

Practical Routes to 2,6-Disubstituted Pyridine Derivatives

Lucie Vandromme,^[a] Hans-Ulrich Reißig,^{*[a]} Susie Gröper,^[b] and Jürgen P. Rabe^[b]

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We report the synthesis of a series of 2,6-disubstituted pyridines in a straightforward manner starting from readily available 2-substituted pyridines. The main sequence involves a selective α -lithiation reaction with halogen functionalization followed by a Grignard reaction catalyzed by Fe(acac)₃. After demonstration of the easy feasibility of this strategy by synthesizing 2,6-disubstituted pyridines **1**, the route was applied to obtain pyridine derivatives bearing electron-donating or electron-withdrawing groups. Thus, a

series of pyridines bearing an aryl moiety in the 6-position and an alkyl chain in the 2-position was obtained. The pyridines were studied for their self-assembly abilities at the interface between an organic solution and the basal plane of graphite. Preliminary STM results for one compound are reported.

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Introduction

The pyridine ring is one of the most common heterocyclic scaffolds in pharmaceuticals, including antibiotics,^[1] as well as in many natural products.^[2] It also finds frequent applications in physical organic chemistry and in supramolecular chemistry to study ion recognition. Two-dimensional supramolecular chemistry is often studied by scanning tunnelling microscopy (STM).^[3] As part of an ongoing project, we were interested in the development of a rapid and highly flexible route to functionalized pyridine derivatives, whose behaviour at the interface between an organic solution and highly oriented pyrolytic graphite (HOPG) should be studied.^[4] Herein, we describe a convenient and straightforward approach to 2,6-disubstituted pyridine derivatives **1** bearing an aryl moiety to facilitate π -stacking interactions with the graphite surface and a suitable alkyl-chain moiety to favour the subsequent autoassembly of the molecules (Figure 1).

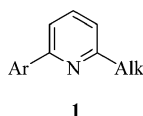
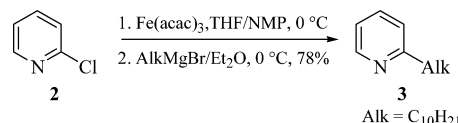


Figure 1. Target compounds **1** required for STM studies.

Results and Discussion

The synthesis of 2,6-disubstituted pyridine derivatives **1** was attempted by using different reported methods, but

which have up to now never been combined. Whereas the preparation of 2,6-diaryl- or 2,6-dialkylpyridines has been described previously,^[5] the syntheses of mixed alkyl/aryl pyridines have been rarely achieved.^[5c,5k,6] 2-Alkylpyridine derivatives **3** are easily accessible from 2-chloropyridine (**2**) by using an iron-catalyzed coupling reaction^[5g,7] with a freshly prepared solution of an alkyl Grignard reagent and Fe(acac)₃ as a catalyst (Scheme 1). The iron-catalyzed coupling proved to be the best choice in this case, as it is an efficient method when an aromatic moiety and an alkyl chain are involved. In an initial set of experiments we found that the presence of *N*-methylpyrrolidone (NMP) as a co-solvent greatly accelerated the reaction:^[8] completion of the coupling after 15 min was observed with NMP, whereas a 2:1 mixture of product and starting material was obtained after 1 h in the absence of NMP.



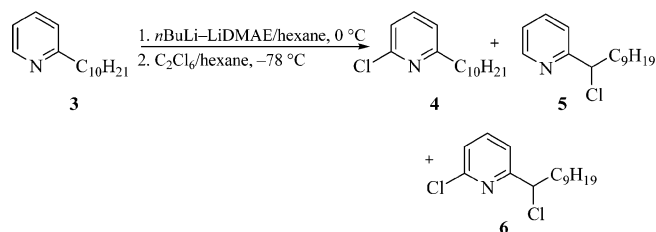
Scheme 1. Fe(acac)₃ catalyzed coupling of 2-chloropyridine (**2**) with an alkyl Grignard reagent to pyridine **3**.

