

Synthesis of a New Family of Adamantylpyridin-2-amines by Palladium-Catalyzed Amination

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Abstract: Palladium-catalyzed arylation of various adamantane-containing amines with 2-bromopyridine has been studied, and the influence of the phosphane ligand, concentration, and molar ratio of the reagents on the composition of the reaction mixture and on the yield of the target adamantylpyridin-2-amines has been analyzed. The dependence of the formation of N,N-diarylated products on the nature of the starting adamantylamines is shown.

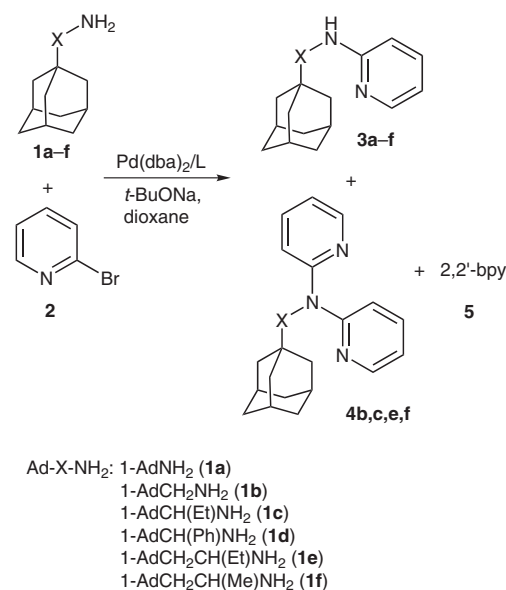
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Aminoadamantanes and their derivatives are important compounds, which have found wide application as drugs, and are extensively investigated for various applications in pharmacology and biological studies. For example, 1-aminoadamantane hydrochloride (amantadine), the simplest compound of this type, has proved to be an efficient medicine against Parkinson's disease,^{1,2} and has also found application in the treatment of hepatitis C infection.³ 1-(1-Adamantyl)ethanamine (rimantadine)⁴ is widely used as an antiviral agent, and memantine⁵ serves as an *N*-methyl-D-aspartate (NMDA) antagonist; other drugs have more complex structures, and often include aromatic moieties, as in chlodantane⁶ (immunostimulant) and ladasten⁷ (neurostimulating agent). From this perspective, we decided to elaborate a convenient procedure to obtain a new family of N-arylated adamantane-containing amines for their further screening as potentially bioactive molecules. In this communication we report the synthesis of a series of adamantane-containing 2-aminopyridines by palladium-catalyzed amination of 2-bromopyridine with appropriate amines.

Amines **1a–f** were employed in the reaction with 2-bromopyridine (**2**) (Scheme 1). At first we used the catalytic system Pd(dba)₂/BINAP (2–4 mol%) [dba = dibenzylideneacetone; BINAP = 2,2'-bis(diphenylphosphanyl)-1,1'-binaphthyl], proposed by Buchwald for the amination of 2- and 3-bromopyridines.⁸ The reactions were run in boiling 1,4-dioxane (0.1–0.2 M), sodium *tert*-butoxide was used as a base, and the composition of the reaction mixtures was analyzed by ¹H NMR spectroscopy. Target

compounds **3a–f** as well as byproducts were isolated by column chromatography on silica gel. The reaction conditions, yields, and other experimental data are summarized in Table 1.

The result of the reaction (Scheme 1) proved to be strongly dependent on the nature of the starting amines **1a–f** and mainly on the number of covalent bonds between the amino group and the adamantane fragment. Thus, 1-aminoadamantane (**1a**) showed low activity in the amination process, and was converted into its pyridyl derivative **3a** in only 20% yield (Table 1, entries 1 and 2).⁹ Simultaneously, a notable amount of 2,2'-bipyridyl (**5**) formed. This may be due to the bulkiness of the 1-adamantyl substituent at the nitrogen atom in **1a**.



Scheme 1 The arylation of amines **1a–f** with 2-bromopyridine (**2**)

The amination was more successful with amines **1b–d** where the amino and adamantyl groups are separated by two bonds (Table 1, entries 6, 9–11). Bipyridyl **5** formed in smaller amounts, whereas the formation of N,N-diarylated byproducts **4** depended strongly on the nature of the amine: (aminomethyl)adamantane (**1b**) provided substantial amounts of byproduct **4b** (Table 1, entry 6), whereas more sterically hindered **1c** gave the corresponding **4c** in

