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.

Key words: amines, aminations, homogeneous catalysis, polycycles, pyridines

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 amine 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](image)

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...
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

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ratio 1/2</th>
<th>Ligandb</th>
<th>Amounts Pd(dba)_2/L (mol%)</th>
<th>Conc (M)</th>
<th>Reaction time (h)</th>
<th>Ratio 3/4/5</th>
<th>Conversion of amine (%)</th>
<th>Product 3 Yieldc (%)</th>
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<td>1:1</td>
<td>BINAP</td>
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<td>5</td>
<td>1:0:0.03</td>
<td>20</td>
<td>3a</td>
<td>12</td>
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<td>4/4.5 0.2</td>
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<td>13</td>
<td>3f</td>
<td>60</td>
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</table>

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.
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 large 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 bipyrild 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 tetaarylated 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).

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.
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 purified by sublimation and was recrystallized from Acros, 1,4-dioxane was distilled successively over NaOH and Na, and CH2Cl2 and MeOH were used freshly distilled. Unspecified solvents were evaporated. The residue was collected by filtration and washed with CH2Cl2 or Et2O.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ratio 6/2</th>
<th>Liganda</th>
<th>Amounts Pd(dba)2/L (mol%)</th>
<th>Conc'n (M)</th>
<th>Time (h)</th>
<th>Ratio pyNH/py2N</th>
<th>Product 7</th>
<th>Yield (%)</th>
</tr>
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<tbody>
<tr>
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<td>BINAP</td>
<td>4/4.5</td>
<td>0.1</td>
<td>6</td>
<td>2:1</td>
<td>7a</td>
<td>32d</td>
</tr>
<tr>
<td>2</td>
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<td>1:2</td>
<td>L1</td>
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<td>81</td>
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<td>BINAP</td>
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<td>–</td>
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<td>1:2</td>
<td>L1</td>
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<td>1:0:11</td>
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<td>4/4.5</td>
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<td>7</td>
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<td>6b</td>
<td>1:2</td>
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<td>2/2.5</td>
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<td>–</td>
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<tr>
<td>8</td>
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<td>1:2</td>
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<td>2/2.5</td>
<td>0.1</td>
<td>7</td>
<td>1:2:0</td>
<td>–</td>
<td>1:2:0</td>
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</table>

a The reaction conditions are shown in Scheme 2.

b The ligands are defined in Figure 1.

The yield of mixture of 7a and 8a.

c Isolated yields: 23% (7b), 17% (8b).

d Isolated yield of 7.

e Isolated yield of 7a.

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), 23.80 (1 C), 28.30 (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·HCl: C, 68.97; H, 10.75; N, 5.74. Found: C, 68.50; 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 C15H29N·HCl: 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% 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 conc 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).


**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 (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–MeOH, 500:1 to 200:1).

**N-(1-Adamantyl)methylpyridin-2-amine (3b)**

Compound 3b was obtained by a mixture of 3b (isolated as a mixture with 3c; molar ratio 4e/3c ca. 1:1); chromatography (silica gel, CH₂Cl₂–MeOH, 100:1).

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

Compound 4b was obtained by a mixture of 3b from 1b (83 mg, 0.5 mmol) and 2 (79 mg, 0.5 mmol) in the presence of Pd(dbca)₂ (12 mg, 4 mol%) and BINAP (14 mg, 4 mol%).

**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(dbca)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).

**Synthesis of Adamantylpyridin-2-amines**
C), 116.54 (2 C), 116.64 (2 C), 136.59 (2 C), 148.16 (2 C), 158.15 (2 C).


N-[(1-Adamantyl)-1-methylthyl]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, CH2Cl2–MeOH, 50:1).

1H NMR (400 MHz, CDCl3): 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 = 7.0 Hz, 1 H).

13C NMR (100.6 MHz, CDCl3): 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).


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, CH2Cl2–MeOH, 50:1 to 2:1).

1H NMR (400 MHz, CDCl3): 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 (dd, J = 4.1, 1.8, 0.8 Hz, 2 H).

13C NMR (100.6 MHz, CDCl3): 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).

Yield: 580 mg (77%); yellowish oil; chromatography (silica gel, CH2Cl2–MeOH, 100:1 to 25:1).

1H NMR (400 MHz, CDCl3): 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).

13C NMR (100.6 MHz, CDCl3): 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).


1,3-Bis(2-pyridylamino)methyl]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, CH2Cl2–MeOH, 100:1 to 25:1).

1H NMR (400 MHz, CDCl3): 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).

13C NMR (100.6 MHz, CDCl3): 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).

1H NMR (400 MHz, CDCl3): 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).

13C NMR (100.6 MHz, CDCl3): 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 C29H35N5: 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 Pd(dba)2 (92 mg, 8 mol%) and BINAP (110 mg, 9 mol%).

Yield: 241 mg (23%); yellow oil; chromatography (silica gel, CH2Cl2–MeOH, 100:1 to 50:1).

1H NMR (400 MHz, CDCl3): 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).

13C NMR (100.6 MHz, CDCl3): 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 C34H38N6: 530.32; found: 530.46.

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References

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