Among the several methods available to halogenate the pyridine core,^[5a,9] the α -lithiation route described by Gros and Fort, which employs the *n*BuLi–Me₂N(CH₂)₂OLi superbase (hereafter described as *n*BuLi–LiDMAE), is very efficient and convenient, as it is highly regioselective. This regioselectivity is attributed to the complexation of the intermediate aggregate with the pyridine nitrogen atom.^[10] Interestingly, 2-alkylpyridine derivatives **3**, when subjected to the lithiation reaction with *n*BuLi–LiDMAE, afforded a

[a] Institut für Chemie und Biochemie, Freie Universität Berlin
Takustrasse 3, 14195 Berlin, Germany
Fax: +49 -30-838-55367
E-mail: hans.reissig@chemie.fu-berlin.de

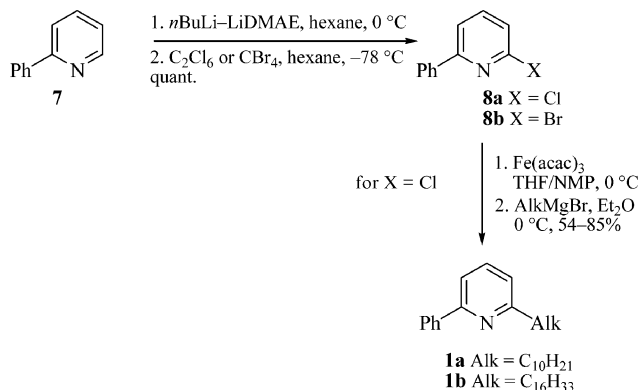
[b] Institut für Physik, Humboldt Universität zu Berlin
Newtonstrasse 15, 12489 Berlin, Germany

complex mixture consisting of the expected 2-halogenated pyridines **4**, along with the product of halogenation in the alkyl chain **5** and dihalogenated pyridine **6** (Scheme 2).



Scheme 2. Initial attempts at chlorination of 2-decylpyridine (**3**).

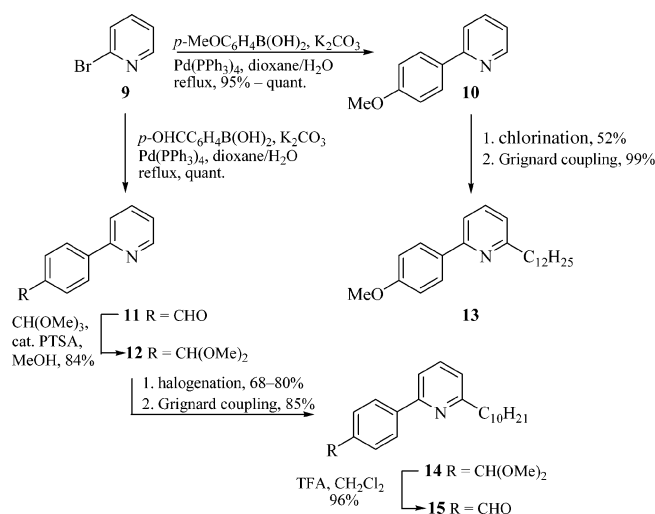
Because of this lack of selectivity in the presence of an alkyl chain, we investigated a new route to 2,6-disubstituted pyridines **1** starting from 2-phenylpyridine (**7**). The lithiation reaction occurred selectively at the 6-position under the conditions described by Gros and Fort to afford halogenated pyridines **8a** and **8b** in excellent yields. The Grignard reactions were attempted with both halogenated pyridines, but only chloropyridine derivative **8a** afforded the expected pyridines **1** in moderate to good yields (Scheme 3). Unexpectedly, the use of bromopyridine **8b** either led to loss of the bromine or to complete recovery of unchanged starting material.



Scheme 3. Halogenation of 2-phenylpyridine (**7**) followed by Fe(acac)₃ catalyzed reactions with alkyl Grignard reagents.