Table 1 Synthesis of Adamantylpyridin-2-amines **3a–f**^a

Entry	Amine	Ratio 1/2	Ligand ^b	Amounts Pd(dba) ₂ /L (mol%)	Concn (M)	Reaction time (h)	Ratio 3/4/5	Conversion of amine (%)	Product 3	Yield ^c (%)
1	1a	1:1	BINAP	4/4.5	0.1	4	1:0:0.33	20	3a	12
2	1a	1:1	BINAP	4/4.5	0.2	4.5	1:0:0.35	20	3a	12
3	1a	1:1	L1	4/4.5	0.1	5	1:0:0	80		
4	1a	1:1	L2	4/4.5	0.1	5	1:0:0.06	35		
5	1a	1:1	L3	4/4.5	0.1	5	1:0:0.33	25		
6	1b	1:1	BINAP	4/4.5	0.1	6	1:0.65:0.01	70	3b	41
7	1b	1:1	L1	4/4.5	0.1	5	1:0:0.01	95	3b	92
8	1b	1:1	BINAP	4/4.5	0.1	5	1:0:0	10 ^d		
9	1c	1:1.25	BINAP	4/4.5	0.1	6	1:0.08:0.07	45	3c	41
10	1d	1:1.5	BINAP	4/4.5	0.1	5	1:0:0.06	70	3d	37
11	1d	1:1.5	BINAP	4/4.5	0.16	4	1:0:0.08	75	3d	64
12	1e	1:1	BINAP	4/4.5	0.1	4	1:0.75:0.03	62		
13	1e	1:1	BINAP	2/2.5	0.1	4	1:0.6:0.05	50		
14	1e	1:1.5	BINAP	2/2.5	0.13	6	1:0.5:0.12	50	3e	19
15	1e	1:1.5	BINAP	4/4.5	0.16	4	1:0.2:0.11	75	3e	48
16	1e	1:1	L1	4/4.5	0.1	4	1:0.02:0.005	95		
17	1f	1:1.25	BINAP	4/4.5	0.1	6	1:1.1:0.4	55	3f	31
18	1f	1:1	L1	2/2.5	0.1	8	1:0.05:0.01	82	3f	60
19	1f	1:1	L2	2/2.5	0.1	8	1:0.04:0.01	84		
20	1f	1:1	L3	2/2.5	0.1	8	1:0.03:0.005	84		
21	1f	1:1	L4	2/2.5	0.1	8	1:0.05:0	70		
22	1f	1:1	L5	2/2.5	0.1	9	1:0.03:0.06	33		
23	1f	1:1	L6	2/2.5	0.1	7	1:0.02:0.06	22		
24	1f	1:1	L7	2/2.5	0.1	9	1:0.02:0.04	17		
25	1f	1:1	L8	2/2.5	0.1	7	1:0.02:0.04	13		

^a The reaction conditions are shown in Scheme 1.^b The ligands are defined in Figure 1.^c Isolated yield of **3**.^d Cs₂CO₃ was used as the base instead of *t*-BuONa.

small quantities (entry 9). Amine **1d** did not give the N,N-diarylated derivative at all (Table 1, entries 10, 11), and BINAP proved to be quite efficient for the synthesis of **3d**. As shown in Table 1, the application of an excess of 2-bromopyridine (1.25–1.5 equiv) as well as a higher concentration (0.16 M instead of 0.1 M) can lead to a higher conversion and better yield of the product.

The use of the BINAP ligand was moderately efficient for amines **1e** and **1f** where the amino group is less hindered

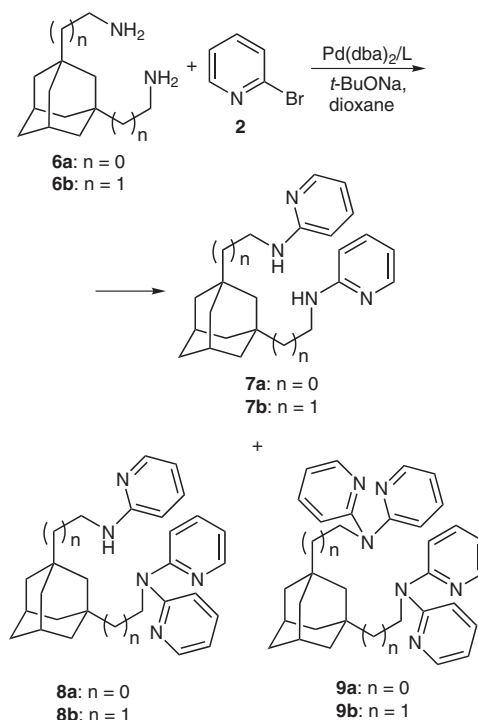
than in **1c** and **1d**. N,N-Diarylated derivatives **4e** and **4f** formed in substantial amounts (Table 1, entries 12–15, 17), like **4b** (entry 6). Higher concentrations of the starting materials partially helped to solve the problem, with the yield of monoarylated species **3e** increasing and the amount of diarylated product **4e** decreasing, even when an excess of bromopyridine was used (Table 1, entry 15). On the other hand, a lower catalyst loading (2 mol% rather than 4 mol%) led in all cases to lower conversions of the

amine and to worse yields (Table 1, entries 13, 14). It should be noted that BINAP normally does not provide diarylation products, unlike 1,1'-bis(diphenylphosphanyl)ferrocene (dppf).¹⁰ Our own experiments on the polyarylation of diamines showed that N,N-diarylation of linear polyamines occurred only when a great excess of the arylating agent and generous amounts of the catalyst were used.¹¹

Taking all these facts into consideration, we tried another ligand, 2-(dicyclohexylphosphanyl)-2'-(dimethylamino)biphenyl (L1) (Figure 1), in the reaction of **1e** with **2**.¹² The result was excellent: 95% conversion of the starting amine was achieved and only traces of diarylated compound **4e** were observed after the reaction ran to completion (Table 1, entry 16). The same ligand, even in smaller amount, allowed the isolation of **3b** in 92% yield (Table 1, entry 7). Using amine **1f**, we compared the efficiency of different donor ligands (Figure 1) in the arylation of adamantane-containing amines. As is clear from Table 1, biphenyl-based phosphane ligands L1–L3 provided high yields of the target derivative **3f** owing to high conversion of the starting amine and insignificant formation of the diarylated byproduct **4f** (Table 1, entries 18–20). Ligand L4 afforded a somewhat poorer result (Table 1, entry 21), whereas ligands L5–L8¹³ based on xanthene and diphenyl ether were inefficient (Table 1, entries 22–25). As for the most sterically hindered amine, 1-aminoadamantane (**1a**), use of ligand L1 led to its highest conversion into the corresponding product **2a**, with no bipyridyl formation (Table 1, entry 3), while ligands L2 and L3 were less active (Table 1, entries 4, 5). We also tried cesium carbonate as a base instead of sodium *tert*-butoxide, but this led to insignificant conversion of the amine (Table 1, entry 8).

