma-Aldrich Co. and used without further purification. Amines **1a**,**b,e** were obtained according to the known procedures,[22] amine **1c** was synthesized by the published method,[23] amine **1d** was obtained according to known method,[24] amine **1f** was obtained as earlier described.[15] Amines **1g** and **1h** were synthesized according to published method.[25] Amine **1i** was obtained from commercially available hydrochloride by treatment with NaOH in MeOH. Amines **1j** and **1k** were prepared from 1-aminoadamantane according to known procedures.[26,27] ^{1}H and ^{13}C NMR spectra were registered with Bruker Avance-400 spectrometer in $CDCl_3$, chemical shifts are given in δ scale in ppm relative to the residual solvent peak ($CHCl_3$: δ = 7.26 ppm for ^{1}H) or to solvent ($CDCl_3$: δ = 77.00 ppm for ^{13}C) as internal standards. Mass-spectra MALDI-TOF of positive ions were recorded with Bruker Daltonics Ultraflex device using 1,8,9-trihydroxyanthracene (dithranol) as matrix and polyethyleneglycols as internal standards. Preparative column chromatography was carried out using silica gel 40/60 from Merck Co. Melting points were measured with an Electrothermal IA 9200 apparatus. DMF was distilled over CaH_2 under reduced pressure, CH_2Cl_2 was distilled over CaH_2, MeOH and petroleum ether were used freshly distilled.

General procedure

A dry vial with a screwcap equipped with a magnetic stirrer was filled with dry argon, charged with CuI (10-20 mol%, 10-20 mg), ligand **L1** or **L2**, 20-40 mol%, 2-fluoro-5-iodopyridine (0.5 mmol, 112 mg), DMF (1 mL) and adamantylalkyl amine (0.5 mmol) in stream of dry argon. The reaction mixture was stirred for 1 min, then cesium carbonate (1 mmol, 326 mg) was added and the reaction was stirred at 140 ºC or 110 ºC. After ca. 24 h the mixture was cooled down to ambient temperature, CH_2Cl_2 (5 mL) was added, the organic solution was filtered, the residue was washed additionally with CH_2Cl_2 (2 × 5 mL), the combined organic fractions were evaporated *in vacuo*. To obtain individual compounds, the residue was chromatographed on silica gel using a sequence of eluents: petroleum ether, petroleum ether (PE)/CH_2Cl_2 (2:1, 1:1, 1:2 v/v), CH_2Cl_2, CH_2Cl_2/MeOH (200:1, 100:1, 50:1, 33:1; 25:1 v/v).

Catalyst-free amination was carried out according to the same procedure without adding catalyst and using dry K_2CO_3 (4 equiv., 2 mmol) instead of Cs_2CO_3.

***N*-[2-(1-Adamantyl)ethyl]-6-fluoropyridin-3-amine (2a)** was obtained according to general procedure from amine **1a** (0.5 mmol, 90 mg) in the presence of CuI (10 mg, 10 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 17 mg, 20 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2, yield 45 mg (33%), beige crystals, mp 145-147 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36-1.40 (m, 2 H), 1.53-1.54 (m, 6 H), 1.61-1.74 (m, 6 H), 1.96 (br. s, 3 H), 3.07 (t, J = 7.8 Hz, 2 H), 3.49 (br. s, 1 H), 6.72 (dd, J = 8.6, 3.0 Hz, 1 H), 6.98 (ddd, J = 9.4, 6.7, 3.0 Hz, 1 H), 7.49 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.5 (3 C), 31.9 (1 C), 37.0

(3 C), 38.9 (1 C), 42.5 (3 C), 43.8 (1 C), 109.1 (d, J_{CF} = 39.2 Hz, 1 C), 124.9 (1 C), 130.3 (d, J_{CF} = 15.1 Hz, 1 C), 142.7 (1 C), 156.5 (d, J_{CF} = 228.2 Hz, 1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{24}FN_2$: 275.1923; found: 275.1881.