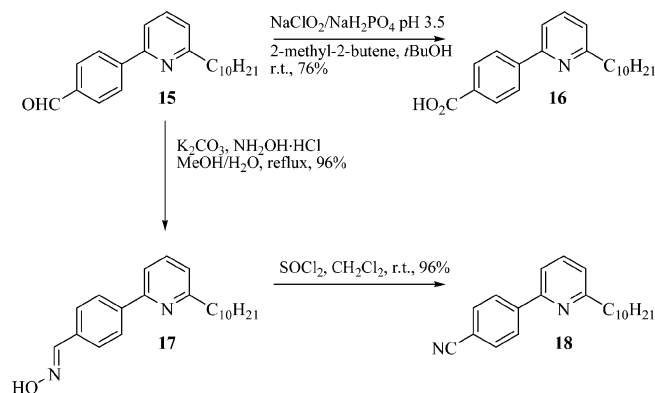
Having demonstrated the feasibility of this new strategy in a straightforward route, we went on to investigate the effect of substituents on the aryl ring that should have an influence on the self-assembly of the resulting pyridine derivatives. We therefore introduced electron-withdrawing groups (CN or COOH) or an electron-donating substituent (OMe) on the aryl ring. Thus, Suzuki coupling^[11] of 2-bromopyridine (**9**) with the corresponding arylboronic acids afforded 2-arylpyridines **10** and **11**. The aldehyde group was selected because of its versatility of transformations; for example, the aldehyde functionality could be easily transformed into either a carboxylic acid or a nitrile group in good yields under mild conditions.^[12] Therefore, aldehyde **11** was first converted into dimethylacetal **12** by using trimethylorthoformate under acidic conditions (catalytic amount of PTSA).^[13] Both pyridines **10** and **12** were halogenated in moderate to good yields, and the subsequent

iron-catalyzed Grignard reaction smoothly proceeded to furnish products **13** and **14** (Scheme 4). Deprotection of acetal **14** with TFA afforded required aldehyde **15**.



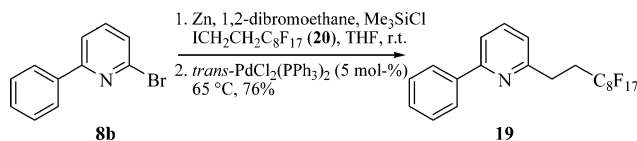
Scheme 4. Syntheses of arylpyridine derivatives **13**–**15**.

Aldehyde **15** was either smoothly oxidized to carboxylic acid **16** with sodium chlorite by using 2-methyl-2-butene as a chlorine scavenger^[14] – a method which tolerates a large range of functionalities – or transformed into oxime **17**, which was subsequently converted into nitrile **18** by treatment with thionyl chloride (Scheme 5).^[12]



Scheme 5. Conversion of aldehyde **15** into arylpyridine derivatives **16**–**18**.

It is well known that fluorinated substituents induce crucial but not always well understood properties.^[15] It was therefore interesting to develop a method that could provide asymmetrically substituted pyridine derivatives bearing a fluorinated side chain, as we were unable to form the required Grignard reagent with our chosen fluorinated iodide **20**. However, we could prepare the mixed aryl/fluoroalkylpyridine **19** by employing a Negishi coupling, as reported by Gladysz and coworkers.^[16] In situ formation of the fluorinated alkylzinc derivative and subsequent reaction with bromopyridine **8b** in the presence of catalytic amounts of *trans*-Cl₂Pd(PPh₃)₂ furnished the desired pyridine derivative **19** in 76% yield (Scheme 6).



Scheme 6. Negishi coupling reaction of bromopyridine **8b** to the fluoroalkyl-substituted arylpyridine derivative **19**.

These straightforward methods allowed the preparation of a series of disubstituted pyridine derivatives. Preliminary STM experiments of 2,6-disubstituted pyridines at the interface between an organic solution and the basal plane of highly oriented pyrolytic graphite (HOPG) demonstrated that carboxylic acid derivative **16** can self-assemble into epitaxial two-dimensional crystals with one hydrogen-bonded dimer per unit cell (Figure 2).

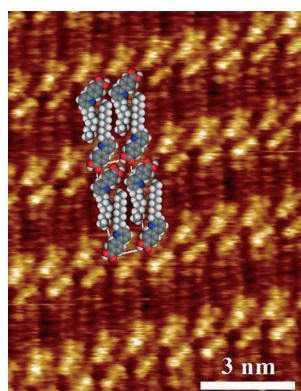


Figure 2. STM current image of pyridine derivative **16** at the interface between an organic solution and the basal plane of HOPG. Bright areas correspond to high current, indicating that the carboxyl groups dimerize and that the lamellae are formed by interdigitating dimers (see implemented molecular model of 4×16).^[3c] Between the lined-up head groups contrast due to the methylene groups and the underlying graphite lattice can be recognized. Unit cell size: $a = 2.65$ nm, $b = 1.01$ nm, $\alpha = 92.4^\circ$, $A = 2.67$ nm².