We also investigated the reactions of adamantane-based diamines **6a,b** with two equivalents of 2-bromopyridine

(Scheme 2, Table 2). Two equivalents of 2-bromopyridine were used because products **7a,b** of monoarylation of both amino groups were the target compounds. It was found that BINAP was useless for this purpose: in the case of **6a** it provided a 2:1 mixture of tri- and diarylated products **8a** and **7a** (Scheme 2, Table 2, entry 1), whereas with **6b** only tri- and tetraarylated derivatives **8b** and **9b** were detected and isolated (Table 2, entry 3). It is possible that the use of a greater amount of catalyst and a more concentrated solution additionally aggravated the situation. The ligand L1 gave much better results: in the reaction with **6a** no triarylated byproduct **8a** was detected at all, and the isolated yield of the target compound reached 81% (Table 2, entry 2); the reaction with **6b** provided 77% of the desired product **7b** owing to a substantial decrease of N,N-diarylation (Table 2, entry 4). It was possible to reduce the amount of catalyst from 4% to 2%, and this led to a further decrease in **8b** formation (Table 2, entry 5). Ligands L2 and L3 proved to be equally effective in the reaction (Table 1, entries 6–8).



Scheme 2 Arylation of adamantane-based diamines **6a,b**

Some of synthesized adamantane-containing pyridylamines, namely **3b–f**, were tested on mice for their physiological activity, and phenyl-containing amine **3d** was found to act as a depressant.

To summarize, we have investigated the reactions of various adamantane-containing amines with 2-bromopyridine and optimized the conditions to obtain preparatory yields of N-monoarylated derivatives **3** and **7**. The application of biphenyl-based donor phosphane ligands was shown to be advantageous over BINAP in many cases.

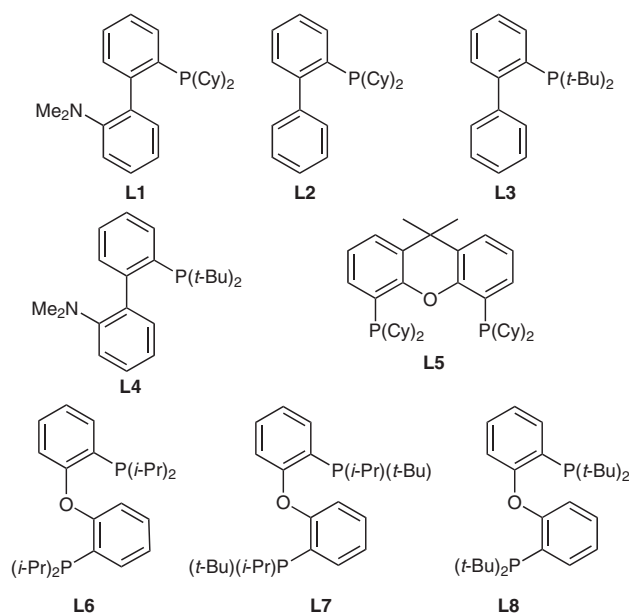


Figure 1 Donor phosphane ligands L1–L8

Table 2 Synthesis of Bis(2-pyridyl)-Substituted Diamines **7a,b**^a

Entry	Amine	Ratio 6/2	Ligand ^b	Amounts Pd(dba) ₂ /L (mol%)	Concn (M)	Time (h)	Ratio pyNH/py ₂ N	Product 7	Yield ^c (%)
1	6a	1:2	BINAP	4/4.5	0.1	6	2:1	7a	32 ^d
2	6a	1:2	L1	4/4.5	0.1	5	1:0	7a	81
3	6b	1:2.5	BINAP	8/9	0.2	5	1:3.2	—	— ^e
4	6b	1:2	L1	4/4.5	0.1	5	1:0.15	7b	77
5	6b	1:2	L1	2/2.5	0.1	5	1:0.11		
6	6b	1:2	L2	4/4.5	0.1	7	1:0.11		
7	6b	1:2	L2	2/2.5	0.1	7	1:0.1		
8	6b	1:2	L3	2/2.5	0.1	7	1:0.2		

^a The reaction conditions are shown in Scheme 2.^b The ligands are defined in Figure 1.^c Isolated yield of **7**.^d Yield of mixture of **7a** and **8a**.^e Isolated yields: 23% (**9b**), 17% (**8b**).

NMR spectra were recorded on a Bruker Avance-400 spectrometer at r.t.; the chemical shifts δ were measured in ppm relative to TMS. MALDI-TOF mass spectra were recorded on a Bruker Daltonics Ultraflex spectrometer with dithranol or trihydroxyacetophenone as matrix. Column chromatography was performed on 40–60-mesh silica gel purchased from Fluka. 2-Bromopyridine (pyBr) was purchased from Acros, 1,4-dioxane was distilled successively over NaOH and Na, and CH₂Cl₂ and MeOH were used freshly distilled. Pd(dba)₂ was obtained by a described method.¹⁴ The starting amines 1-aminoadamantane (**1a**),¹⁵ 1-(aminomethyl)adamantane (**1b**),¹⁶ 1,3-bis(aminomethyl)adamantane (**6a**), and 1,3-bis(2-aminoethyl)adamantane (**6b**)¹⁷ were synthesized according to known procedures.

1-(1-Adamantyl)-1-phenylmethanamine (**1d**)

A three-necked flask equipped with a stirrer, dropping funnel, and condenser was charged with Mg (3.6 g, 0.15 mol) and absolute Et₂O (100 mL). PhBr (15.75 mL, 0.15 mol) dissolved in absolute Et₂O (300 mL) was added in 30 min, followed by the addition of 1-cyanoadamantane (16.1 g, 0.1 mol) dissolved in THF (300 mL). The reaction mixture was stirred for an additional 8 h and was then added to a suspension of LAH (7.8 g, 0.21 mol) in THF (300 mL). The mixture was refluxed for 40 h, cooled to r.t., and then H₂O (11 mL), 12% aq NaOH (30 mL), and again H₂O (30 mL) were added sequentially. The residue was collected by filtration and washed with Et₂O (3 × 150 mL). The organic phases were combined and the solvents were evaporated. The residue was distilled under vacuum.