***N*-[2-(2-Adamantyl)ethyl]-6-fluoropyridin-3-amine (2b)** was obtained according to general procedure from amine **1b** (0.5 mmol, 90 mg) in the presence of CuI (10 mg, 10 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 17 mg, 20 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: PE-CH_2Cl_2 (2:1), yield 47 mg (34%), beige crystals, mp 139-141 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51-1.55 (m, 2 H), 1.65-1.93 (m, 15 H), 3.07 (br. s, 2 H), 3.61 (br. s, 1 H), 6.71-6.75 (m, 1 H), 6.98 (ddd, *J* = 9.3, 6.8, 3.0 Hz, 1 H), 7.51 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.9 (1 C), 28.1 (1 C), 31.6 (2 C), 31.9 (2 C), 32.4 (1 C), 38.2 (1 C), 39.1 (2 C), 42.0 (1 C), 42.8 (1 C), 109.1 (d, J_{CF} = 39.4 Hz, 1 C), 125.0 (1 C), 130.4 (d, J_{CF} = 14.5 Hz, 1 C), 142.7 (1 C), 156.5 (d, J_{CF} = 228.1 Hz, 1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{24}FN_2$: 275.1923; found: 275.1894.

***N*-[2-(1-Adamantyloxy)ethyl]-6-fluoropyridin-3-amine (2c)** was obtained according to general procedure from amine **1c** (0.5 mmol, 98 mg) in the presence of CuI (19 mg, 20 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 34 mg, 40 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2-MeOH (200:1), yield 39 mg (27%), beige crystals, mp 70-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55-1.68 (m, 6 H), 1.71 (br. s, 6 H), 2.12 (br. s, 3 H), 3.20 (br. s, 2 H), 3.60 (t, *J* = 4.9 Hz, 2 H), 4.02 (br. s, 1 H), 6.76 (br. s, 1 H), 7.01 (br. s, 1 H), 7.60 (br. s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 30.3 (3 C), 36.2 (3 C), 41.4 (3 C), 44.5 (1 C), 57.9 (1 C), 72.4 (1 C), 109.2 (1 C), 125.6 (1 C), 130.8 (1 C), 142.6 (1 C), 156.5 (d, J_{CF} = 228.0 Hz, 1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{24}FN_2O$: 291.1873; found: 291.1840.

***N*-(1-Adamantylmethyl)-6-fluoropyridin-3-amine (2d)** was obtained according to general procedure from amine **1d** (0.5 mmol, 83 mg) in the presence of CuI (10 mg, 10 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 17 mg, 20 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2, yield 43 mg (33%), beige crystals, mp 110-111 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56 (br. s, 6 H), 1.61-1.78 (m, 6 H), 2.01 (br. s, 3 H), 2.75 (s, 2 H), 3.48 (br. s, 1 H), 6.71-6.74 (m, 1 H), 7.02 (ddd, *J* = 9.3, 6.7, 3.1 Hz, 1 H), 7.54 (br. s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.2 (3 C), 33.9 (1 C), 37.0 (3 C), 40.6 (3 C), 56.8 (1 C), 109.0 (d, *J* = 39.5 Hz, 1 C), 124.8 (1 C), 130.5 (d, J_{CF} = 14.5 Hz, 1 C), 143.4 (1 C), 156.4 (d, J_{CF} = 228.0 Hz, 1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{22}FN_2$: 261.1767; found: 261.1768.