Conclusions

We have developed a simple and efficient route to pyridine derivatives by employing a combination of reported cross-coupling methodologies, including Suzuki, Grignard and Negishi reactions. The regioselective functionalization of the pyridine core is induced by using the superbases $n\text{BuLi}$ – LiDMAE , as described by Gros and Fort, and this base plays a crucial role in our sequences. By this way, a broad range of unsymmetrically substituted and functionalized pyridine derivatives can be prepared within a few steps in high yields and excellent regioselectivities. Preliminary investigations of the properties of these derivatives on HOPG are encouraging and further studies will be published in due course.

Experimental Section

General Information: Reactions were performed under an atmosphere of argon in flame-dried flasks; solvents and reagents were

added by syringe. Solvents were dried by standard procedures. TLC was performed with precoated silica gel plates (Sil G-60 F₂₅₄) and detected under UV light at 254 nm. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck). Unless stated otherwise, ¹H and ¹³C NMR spectra were determined with Bruker DRX 500 or Jeol Eclipse 500 instruments. Chemical shifts (in δ units, ppm) are referenced to TMS by using CHCl_3 ($\delta = 7.26$ ppm) and CDCl_3 ($\delta = 77.0$ ppm) as the internal standards for ¹H and ¹³C NMR spectra, respectively. IR spectra were measured with a Nicolet 205 FTIR spectrometer. MS and HRMS analyses were performed with Finnigan MAT 711 (EI = 80 eV, 8 kV), MAT 95 (EI = 70 eV) or MAT CH7A (EI = 80 eV, 3 kV) instruments. ESI-TOF MS were measured with an Agilent 6210 ESI-TOF (solvent flow rate was adjusted to 4 $\mu\text{L}/\text{min}$, spray voltage set to 4.000 V; drying gas flow rate was set to 15 psi). Elemental analyses were carried out with a Vario EL instrument. Melting points were measured with a Büchi 510 apparatus and are uncorrected.

Scanning Tunnelling Microscopy: STM imaging was carried out at room temperature at the interface between a freshly cleaved highly oriented pyrolytic graphite (HOPG) substrate and an almost-saturated solution in 1,2,4-trichlorobenzene (Aldrich) by employing a home-made set-up at a scan speed between 10 and 50 lines/s. After visualization of the HOPG lattice, a drop of an almost-saturated solution was applied to the basal plane of HOPG. The STM images were corrected with respect to the hexagonal HOPG lattice underneath by exploiting SPIP software. In this way, the unit cell of the adsorbate crystal could be defined with a high degree of precision.

Typical Procedure for Suzuki Coupling Reaction (Procedure A): $\text{Pd}(\text{PPh}_3)_4$ (5 mol-%) was added to a degassed solution of halogenated pyridine, K_2CO_3 (3 equiv.) and boronic acid (1.5 equiv.) in dioxane/ H_2O (4:1 mL/0.4 mmol). The resulting mixture was heated at reflux until completion as shown by TLC. After cooling to room temperature, water was added, and the mixture was extracted with CH_2Cl_2 . The combined organic layer was dried with MgSO_4 , filtered and concentrated. The crude product was purified by chromatography (silica gel, hexane/EtOAc).

Typical Procedure for Halogenation (Procedure B): A solution of $n\text{BuLi}$ (2.5 M in hexane, 6 equiv.) was added dropwise at 0 °C to a solution of 2-(dimethylamino)ethanol (3 equiv.) in hexane (1 mL/mmole). After 30 min stirring at 0 °C, a solution of the corresponding pyridine derivative in hexane (1 mL/mmole) was added dropwise. The mixture was stirred at 0 °C for 1 h and then cooled to –78 °C before the addition of a solution of the halogen source (3.5 equiv., tetrabromomethane or hexachloroethane) in hexane (1 mL/mmole). The reaction mixture was stirred at –78 °C for 1 h before it was allowed to warm to room temperature overnight. The hydrolysis was then performed at 0 °C by the addition of water. The organic layer was extracted with Et_2O , dried with MgSO_4 and concentrated. The crude oil was purified by chromatography (silica gel, hexane/EtOAc).

Typical Procedure for Grignard Coupling Reaction (Procedure C): The bromoalkane (2.5 equiv.) was added dropwise to a suspension of magnesium turnings (10 equiv.) and iodine (few crystals) in dry diethyl ether (1 mmol/mL). The reaction mixture was heated at reflux for 1 h and then added to a solution of the corresponding chloropyridine derivative and $\text{Fe}(\text{acac})_3$ (10 mol-%) in THF/NMP (10 mL/1 mL/mmole) cooled to 0 °C. The reaction mixture was stirred at 0 °C for 15 min and then quenched with brine. After extraction with CH_2Cl_2 , the combined organic layer was dried with MgSO_4 , filtered and concentrated. The resulting crude product was purified by chromatography (silica gel, hexane/ethyl acetate).