Yield: 15.7 g (65%); colorless crystals; bp 159–163 °C/4 Torr; mp 67–68 °C.

¹H NMR (400 MHz, CDCl₃): δ = 1.47 (d, J = 11.6 Hz, 3 H), 1.54–1.66 (m, 11 H), 1.95 (s, 3 H), 3.49 (s, 1 H), 7.22–7.30 (m, 5 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 28.41 (3 C), 37.00 (3 C), 38.63 (3 C), 39.00 (1 C), 65.94 (1 C), 126.62 (1 C), 127.35 (2 C), 128.37 (2 C), 142.69 (1 C).

Anal. Calcd for C₁₇H₂₃N: C, 84.59; H, 9.60; N, 5.80. Found: C, 84.32; H, 9.94; N, 5.48.

1-(1-Adamantyl)butan-2-amine (**1e**)

The procedure is analogous to the synthesis of **1d** described above, but EtI (11.3 g, 0.14 mol) was used instead of PhBr, 1-(cyanomethyl)adamantane (17.5 g, 0.1 mol) was used instead of 1-cyanoadamantane, and the amount of LAH was decreased (5.63 g, 0.15 mol). The reaction time was reduced to 3 h (first stage) and 20 h (second stage).

Yield: 16.6 g (80%); colorless liquid; bp 98–102 °C/4 Torr.

¹H NMR (400 MHz, CDCl₃): δ (**1e**·HCl) = 1.04 (t, J = 7.4 Hz, 3 H), 1.43 (dd, J = 14.9, 5.1 Hz, 1 H), 1.48–1.56 (m, 7 H), 1.59–1.70 (m, 6 H), 1.71–1.82 (m, 2 H), 1.95 (s, 3 H), 3.22 (q, J = 5.5 Hz, 1 H), 8.24 (br s, 3 H).

¹³C NMR (100.6 MHz, CDCl₃): δ (**1e**·HCl) = 9.97 (1 C), 28.30 (1 C), 28.38 (3 C), 32.11 (1 C), 36.69 (3 C), 42.36 (3 C), 46.92 (1 C), 49.33 (1 C).

Anal. Calcd for C₁₄H₂₆ClN: C, 68.97; H, 10.75; N, 5.74. Found: C, 68.59; H, 10.61; N, 5.37.

1-(1-Adamantyl)propan-1-amine (**1c**)

The procedure is analogous to the synthesis of **1e** described above, but 1-cyanoadamantane (16.1 g, 0.1 mol) was used instead of 1-(cyanomethyl)adamantane. The reaction time was 3 h (first stage) and 25 h (second stage).

Yield: 13.5 g (70%); colorless liquid; bp 98–102 °C/4 Torr.

¹H NMR (400 MHz, CDCl₃): δ = 0.88–0.90 (m, 3 H), 0.99 (br s, 2 H), 1.45 (s, 6 H), 1.54–1.65 (m, 8 H), 1.90 (s, 3 H), 1.96 (d, J = 8.9 Hz, 1 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 12.23 (1 C), 23.00 (1 C), 28.42 (3 C), 36.00 (1 C), 37.21 (3 C), 38.27 (3 C), 62.50 (1 C).

Anal. Calcd for C₁₃H₂₃N: C, 80.76; H, 11.99; N, 7.25. Found: C, 80.50; H, 12.27; N, 6.94.

1-(1-Adamantyl)propan-2-amine (**1f**)

A two-necked flask equipped with a condenser and thermometer was charged with 1-adamantylpropan-2-one (38.4 g, 0.2 mol), 99.7% formic acid (45 g, 1 mol), and formamide (135 g, 3 mol). The reaction mixture was refluxed at 165–175 °C for 20 h, cooled down

to r.t., poured into H₂O (200 mL), and extracted with benzene (3 × 150 mL). The organic layers were combined and evaporated. The residue was worked up with H₂O (100 mL) and concd HCl (100 mL) to fully dissolve the residue. Then it was neutralized with 40% aq NaOH and extracted with benzene (3 × 150 mL). After the solvent had been evaporated, the residue was distilled under vacuum.

Yield: 32.8 g (85%); colorless liquid; bp 135–138 °C/20 Torr.

¹H NMR (400 MHz, CDCl₃): δ = 0.89 (d, *J* = 6.3 Hz, 3 H), 0.96 (dd, *J* = 14.0, 6.3 Hz, 1 H), 1.02 (dd, *J* = 14.0, 4.0 Hz, 1 H), 1.23 (br s, 2 H), 1.37 (s, 6 H), 1.45–1.55 (m, 6 H), 1.78 (s, 3 H), 2.88–2.96 (m, 1 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 26.55 (1 C), 28.34 (3 C), 32.17 (1 C), 36.74 (3 C), 42.01 (1 C), 42.72 (3 C), 54.98 (1 C).

Anal. Calcd for C₁₃H₂₃N: C, 80.76; H, 11.99; N, 7.25. Found: C, 80.58; H, 11.67; N, 6.98.