***N*-(2-Adamantylmethyl)-6-fluoropyridin-3-amine (2e)** was obtained according to general procedure from amine **1e** (0.5 mmol, 83 mg) in the presence of CuI (10 mg, 10 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 17 mg, 20 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: PE-CH_2Cl_2 (1:1), yield 55 mg (42%), beige crystals, mp 134-135 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54-1.60 (m, 2 H), 1.72-2.00 (m, 13 H), 3.18 (br. s, 2 H), 3.18 (br. s, 1 H), 6.75 (br. s, 1 H), 6.98-7.01 (m, 1 H), 7.53 (br. s, 1 H). NH proton signal

was not observed. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.8 (1 C), 28.2 (1 C), 30.3 (2 C), 31.8 (2 C), 38.0 (1 C), 38.8 (2 C), 44.1 (1 C), 46.9 (1 C), 109.1 (d, J_{CF} = 39.4 Hz, 1 C), 125.0 (1 C), 130.3 (1 C), 142.9 (1 C), 156.4 (d, J_{CF} = 228.1 Hz, 1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{16}H_{22}FN_2$: 261.17670; found: 261.1736.

***N*-[2-(1-Adamantyl)-1-methylethyl]-6-fluoropyridin-3-amine (2f)** was obtained according to general procedure from amine **1f** (0.5 mmol, 97 mg) in the presence of CuI (10 mg, 10 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 17 mg, 20 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2, yield 13 mg (18%), beige crystals, mp 97-98 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 6.3 Hz, 3 H), 1.21-1.34 (m, 2 H), 1.53 (s, 6 H), 1.58-1.69 (m, 6 H), 1.93 (br. s, 3 H), 3.36 (br. s, 1 H), 3.52 (quint., *J* = 5.9, 1 H), 6.72 (dd, *J* = 8.8, 3.1 Hz, 1 H), 6.96 (ddd, *J* = 9.6, 6.8, 3.1 Hz, 1 H), 7.48 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.0 (1 C), 28.6 (3 C), 32.5 (1 C), 36.9 (3 C), 43.1 (3 C), 45.0 (1 C), 52.7 (1 C), 109.2 (d, J_{CF} = 39.3 Hz, 1 C), 123.3 (1 C), 130.8 (d, J_{CF} = 15.1 Hz, 1 C), 141.4 (1 C), 156.4 (d, J_{CF} = 228.2 Hz, 1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{26}FN_2$: 289.2080; found: 289.2072.

***N*-[2-(2-Adamantyl)propyl]-6-fluoropyridin-3-amine (2g)** was obtained according to general procedure from amine **1g** (0.5 mmol, 97 mg) in the presence of CuI (19 mg, 20 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 34 mg, 40 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2, yield 39 mg (27%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.7 Hz , 3 H), 1.38 (br. d, *J* = 10.6 Hz, 1 H), 1.49-1.59 (m, 2 H), 1.70-1.94 (m, 12 H), 2.00-2.11 (m, 1 H), 2.79 (dd, *J* = 12.2, 8.2 Hz, 1 H), 3.22 (dd, *J* = 12.2, 3.3 Hz, 1 H), 6.74 (dd, *J* = 8.7, 3.2 Hz, 1 H), 6.96 (ddd, *J* = 9.6, 6.8, 3.2 Hz, 1 H), 7.55 (s, 1 H). NH proton signal was not observed. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 16.0 (1 C), 27.6 (1C), 27.9 (1 C), 29.1 (1 C), 29.3 (1 C), 31.6 (2 C), 31.9 (1 C), 32.2 (1 C), 38.1 (1 C), 39.1 (1 C), 39.2 (1 C), 47.4 (1 C), 109.2 (d, J_{CF} = 39.3 Hz, 1 C), 125.3 (1 C), 130.7 (d, J_{CF} = 15.1 Hz, 1 C), 142.5 (1 C), 156.7 (d, J_{CF} = 228.2 Hz, 1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{18}H_{26}FN_2$: 289.2080; found: 289.2069.