2-Chloro-6-phenylpyridine (8a): According to general procedure B, 2-DMAE (2.0 mL, 19 mmol) in hexane (15 mL), *n*BuLi (2.5 M in hexane, 15.6 mL, 39 mmol), 2-phenylpyridine (**7**) (1.00 g, 6.40 mmol) in hexane (10 mL) and C₂Cl₆ (5.34 g, 22.6 mmol) in hexane (15 mL) provided the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 1:0 to 95:5) to afford **8a** as a slightly yellow oil (1.22 g, quant.). ¹H NMR (500 MHz, CDCl₃): δ = 7.25 (dd, *J* = 0.8, 7.8 Hz, 1 H, 5-H), 7.35 (dd, *J* = 0.8, 7.8 Hz, 1 H, 3-H), 7.40–7.49 (m, 3 H, Ar), 7.69 (t, *J* = 7.8 Hz, 1 H, 4-H), 7.99 (br. d, *J* = 7.3 Hz, 2 H, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 118.8 (d, C-5), 122.6 (d, C-3), 127.1, 128.9, 129.7, 137.8 (3 d, s, Ar), 139.4 (d, C-4), 151.4 (s, C-2), 158.2 (s, C-6) ppm. MS (ESI): *m/z* (%) = 189 (100) [M + H]⁺, 154 (40) [M – Cl]⁺. Spectroscopic data are consistent with data reported in the literature.^[6a]

2-Bromo-6-phenylpyridine (8b): According to general procedure B, 2-DMAE (2.0 mL, 19 mmol) in hexane (15 mL), *n*BuLi (2.5 M in hexane, 15.5 mL, 38.7 mmol), 2-phenylpyridine (**7**) (1.00 g, 6.40 mmol) in hexane (10 mL) and CBr₄ (7.48 g, 22.6 mmol) in hexane (15 mL) afforded the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 1:0 to 95:5) to provide **8b** as a yellow solid (1.51 g, quant.). M.p. 44–46 °C. ¹H NMR (500 MHz, CDCl₃): δ = 7.38 (dd, *J* = 1.3, 7.7 Hz, 1 H, 5-H), 7.39–7.50 (m, 3 H, Ar), 7.65 (t, *J* = 7.7 Hz, 1 H, 4-H), 7.65 (dd, *J* = 1.3, 7.7 Hz, 1 H, 3-H), 7.97 (br. dd, *J* = 1.3, 7.7 Hz, 2 H, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 119.1 (d, C-5), 126.4 (d, C-3), 127.1, 128.9, 129.8, 137.7 (3 d, s, Ar), 139.1 (d, C-4), 142.2 (s, C-2), 158.6 (s, C-6) ppm. MS (ESI): *m/z* (%) = 233 (65) [M]⁺, 235 (64) [M + H]⁺, 154 (100) [M – Br]⁺. Spectroscopic data are consistent with data reported in the literature.^[6a]

2-Decyl-6-phenylpyridine (1a): According to general procedure C, Mg (256 mg, 10.5 mmol), I₂ (few crystals), bromodecane (0.60 mL, 2.64 mmol) in dry Et₂O (3 mL), **8a** (200 mg, 1.05 mmol) and Fe(acac)₃ (37 mg, 0.10 mmol) in dry THF/NMP (10 mL/1 mL) provided the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 95:5) to afford **1a** (265 mg, 85%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ = 0.91 (t, *J* = 7.0 Hz, 3 H, CH₃), 1.28–1.43 (m, 14 H, 7 CH₂), 1.82 (quint., *J* = 7.7 Hz, 2 H, CH₂), 2.87 (t, *J* = 7.7 Hz, 2 H, CH₂), 7.08 (d, *J* = 7.7 Hz, 1 H, 3-H), 7.38–7.43 (br. t, *J* = 7.5 Hz, 1 H, Ar), 7.47 (t, *J* = 7.5 Hz, 2 H, Ar), 7.53 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.64 (t, *J* = 7.7 Hz, 1 H, 4-H), 8.02 (dd, *J* = 1.0, 7.5 Hz, 2 H, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 14.2 (q, CH₃), 22.8, 29.9, 29.8, 29.7, 29.6, 29.5, 29.4, 32.0, 38.7 (9t, CH₂), 117.7 (d, C-5), 121.0 (d, C-3), 127.1 (d, Ar), 128.7 (d*, Ar), 136.8 (d, C-4), 140.0 (s, Ar), 156.9 (s, C-6), 162.5 (s, C-2) ppm. *Higher intensity. IR (film): ν̄ = 3085–2850 (CH), 1590–1445 (C=C) cm⁻¹. MS (ESI-TOF): *m/z* (%) = 296 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₁H₃₀N [M + H]⁺ 296.2378; found 296.2379. C₂₁H₂₉N (295.5): calcd. C 85.37, H 9.89, N 4.74; found C 85.00, H 10.25, N 4.07.