Amines 3a–f; General Procedure

A flask flushed with anhyd argon and equipped with a magnetic stirrer and condenser was charged with pyBr (**2**; 0.5 mmol), Pd(dba)₂ (2–4 mol%), the phosphane ligand (2.5–4.5 mol%), the appropriate amine **1a–f** (0.5 mmol), and absolute 1,4-dioxane (5 mL). *t*-BuONa (0.55 mmol) was added, and the mixture was stirred under reflux for 4–9 h, and then cooled down to r.t.; the 1,4-dioxane was evaporated under vacuum, and the residue was chromatographed (silica gel, CH₂Cl₂, then CH₂Cl₂–MeOH, 500:1 to 3:1).

N-(1-Adamantylmethyl)pyridin-2-amine (**3b**)

Compound **3b** was obtained from **1b** (330 mg, 2 mmol) and **2** (316 mg, 2 mmol) in the presence of Pd(dba)₂ (23 mg, 2 mol%) and ligand L1 (20 mg, 2.5 mol%).

Yield: 444 mg (92%); pale yellow oil; chromatography (silica gel, CH₂Cl₂–MeOH, 500:1 to 200:1).

¹H NMR (400 MHz, CDCl₃): δ = 1.56 (s, 6 H), 1.62–1.72 (m, 6 H), 1.98 (s, 3 H), 2.94 (d, *J* = 6.1 Hz, 2 H), 4.55 (br s, 1 H), 6.37 (d, *J* = 8.3 Hz, 1 H), 6.48–6.53 (m, 1 H), 7.33–7.40 (m, 1 H), 8.03 (d, *J* = 4.1 Hz, 1 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 28.29 (3 C), 33.89 (1 C), 37.00 (3 C), 40.48 (3 C), 54.15 (1 C), 106.18 (1 C), 112.29 (1 C), 137.30 (1 C), 148.06 (1 C), 159.48 (1 C).

MS (MALDI-TOF): *m/z* [M⁺] calcd for C₁₆H₂₂N₂: 242.18; found: 242.20.

N-(1-Adamantylmethyl)-*N*-(2-pyridyl)pyridin-2-amine (**4b**)

Compound **4b** was obtained as a byproduct in the synthesis of **3b** from **1b** (83 mg, 0.5 mmol) and **2** (79 mg, 0.5 mmol) in the presence of Pd(dba)₂ (12 mg, 4 mol%) and BINAP (14 mg, 4.5 mol%).

Yield: 38 mg (24%); yellow oil; chromatography (silica gel, CH₂Cl₂–MeOH, 200:1).

¹H NMR (400 MHz, CDCl₃): δ = 1.48 (s, 6 H), 1.56–1.74 (m, 6 H), 1.84 (s, 3 H), 4.03 (s, 2 H), 6.77–6.81 (m, 2 H), 7.03 (d, *J* = 8.3 Hz, 2 H), 7.42–7.47 (m, 2 H), 8.27 (d, *J* = 3.8 Hz, 2 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 28.38 (3 C), 36.26 (1 C), 36.86 (3 C), 41.10 (3 C), 58.75 (1 C), 115.25 (2 C), 116.74 (2 C), 136.77 (2 C), 147.87 (2 C), 158.86 (2 C).

MS (MALDI-TOF): *m/z* [M⁺] calcd for C₂₁H₂₅N₃: 319.20; found: 319.25.

N-[1-(1-Adamantyl)propyl]pyridin-2-amine (**3c**)

Compound **3c** was obtained from **1c** (386 mg, 2 mmol) and **2** (395 mg, 2.5 mmol) in the presence of Pd(dba)₂ (46 mg, 4 mol%) and BINAP (55 mg, 4.5 mol%).

Yield: 221 mg (41%); pale yellow oil; chromatography (silica gel, CH₂Cl₂–MeOH, 500:1 to 250:1).

¹H NMR (400 MHz, CDCl₃): δ = 0.88 (t, *J* = 7.4 Hz, 3 H), 1.10–1.22 (m, 1 H), 1.50–1.72 (m, 12 H), 1.73–1.82 (m, 1 H), 1.95 (s, 3 H), 3.17 (t, *J* = 10.2 Hz, 1 H), 4.26 (d, *J* = 9.3 Hz, 1 H), 6.37 (d, *J* = 8.6 Hz, 1 H), 6.42–6.47 (m, 1 H), 7.31–7.36 (m, 1 H), 8.00 (d, *J* = 5.0 Hz, 1 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 11.58 (1 C), 22.33 (1 C), 28.28 (3 C), 36.97 (3 C), 37.30 (1 C), 38.68 (3 C), 62.15 (1 C), 105.83 (1 C), 111.47 (1 C), 137.05 (1 C), 147.77 (1 C), 160.24 (1 C).

MS (MALDI-TOF): *m/z* [M⁺] calcd for C₁₈H₂₆N₂: 270.21; found: 270.17.

N-[1-(1-Adamantyl)(phenyl)methyl]pyridin-2-amine (**3d**)

Compound **3d** was obtained from **1d** (964 mg, 4 mmol) and **2** (948 mg, 6 mmol) in the presence of Pd(dba)₂ (92 mg, 4 mol%) and BINAP (110 mg, 4.5 mol%).

Yield: 810 mg (64%); pale yellow oil; chromatography (silica gel, CH₂Cl₂).

¹H NMR (400 MHz, CDCl₃): δ = 1.45–1.60 (m, 6 H), 1.63–1.75 (m, 6 H), 1.97 (s, 3 H), 4.05 (d, *J* = 7.6 Hz, 1 H), 5.35 (d, *J* = 7.6 Hz, 1 H), 6.11 (d, *J* = 8.3 Hz, 1 H), 6.44–6.48 (m, 1 H), 7.19–7.29 (m, 6 H), 8.00–8.02 (m, 1 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 28.30 (3 C), 36.38 (1 C), 36.78 (3 C), 39.02 (3 C), 66.39 (1 C), 105.91 (1 C), 112.66 (1 C), 126.83 (1 C), 127.55 (2 C), 128.54 (2 C), 137.41 (1 C), 139.59 (1 C), 148.05 (1 C), 158.49 (1 C).