***N*-[2-(2-Adamantyl)butyl]-6-fluoropyridin-3-amine (2h)** was obtained according to general procedure from amine **1h** (0.5 mmol, 104 mg) in the presence of CuI (19 mg, 20 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 34 mg, 40 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2, yield 29 mg (19%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.3 Hz, 3 H), 1.31-1.38 (m, 1 H), 1.49-1.98 (m, 17 H), 2.97 (dd, *J* = 12.0, 6.5 Hz, 1 H), 3.22 (dd, *J* = 12.0, 3.3 Hz, 1 H), 3.52 (br. s, 1 H), 6.73 (dd, *J* = 8.8, 3.2 Hz, 1 H), 6.96 (ddd, *J* = 9.7, 6.8, 3.2 Hz, 1 H), 7.52 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 9.9 (1 C), 20.6 (1 C), 27.7 (1C), 27.9 (1 C), 28.8 (1 C), 29.2 (1 C), 31.8 (1 C), 32.0 (1 C), 37.0 (1 C), 38.1 (1 C), 39.3 (2 C), 43.3 (1 C), 44.5 (1 C), 109.1 (d, J_{CF} = 39.2 Hz, 1 C), 124.9 (1 C), 130.3 (d, J_{CF} = 15.1 Hz, 1 C), 142.9 (1 C), 156.5 (d, J_{CF} = 228.2 Hz, 1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{28}FN_2$: 303.223; found: 303.224.

***N*-[1-(1-Adamantyl)ethyl]-6-fluoropyridin-3-amine (2i)** was obtained according to general procedure

from amine **1i** (0.5 mmol, 90 mg) in the presence of CuI (10 mg, 10 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 17 mg, 20 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2, yield 13 mg (18%), beige crystals, mp 113-114 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, J = 6.6 Hz, 3 H) 1.49-1.73 (m, 12 H), 2.01 (br. s, 3 H), 2.94 (q, J = 6.6 Hz, 1 H), 3.39 (br. s, 1 H), 6.72 (dd, J = 8.8, 3.1 Hz, 1 H), 6.97-7.03 (m, 1 H), 7.52 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2 (1 C), 28.4 (3 C), 36.6 (1 C), 37.1 (3 C), 38.7 (3 C), 58.8 (1 C), 109.1 (d, J_{CF} = 39.2 Hz, 1 C), 125.2 (1 C), 131.2 (1 C), 142.8 (1 C), 156.3 (d, J_{CF} = 228.0 Hz, 1 C). HRMS (MALDI TOF): m/z $[M+H]^+$ calcd for $C_{17}H_{24}FN_2$: 275.1923; found: 275.1882.

***N*-1-Adamantyl-*N*'-(6-fluoropyridin-3-yl)propane-1,3-diamine (2j)** was obtained according to general procedure from amine **1j** (0.5 mmol, 104 mg) in the presence of CuI (10 mg, 10 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 17 mg, 20 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2-MeOH (20:1), yield 88 mg (58%), yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43-1.59 (m, 6 H), 1.87 (s, 6 H), 2.01 (br. s, 3 H), 2.07 (quint., J = 6.9 Hz, 2 H), 2.93 (t, J = 7.5 Hz, 2 H), 3.07 (t, J = 6.3 Hz, 2 H), 6.55 (dd, J = 8.8, 3.2 Hz, 1 H), 7.02 (ddd, J = 9.2, 6.9, 3.2 Hz, 1 H), 7.37 (s, 1 H). NH proton signals was not observed. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.2 (1 C), 28.5 (3 C), 35.1 (3 C), 37.4 (1 C), 38.0 (3 C), 40.9 (3 C), 57.6 (1 C), 108.7 (d, J_{CF} = 39.1 Hz, 1 C), 125.3 (1 C), 129.3 (d, J_{CF} = 15.1 Hz, 1 C), 142.3 (1 C), 155.8 (d, J_{CF} = 228.1 Hz, 1 C). MS (MALDI TOF): m/z $[M+H]^+$ calcd for $C_{18}H_{27}FN_3$: 304.22; found: 304.20.