2-Hexadecyl-6-phenylpyridine (1b): According to general procedure C, Mg (640 mg, 26.4 mmol), bromohexadecane (2.0 mL, 6.6 mmol) in dry Et₂O (6 mL), 2-chloropyridine (**8a**) (500 mg, 2.64 mmol) and Fe(acac)₃ (93 mg, 0.26 mmol) in dry THF/NMP (15 mL/1 mL) afforded the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 1:0 to 95:5) to give **1b** as a colourless solid (543 mg, 54%). M.p. 33–34 °C. ¹H NMR (500 MHz, CDCl₃): δ = 0.91 (t, *J* = 6.9 Hz, 3 H, CH₃), 1.25–1.45 (m, 26 H, 13 CH₂), 1.82 (quint., *J* = 7.7 Hz, 2 H, CH₂), 2.87 (t, *J* = 7.7 Hz, 2 H, CH₂), 7.08 (d, *J* = 7.7 Hz, 1 H, 3-H), 7.41 (br. t, *J* = 7.2 Hz, 1 H, Ar), 7.47 (t, *J* = 7.2 Hz, 2 H, Ar), 7.53 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.64 (t, *J* = 7.7 Hz, 1 H, 4-H), 8.03 (br. d, *J* = 7.2 Hz, 2 H, Ar) ppm.

¹³C NMR (126 MHz, CDCl₃): δ = 14.1 (q, CH₃), 22.7 (t, CH₂), 29.4–29.8 (br. signal, CH₂), 31.9, 38.6 (2t, CH₂), 117.6 (d, C-5), 120.9 (d, C-3), 127.0 (d, Ar), 128.6 (d*, Ar), 136.7 (d, C-4), 139.9 (s, Ar), 156.7 (s, C-6), 162.4 (s, C-2) ppm. *Higher intensity. IR (KBr): ν̄ = 3090–2850 (CH), 1595–1445 (C=C) cm⁻¹. MS (ESI-TOF): *m/z* (%) = 379 (35) [M]⁺, 196 (34) [M – C₁₃H₂₇]⁺, 182 (46) [M – C₁₄H₂₉]⁺, 169 (100) [M – C₁₅H₃₁]⁺. C₂₇H₄₁N (379.6): calcd. C 85.42, H 10.89, N 3.69; found C 85.32, H 11.27, N 3.62.

2-Decylpyridine (3): According to general procedure C, Mg (2.14 g, 88.1 mmol), bromodecane (5.0 mL, 22 mmol) in dry Et₂O (20 mL), 2-chloropyridine (**2**) (1.00 g, 8.81 mmol) and Fe(acac)₃ (311 mg, 0.88 mmol) in dry THF/NMP (40 mL/4 mL) afforded the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 95:5) to give pyridine **3** as a colourless oil (1.51 g, 78%). ¹H NMR (500 MHz, CDCl₃): δ = 0.86 (t, *J* = 7.0 Hz, 3 H, CH₃), 1.23–1.35 (m, 14 H, 7 CH₂), 1.70 (quint., *J* = 7.7 Hz, 2 H, CH₂), 2.76 (t, *J* = 7.7 Hz, 2 H, CH₂), 7.06 (m, 1 H, 5-H), 7.11 (d, *J* = 7.7 Hz, 1 H, 3-H), 7.55 (td, *J* = 1.8, 7.7 Hz, 1 H, 4-H), 8.50 (m, 1 H, 6-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 14.2 (q, CH₃), 22.7, 29.4, 29.5, 29.6, 29.6, 29.7, 30.0, 32.0, 38.6 (9t, CH₂), 120.1 (d, C-5), 122.7 (d, C-3), 136.2 (d, C-4), 149.3 (d, C-6), 162.6 (s, C-2) ppm. MS (ESI-TOF): *m/z* (%) = 220 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₁₅H₂₆N [M + H]⁺ 220.2060; found 220.2060. C₁₅H₂₅N (219.4): calcd. C 82.13, H 11.49, N 6.39; found C 81.80, H 11.45, N 6.50.