MS (MALDI-TOF): *m/z* [M⁺] calcd for C₂₂H₂₆N₂: 318.21; found: 318.22.

N-[1-(1-Adamantylmethyl)propyl]pyridin-2-amine (**3e**)

Compound **3e** was obtained from **1e** (828 mg, 4 mmol) and **2** (948 mg, 6 mmol) in the presence of Pd(dba)₂ (92 mg, 4 mol%) and BINAP (110 mg, 4.5 mol%).

Yield: 541 mg (48%); pale yellow oil; chromatography (silica gel, CH₂Cl₂–MeOH, 1:0, then 250:1).

¹H NMR (400 MHz, CDCl₃): δ = 0.88 (t, *J* = 7.5 Hz, 3 H), 1.17 (dd, *J* = 14.4, 8.6 Hz, 1 H), 1.32 (dd, *J* = 14.4, 2.6 Hz, 1 H), 1.44–1.58 (m, 8 H), 1.56–1.69 (m, 6 H), 1.90 (s, 3 H), 3.64–3.70 (m, 1 H), 4.24 (d, *J* = 8.3 Hz, 1 H), 6.30 (d, *J* = 8.3 Hz, 1 H), 6.48 (ddd, *J* = 7.1, 5.1, 0.8 Hz, 1 H), 7.37 (ddd, *J* = 8.7, 7.7, 2.0 Hz, 1 H), 8.04 (ddd, *J* = 5.1, 2.1, 0.8 Hz, 1 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 9.73 (1 C), 28.62 (3 C), 29.53 (1 C), 32.38 (1 C), 36.96 (3 C), 42.95 (3 C), 48.00 (1 C), 50.02 (1 C), 106.04 (1 C), 111.91 (1 C), 137.31 (1 C), 148.29 (1 C), 158.03 (1 C).

MS (MALDI-TOF): *m/z* [M + H⁺] calcd for C₁₉H₂₉N₂: 285.23; found: 285.19.

N-[1-(1-Adamantylmethyl)propyl]-*N*-(2-pyridyl)pyridin-2-amine (**4e**)

Compound **4e** was obtained as a byproduct in the synthesis of **3e** (isolated as a mixture with **3e**; molar ratio **4e**/**3e** ca. 1:1); chromatography (silica gel, CH₂Cl₂–MeOH, 100:1).

¹H NMR (400 MHz, CDCl₃): δ = 0.85 (t, *J* = 7.3 Hz, 3 H), 1.32 (dd, *J* = 14.7, 4.3 Hz, 1 H), 1.43–1.67 (m, 13 H), 1.81 (dd, *J* = 14.9, 6.8 Hz, 1 H), 1.85 (s, 3 H), 1.98 (ddd, *J* = 16.6, 9.1, 7.3 Hz, 1 H), 5.08–5.10 (m, 1 H), 6.78 (ddd, *J* = 7.1, 4.8, 0.8 Hz, 2 H), 6.85 (d, *J* = 8.4 Hz, 2 H), 7.41 (ddd, *J* = 9.1, 7.0, 1.0 Hz, 2 H), 8.33 (ddd, *J* = 5.0, 2.0, 0.8 Hz, 2 H).

¹³C NMR (100.6 MHz, CDCl₃): δ = 11.69 (1 C), 28.55 (3 C), 29.33 (1 C), 32.59 (1 C), 36.90 (3 C), 42.43 (3 C), 48.66 (1 C), 54.95 (1 C).

C), 116.54 (2 C), 116.64 (2 C), 136.59 (2 C), 148.16 (2 C), 158.15 (2 C).

MS (MALDI-TOF): m/z [$M + H^+$] calcd for $C_{24}H_{32}N_3$: 362.25; found: 362.23.

N-[2-(1-Adamantyl)-1-methylethyl]pyridin-2-amine (3f)

Compound **3f** was obtained from **1f** (97 mg, 0.5 mmol) and **2** (79 mg, 0.5 mmol) in the presence of $Pd(dba)_2$ (6 mg, 2 mol%) and ligand L1 (5 mg, 2.5 mol%).

Yield: 81 mg (60%); yellowish oil; chromatography (silica gel, CH_2Cl_2 , then CH_2Cl_2 -MeOH, 500:1).

1H NMR (400 MHz, $CDCl_3$): δ = 1.15 (d, J = 6.3 Hz, 3 H), 1.22–1.32 (m, 2 H), 1.53 (s, 6 H), 1.55–1.67 (m, 6 H), 1.90 (s, 3 H), 3.80–3.91 (m, 1 H), 4.30 (d, J = 8.0 Hz, 1 H), 6.31 (d, J = 8.3 Hz, 1 H), 6.46–6.50 (m, 1 H), 7.33–7.39 (m, 1 H), 8.04 (d, J = 5.0 Hz, 1 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.42 (1 C), 28.56 (3 C), 32.45 (1 C), 36.91 (3 C), 42.82 (1 C), 42.88 (3 C), 52.68 (1 C), 106.34 (1 C), 112.02 (1 C), 137.22 (1 C), 148.31 (1 C), 157.75 (1 C).

MS (MALDI-TOF): m/z [$M + H^+$] calcd for $C_{18}H_{27}N_2$: 271.21; found: 271.17.

N-[2-(1-Adamantyl)-1-methylethyl]-*N*-(2-pyridyl)pyridin-2-amine (4f)

Compound **4f** was obtained as a byproduct in the synthesis of **3f** from **1f** (386 mg, 2 mmol) and **2** (395 mg, 2.5 mmol) in the presence of $Pd(dba)_2$ (46 mg, 4 mol%) and BINAP (55 mg, 4.5 mol%).