***N*-1-Adamantyl-*N*'-(6-fluoropyridin-3-yl)ethane-1,2-diamine (2k)** was obtained according to general procedure from amine **1k** (0.5 mmol, 97 mg) in the presence of CuI (10 mg, 10 mol%), 2-(isobutyryl)cyclohexanone (**L1**, 17 mg, 20 mol%) and Cs_2CO_3 (1 mmol, 326 mg). Eluent: CH_2Cl_2-MeOH (20:1), yield 45 mg (31%), beige crystals, mp 150-152 °C (decomp.). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.54-1.68 (m, 6 H), 1.91 (s, 6 H), 2.06 (br. s, 3 H), 3.11 (br. s, 2 H), 3.55 (br. s, 2 H), 6.69 (dd, J = 8.8, 3.1 Hz, 1 H), 7.00-7.23 (m, 3 H), 7.53 (s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.9 (3 C), 35.5 (3 C), 38.7 (3 C), 40.3 (1 C), 57.4 (1 C), 109.4 (d, J_{CF} = 39.1 Hz, 1 C), 126.1 (1 C), 129.7 (d, J_{CF} = 14.9 Hz, 1 C), 141.3 (1 C), 156.6 (d, J_{CF} = 228.4 Hz, 1 C). HRMS (MALDI TOF): m/z $[M+H]^+$ calcd for $C_{17}H_{25}FN_3$: 290.20325; found: 290.1988.

***N*-[2-(1-Adamantyl)ethyl]-5-iodopyridin-2-amine (3a)** was obtained according to general procedure from amine **1a** (0.5 mmol, 90 mg) in the presence of K_2CO_3 (2 mmol, 276 mg). Eluent: PE-CH_2Cl_2 (2:1), yield 157 mg (82%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34-1.40 (m, 2 H), 1.53-1.55 (m, 6 H), 1.60-1.74 (m, 6 H), 1.96 (br. s, 3 H), 3.16-3.24 (m, 2 H), 4.48 (br. s, 1 H), 6.22 (d, J = 8.8 Hz, 1 H), 7.59 (dd, J = 8.8, 2.0 Hz, 1 H), 8.20 (d, J = 2.0 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.6 (3 C), 31.9 (1 C), 37.0 (3 C), 37.1 (1 C), 42.5 (3 C), 43.7 (1 C), 75.8 (1 C), 108.7 (1 C), 144.9 (1 C), 153.5 (1 C), 157.5 (1 C). HRMS (MALDI TOF): m/z $[M+H]^+$ calcd for $C_{17}H_{24}IN_2$: 383.0984; found: 383.0980.

***N*-[2-(2-Adamantyl)ethyl]-5-iodopyridin-2-amine (3b)** was obtained according to general procedure

from amine **1b** (0.5 mmol, 90 mg) in the presence of K_2CO_3 (2 mmol, 276 mg). Eluent: PE-CH_2Cl_2 (2:1), yield 146 mg (76%), yellowish crystals, mp 96-97 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51-1.55 (m, 2 H), 1.68-1.93 (m, 15 H), 3.19 (q, J = 6.8 Hz, 2 H), 4.68 (br. s, 1 H), 6.22 (d, J = 8.8 Hz, 1 H), 7.58 (dd, J = 8.8, 2.1 Hz, 1 H), 8.19 (d, J = 2.1 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 27.9 (1 C), 28.1 (1 C), 31.6 (2 C), 31.8 (2 C), 32.2 (1 C), 38.2 (1 C), 39.0 (2 C), 40.6 (1 C), 41.8 (1 C), 75.8 (1 C), 108.6 (1 C), 144.8 (1 C), 153.6 (1 C), 157.6 (1 C). HRMS (MALDI TOF): m/z $[M+H]^+$ calcd for $C_{17}H_{24}IN_2$: 383.0984; found: 383.0962.