2-(4-Methoxyphenyl)pyridine (10): According to general procedure A, 2-bromopyridine (**9**) (180 mg, 1.14 mmol), K₂CO₃ (472 mg, 3.42 mmol) and *p*-methoxybenzeneboronic acid (260 mg, 1.71 mmol) in degassed dioxane/H₂O (12 mL/3 mL) and Pd(PPh₃)₄ (66 mg, 0.06 mmol) were heated at reflux for 8 h to afford the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 9:1) to give **10** as a slightly yellow solid (200 mg, 95%). M.p. 52–53 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.83 (s, 3 H, CH₃O), 6.98 (dt, *J* = 2.6, 9.4 Hz, 2 H, Ar), 7.14 (m, 1 H, 5-H), 7.62–7.69 (m, 2 H, 3-H, 4-H), 7.94 (dt, *J* = 2.6, 9.4 Hz, 2 H, Ar), 8.64 (m, 1 H, 6-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 55.4 (q, CH₃O), 114.2 (d, Ar), 119.9 (d, C-3), 121.5 (d, C-5), 128.2, 132.1 (d, s, Ar), 136.8 (d, C-4), 149.6 (d, C-6), 157.2 (s, C-2), 160.5 (s, Ar) ppm. IR (KBr): ν̄ = 3100–2835 (CH), 1610–1405 (C=C, CN) cm⁻¹. MS (ESI-TOF): *m/z* (%) = 186 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₁₂H₁₂NO [M + H]⁺ 186.0919; found 186.0925. C₁₂H₁₁NO (185.2): calcd. C 77.81, H 5.99, N 7.56; found C 77.39, H 5.81, N 7.55. Spectroscopic data are consistent with data reported in the literature.^[17]

4-(Pyridin-2-yl)benzaldehyde (11): According to general procedure A, 2-bromopyridine (**9**) (500 mg, 3.16 mmol), K₂CO₃ (1.31 g, 9.49 mmol) and *p*-formylphenylboronic acid (712 mg, 4.75 mmol) in degassed dioxane/H₂O (40 mL/10 mL) and Pd(PPh₃)₄ (183 mg, 0.16 mmol) were heated at reflux for 8 h to afford the crude product. This was purified by chromatography with silica gel (hexane/EtOAc, 9:1 to 8:2) to give **11** (580 mg, quant.) as a pale-yellow solid. M.p. 50–51 °C. ¹H NMR (500 MHz, CDCl₃): δ = 7.20–7.25 (m, 1 H, 5-H), 7.72 (m, 2 H, 3-H, 4-H), 7.90 (d, *J* = 8.4 Hz, 2 H, Ar), 8.10 (d, *J* = 8.4 Hz, 2 H, Ar), 8.67 (dt, *J* = 1.4, 5.0 Hz, 1 H, 6-H), 10.00 (s, 1 H, CHO) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 121.2 (d, C-3), 123.2 (d, C-5), 127.5, 130.2, 136.4 (2d, s, Ar), 137.0 (d, C-4), 144.9 (s, Ar), 150.0 (d, C-6), 155.8 (s, C-2), 192.0 (d, CHO) ppm. MS (ESI-TOF): *m/z* (%) = 184 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₁₂H₉NO [M + H]⁺ 184.0762; found 184.0768. Spectroscopic data are consistent with data reported in the literature.^[18]