Yield: 28 mg (4%); yellow oil; chromatography (silica gel, CH_2Cl_2 -MeOH, 200:1).

1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, J = 6.7 Hz, 3 H), 1.44–1.70 (m, 7 H), 1.49 (s, 6 H), 1.80 (dd, J = 14.6, 5.5 Hz, 1 H), 1.87 (s, 3 H), 5.25 (td, J = 12.8, 6.5 Hz, 1 H), 6.79 (d, J = 8.4 Hz, 2 H), 6.81–6.86 (m, 2 H), 7.42–7.48 (m, 2 H), 8.36 (d, J = 4.1 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.19 (1 C), 28.69 (3 C), 32.73 (1 C), 37.07 (3 C), 42.59 (3 C), 48.81 (1 C), 50.68 (1 C), 116.93 (2 C), 116.99 (2 C), 136.93 (2 C), 148.40 (2 C), 157.73 (2 C).

MS (MALDI-TOF): m/z [$M + H^+$] calcd for $C_{23}H_{30}N_3$: 348.24; found: 348.21.

Diamines **7a,b**; General Procedure

A flask flushed with anhyd argon and equipped with a magnetic stirrer and condenser was charged with pyBr (**2**; 1 mmol), $Pd(dba)_2$ (2–4 mol%), the phosphane ligand (2.5–4.5 mol%), the appropriate amine **6a,b** (0.5 mmol), and absolute 1,4-dioxane (5 mL). *t*-BuONa (1.1 mmol) was added, and the mixture was stirred under reflux for 5–7 h, and cooled down to r.t. The 1,4-dioxane was evaporated under vacuum, and the residue was chromatographed (silica gel, CH_2Cl_2 -MeOH, 1:0, then 200:1 to 3:1).

1,3-Bis[(2-pyridylamino)methyl]adamantane (7a)

Compound **7a** was obtained from **6a** (388 mg, 2 mmol) and **2** (632 mg, 4 mmol) in the presence of $Pd(dba)_2$ (46 mg, 4 mol%) and ligand L1 (35 mg, 4.5 mol%).

Yield: 562 mg (81%); yellowish oil, slowly solidifying into colorless crystals; mp 185–187 °C; chromatography (silica gel, CH_2Cl_2 -MeOH, 50:1 to 25:1).

1H NMR (400 MHz, $CDCl_3$): δ = 1.34 (s, 2 H), 1.41–1.55 (m, 8 H), 1.59 (s, 2 H), 2.06 (s, 2 H), 2.98 (d, J = 5.9 Hz, 4 H), 4.61 (t, J = 5.9 Hz, 2 H), 6.35 (d, J = 8.5 Hz, 2 H), 6.46–6.50 (m, 2 H), 7.31–7.37 (m, 2 H), 8.01 (ddd, J = 4.1, 1.8, 0.8 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.28 (2 C), 34.55 (1 C), 36.28 (2 C), 39.84 (4 C), 43.15 (1 C), 53.56 (2 C), 106.29 (2 C), 112.32 (2 C), 137.24 (2 C), 147.94 (2 C), 159.32 (2 C).

MS (MALDI-TOF): m/z [M^+] calcd for $C_{22}H_{28}N_4$: 348.23; found: 348.24.

1-[(Di-2-pyridylamino)methyl]-3-[(2-pyridylamino)methyl]adamantane (8a)

Compound **8a** was obtained as a byproduct in the synthesis of **7a** from **6a** (97 mg, 0.5 mmol) and **2** (158 mg, 1 mmol) in the presence of $Pd(dba)_2$ (12 mg, 4 mol%) and BINAP (14 mg, 4.5 mol%).

Yield: 44 mg (21%); yellow oil; chromatography (silica gel, CH_2Cl_2 -MeOH, 50:1).

1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 2 H), 1.37–1.60 (m, 10 H), 1.94 (s, 2 H), 2.88 (d, J = 5.8 Hz, 2 H), 4.06 (s, 2 H), 4.59 (t, J = 5.8 Hz, 1 H), 6.30 (d, J = 8.4 Hz, 1 H), 6.44–6.49 (m, 1 H), 6.76–6.80 (m, 2 H), 6.99 (d, J = 8.4 Hz, 2 H), 7.30–7.36 (m, 1 H), 7.40–7.46 (m, 2 H), 7.98 (d, J = 5.0 Hz, 1 H), 8.25 (d, J = 4.6 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.45 (2 C), 34.64 (1 C), 36.23 (1 C), 36.94 (1 C), 39.80 (2 C), 40.62 (2 C), 43.98 (1 C), 53.79 (1 C), 58.40 (1 C), 106.30 (1 C), 112.17 (1 C), 115.25 (2 C), 116.94 (2 C), 136.98 (2 C), 137.41 (1 C), 147.69 (1 C), 148.03 (2 C), 158.86 (2 C), 159.27 (1 C).

MS (MALDI-TOF): m/z [M^+] calcd for $C_{27}H_{31}N_5$: 425.26; found: 425.39.

1,3-Bis[(di-2-pyridylamino)methyl]adamantane (9a)

Compound **9a** was obtained as a byproduct in the synthesis of **7a** from **6a** (97 mg, 0.5 mmol) and **2** (158 mg, 1 mmol) in the presence of $Pd(dba)_2$ (12 mg, 4 mol%) and BINAP (14 mg, 4.5 mol%).

Yield: 10 mg (4%); yellow oil; chromatography (silica gel, CH_2Cl_2 -MeOH, 50:1).