***N*-[2-(1-Adamantyloxy)ethyl]-5-iodopyridin-2-amine (3c)**[42] was obtained according to general procedure from amine **1c** (0.5 mmol, 97 mg) in the presence of K_2CO_3 (2 mmol, 276 mg). Eluent: CH_2Cl_2-MeOH (200:1), yield 193 mg (97%), light beige crystals, mp 83-85 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53-1.64 (m, 6 H), 1.71 (br. s, 6 H), 2.13 (br. s, 3 H), 3.37 (q, J = 5.3 Hz, 2 H), 3.58 (t, J = 5.2 Hz, 2 H), 4.92 (br. s, 1 H), 6.25 (d, J = 8.7 Hz, 1 H), 7.56 (dd, J = 8.7, 2.0 Hz, 1 H), 8.20 (d, J = 2.0 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 30.4 (3 C), 36.3 (3 C), 41.5 (3 C), 42.4 (1 C), 58.3 (1 C), 72.4 (1 C), 76.2 (1 C), 109.6 (1 C), 144.6 (1 C), 153.6 (1 C), 157.5 (1 C).

***N*-(1-Adamantylmethyl)-5-iodopyridin-2-amine (3d)** was obtained according to general procedure from amine **1d** (0.5 mmol, 83 mg) in the presence of K_2CO_3 (2 mmol, 276 mg). Eluent: PE-CH_2Cl_2 (2:1), yield 71 mg (74%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.51-1.54 (m, 6 H), 1.59-1.73 (m, 6 H), 1.97 (br. s, 3 H), 2.75 (d, J = 6.3 Hz, 2 H), 4.66 (br. s, 1 H), 6.24 (d, J = 8.8 Hz, 1 H), 7.55 (dd, J = 8.8, 2.1 Hz, 1 H), 8.16 (d, J = 2.1 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.2 (3 C), 34.0 (1 C), 36.9 (3 C), 40.3 (3 C), 54.0 (1 C), 75.4 (1 C), 108.6 (1 C), 144.7 (1 C), 153.5 (1 C), 158.2 (1 C). HRMS (MALDI TOF): m/z $[M+H]^+$ calcd for $C_{16}H_{22}IN_2$: 369.0827; found: 369.0814.

***N*-[2-(1-Adamantyl)-1-methylethyl]-5-iodopyridin-2-amine (3f)** was obtained according to general procedure from amine **1f** (0.5 mmol, 97 mg) in the presence of K_2CO_3 (2 mmol, 276 mg). Eluent: PE-CH_2Cl_2 (2:1), yield 67 mg (56%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, J = 6.3 Hz, 3 H), 1.24-1.32 (m, 2 H), 1.51-1.54 (m, 6 H), 1.56-1.72 (m, 6 H), 1.92 (br. s, 3 H), 3.36 (quint., J = 6.0 Hz, 1 H), 4.64-4.66 (m, 1 H), 6.23 (d, J = 8.8 Hz, 1 H), 7.60 (dd, J = 8.8, 2.1 Hz, 1 H), 8.18 (br. s, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.3 (1 C), 28.6 (3 C), 32.5 (1 C), 37.0 (3 C), 42.9 (3 C), 43.2 (1 C), 52.5 (1 C), 74.9 (1 C), 109.1 (1 C), 145.3 (1 C), 153.0 (1 C), 156.1 (1 C). HRMS (MALDI TOF): m/z $[M+H]^+$ calcd for $C_{18}H_{26}IN_2$: 397.1140; found: 397.1119. This compound was also obtained as the second product from Cu-catalyzed synthesis of **2f**. Yield 28 mg (14%).

***N*-[2-(2-Adamantyl)butyl]-5-iodopyridin-2-amine (3h)** was isolated as a second product from Cu-catalyzed synthesis of **2h**. Eluent: PE-CH_2Cl_2 (2:1), yield 129 mg (63%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.3 Hz , 3 H), 1.31-1.41 (m, 1 H), 1.49-2.02 (m, 17 H), 3.07-3.15 (m, 1 H), 3.29-3.37 (m, 1 H), 4.50 (br. s, 1 H), 6.23 (d, J = 8.8 Hz, 1 H), 7.59 (dd, J = 8.8, 2.1 Hz, 1 H), 8.19 (d, J =

2.1 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 10.1 (1 C), 20.6 (1 C), 27.7 (1C), 27.9 (1 C), 28.8 (1 C), 29.2 (1 C), 31.8 (1 C), 32.0 (1 C), 37.2 (1 C), 38.1 (1 C), 39.2 (1 C), 39.3 (1 C), 41.0 (1 C), 44.4 (1 C), 75.7 (1 C), 108.4 (1 C), 144.8 (1 C), 153.7 (1 C), 157.9 (1 C). MS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{19}H_{28}IN_2$: 411.13; found: 411.14.

***N*-[1-(1-Adamantyl)ethyl]-5-iodopyridin-2-amine (3i)** was obtained according to general procedure from amine **1i** (0.5 mmol, 90 mg) in the presence of K_2CO_3 (2 mmol, 276 mg). Eluent: PE-CH_2Cl_2 (2:1), yield 48 mg (42%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.6 Hz, 3 H) 1.45-1.77 (m, 12 H), 1.98 (br. s, 3 H), 3.33-3.43 (m, 1 H), 4.58 (d, *J* = 8.9 Hz, 1 H), 6.23 (d, *J* = 8.8 Hz, 1 H), 7.59 (dd, *J* = 8.8, 2.1 Hz, 1 H), 8.19 (d, *J* = 2.1 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.5 (1 C), 28.4 (3 C), 36.4 (1 C), 37.1 (3 C), 38.6 (3 C), 55.8 (1 C), 74.8 (1 C), 109.0 (1 C), 144.9 (1 C), 153.3 (1 C), 157.6 (1 C). HRMS (MALDI TOF): *m*/*z* $[M+H]^+$ calcd for $C_{17}H_{24}IN_2$: 383.0984; found: 383.0958. This compound was also obtained as the second product from Cu-catalyzed synthesis of **2i**. Yield 17 mg (9%).

***N*-[2-(Adamantan-1-yl)ethyl]pyridin-2-amine (4a)**[18] was isolated as the second product from Cu-catalyzed synthesis of **2a**. Eluent: CH_2Cl_2, yield 29 mg (23%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.38-1.44 (m, 2 H), 1.49-1.74 (m, 12 H), 1.95 (br.s, 3 H), 3.20-3.27 (m, 2 H), 4.42 (br. s, 1 H), 6.36 (d, *J* = 8.5 Hz, 1 H), 6.51-6.55 (m, 1 H), 7.38-7.44 (m, 1 H), 8.05 (d, *J* = 4.3 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.6 (3 C), 32.0 (1 C), 37.1 (4 C), 42.3 (3 C), 43.9 (1 C), 106.3 (1 C), 112.5 (1 C), 137.5 (1 C), 148.0 (1 C), 158.8 (1 C).

***N*-(1-Adamantyl)-*N′*-(pyridin-2-yl)propane-1,3-diamine (4j)**[28] was isolated as the second product from Cu-catalyzed synthesis of **2j**. Eluent: CH_2Cl_2-MeOH (25:1), yield 30 mg (21%), yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$): 1.55-1.69 (m, 6 H), 1.76 (br. s, 6 H), 1.91 (quint., *J* = 6.4 Hz, 2 H), 2.07 (br.s, 3 H), 2.80 (t, *J* = 6.5 Hz, 2 H), 3.41 (t, *J* = 6.3 Hz, 2 H), 5.42 (br.s, 1 H), 6.43 (d, *J* = 8.5 Hz, 1 H), 6.50 (dd, *J* = 6.4, 5.7 Hz, 1 H), 7.35 (ddd, *J* = 8.5, 6.4, 1.6 Hz, 1 H), 8.00 (dd, *J* = 5.7, 1.6 Hz, 1 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 29.0 (1 C), 29.2 (3 C), 36.2 (3 C), 37.6 (1 C), 39.9 (1 C), 41.0 (3 C), 53.1 (1 C), 108.1 (1 C), 112.5 (1 C), 137.3 (1 C), 147.3 (1 C), 159.1 (1 C).

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