1H NMR (400 MHz, $CDCl_3$): δ = 1.30–1.55 (m, 12 H), 1.85 (s, 2 H), 4.00 (s, 4 H), 6.74–6.80 (m, 4 H), 6.98 (d, J = 8.3 Hz, 4 H), 7.40–7.47 (m, 4 H), 8.24 (d, J = 5.2 Hz, 4 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.72 (2 C), 36.17 (2 C), 36.97 (1 C), 40.61 (4 C), 44.65 (1 C), 58.65 (2 C), 115.40 (4 C), 116.82 (4 C), 136.85 (4 C), 147.95 (4 C), 158.89 (4 C).

MS (MALDI-TOF): m/z [M^+] calcd for $C_{32}H_{34}N_6$: 502.28; found: 502.35.

1,3-Bis[2-(2-pyridylamino)ethyl]adamantane (7b)

Compound **7b** was obtained from **6b** (444 mg, 2 mmol) and **2** (632 mg, 4 mmol) in the presence of $Pd(dba)_2$ (46 mg, 4 mol%) and ligand L1 (35 mg, 4.5 mol%).

Yield: 580 mg (77%); yellowish oil; chromatography (silica gel, CH_2Cl_2 -MeOH, 100:1 to 25:1).

1H NMR (400 MHz, $CDCl_3$): δ = 1.33 (s, 2 H), 1.36–1.55 (m, 12 H), 1.59 (s, 2 H), 2.03 (s, 2 H), 3.19–3.26 (m, 4 H), 4.37 (s, 2 H), 6.34 (d, J = 8.3 Hz, 2 H), 6.50–6.54 (m, 2 H), 7.35–7.41 (m, 2 H), 8.05 (d, J = 4.3 Hz, 2 H).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 28.75 (2 C), 32.51 (1 C), 36.27 (2 C), 36.91 (2 C), 41.75 (4 C), 43.42 (2 C), 47.35 (1 C), 106.31 (2 C), 112.37 (2 C), 137.17 (2 C), 148.02 (2 C), 158.80 (2 C).

MS (MALDI-TOF): m/z [M^+] calcd for $C_{24}H_{32}N_4$: 376.26; found: 376.37.

1-[2-(Di-2-pyridylamino)ethyl]-3-[2-(2-pyridylamino)ethyl]adamantane (8b)

Compound **8b** was obtained as a byproduct in the synthesis of **7b** from **6b** (444 mg, 2 mmol) and **2** (790 mg, 5 mmol) in the presence of $Pd(dba)_2$ (92 mg, 8 mol%) and BINAP (110 mg, 9 mol%).

Yield: 158 mg (17%); yellow oil; chromatography (silica gel, CH_2Cl_2 -MeOH, 100:1 to 25:1).

^1H NMR (400 MHz, CDCl_3): δ = 1.31–1.60 (m, 16 H), 2.02 (s, 2 H), 3.19–3.26 (m, 2 H), 4.17–4.24 (m, 2 H), 4.39 (s, 1 H), 6.33 (d, J = 8.3 Hz, 1 H), 6.49–6.54 (m, 1 H), 6.78–6.82 (m, 2 H), 7.05 (d, J = 8.6 Hz, 2 H), 7.35–7.40 (m, 1 H), 7.45–7.50 (m, 2 H), 8.05 (dd, J = 5.1, 1.0 Hz, 1 H), 8.31 (ddd, J = 4.8, 2.0, 0.8 Hz, 2 H).

^{13}C NMR (100.6 MHz, CDCl_3): δ = 28.72 (2 C), 32.40 (1 C), 32.53 (1 C), 36.32 (1 C), 36.84 (1 C), 41.04 (1 C), 41.42 (2 C), 41.78 (2 C), 43.16 (1 C), 43.38 (1 C), 46.99 (1 C), 106.33 (1 C), 112.24 (1 C), 114.36 (2 C), 116.50 (2 C), 136.79 (2 C), 137.08 (1 C), 147.88 (1 C), 148.07 (2 C), 157.06 (2 C), 158.71 (1 C).

MS (MALDI-TOF): m/z [M^+] calcd for $\text{C}_{29}\text{H}_{35}\text{N}_5$: 453.29; found: 453.43.

1,3-Bis[2-(di-2-pyridylamino)ethyl]adamantane (9b)

Compound **9b** was obtained as a byproduct in the synthesis of **7b** from **6b** (444 mg, 2 mmol) and **2** (790 mg, 5 mmol) in the presence of $\text{Pd}(\text{dba})_2$ (92 mg, 8 mol%) and BINAP (110 mg, 9 mol%).

Yield: 241 mg (23%); yellow oil; chromatography (silica gel, CH_2Cl_2 –MeOH, 100:1 to 50:1).

^1H NMR (400 MHz, CDCl_3): δ = 1.38 (s, 2 H), 1.43–1.58 (m, 14 H), 2.00 (s, 2 H), 4.17–4.23 (m, 4 H), 6.75–6.79 (m, 4 H), 7.05 (d, J = 8.3 Hz, 4 H), 7.42–7.47 (m, 4 H), 8.29 (ddd, J = 4.8, 2.0, 0.8 Hz, 4 H).

^{13}C NMR (100.6 MHz, CDCl_3): δ = 28.80 (2 C), 32.53 (2 C), 36.47 (1 C), 41.12 (2 C), 41.54 (4 C), 43.23 (2 C), 46.86 (1 C), 114.37 (4 C), 116.48 (4 C), 136.76 (4 C), 148.07 (4 C), 157.10 (4 C).

MS (MALDI-TOF): m/z [M^+] calcd for $\text{C}_{34}\text{H}_{38}\text{N}_6$: 530.32; found: 530.46.

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