2-(4-Dimethoxymethylphenyl)pyridine (12): A solution of aldehyde **11** (790 mg, 4.31 mmol), trimethyl orthoformate (2.1 mL, 19 mmol)

and *p*-toluenesulfonic acid (40 mg) in MeOH (40 mL) was stirred at 50 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with Et₂O (300 mL) and washed with a solution of NaHCO₃ (1 M, 3×). The combined organic layer was dried with MgSO₄, filtered and concentrated. The crude product was purified by chromatography with silica gel (hexane/EtOAc, 8:2) to afford pyridine **12** (835 mg, 84%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ = 3.32 (s, 6 H, 2 CH₃O), 5.44 (s, 1 H, OCHO), 7.18 (sext., *J* = 5.0 Hz, 1 H, 5-H), 7.54 (br. d, *J* = 8.5 Hz, 2 H, Ar), 7.69 (m, 2 H, 3-H, 4-H), 7.98 (dt, *J* = 1.9, 8.5 Hz, 2 H, Ar), 8.66 (br. d, *J* = 5.0 Hz, 1 H, 6-H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 52.7 (q, CH₃O), 102.8 (d, OCHO), 120.6 (d, C-3), 122.2 (d, C-5), 126.8, 127.2 (2d, Ar), 136.8 (d, C-4), 138.8, 139.6 (2 s, Ar), 149.8 (d, C-6), 157.1 (s, C-2) ppm. MS (ESI-TOF): *m/z* (%) = 252 (5) [M + Na]⁺, 230 (100) [M + H]⁺. MS (ESI-TOF): calcd. for C₁₄H₁₅NO₂ [M + H]⁺ 230.1176; found 230.1172.

2-Dodecyl-6-(4-methoxyphenyl)pyridine (13)

Chlorination: According to general procedure B, 2-DMAE (0.50 mL, 5.40 mmol) in hexane (5 mL), *n*BuLi (2.5 M in hexane, 2.6 mL, 6.5 mmol), pyridine derivative **10** (200 mg, 1.08 mmol) and C₂Cl₆ (895 mg, 3.78 mmol) in hexane (5 mL) afforded the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 95:5) to give the 2-chloropyridine derivative as a colourless solid (123 mg, 52%). M.p. 98–100 °C. ¹H NMR (500 MHz, CDCl₃): δ = 3.85 (s, 3 H, CH₃O), 6.97 (br. d, *J* = 9.0 Hz, 2 H, Ar), 7.17 (dd, *J* = 0.8, 7.8 Hz, 1 H, 5-H), 7.56 (dd, *J* = 0.8, 7.8 Hz, 1 H, 3-H), 7.63 (t, *J* = 7.8 Hz, 1 H, 4-H), 7.95 (br. d, *J* = 9.0 Hz, 2 H, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 55.4 (q, CH₃O), 114.2 (d, Ar), 117.9 (d, C-5), 121.7 (d, C-3), 128.4, 130.4 (d, s, Ar), 139.3 (d, C-4), 151.3 (s, C-2), 157.8 (s, C-6), 161.0 (s, Ar) ppm. MS (ESI-TOF): *m/z* (%) = 220 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₁₂H₁₀ClNO [M + H]⁺ 220.0524; found 220.0523.

Grignard Reaction: According to general procedure C, Mg (111 mg, 4.55 mmol), bromododecane (0.30 mL, 1.14 mmol) in dry Et₂O (1 mL), the 2-chloropyridine derivative (100 mg, 0.46 mmol) and Fe(acac)₃ (16 mg, 0.05 mmol) in dry THF/NMP (10 mL/1 mL) gave the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 95:5) to afford **13** (159 mg, 99%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ = 0.89 (t, *J* = 7.0 Hz, 3 H, CH₃), 1.20–1.43 (m, 18 H, 9 CH₂), 1.80 (quint., *J* = 7.7 Hz, 2 H, CH₂), 2.84 (t, *J* = 7.7 Hz, 2 H, CH₂), 3.85 (s, 3 H, CH₃O), 6.99 (br. d, *J* = 9.0 Hz, 2 H, Ar), 7.02 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.46 (d, *J* = 7.7 Hz, 1 H, 3-H), 7.59 (t, *J* = 7.7 Hz, 1 H, 4-H), 7.97 (dt, *J* = 2.6, 9.0 Hz, 2 H, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 14.2 (q, CH₃), 22.8, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8, 29.8, 29.9, 32.0, 38.7 (11t, CH₂), 55.4 (q, CH₃O), 114.1 (d, Ar), 116.9 (d, C-5), 120.3 (d, C-3), 128.3 (d, Ar), 132.7 (s, Ar), 136.7 (d, C-4), 156.5 (s, C-6), 160.3 (s, Ar), 162.3 (s, C-2) ppm. IR (film): ν̄ = 3065–2850 (CH), 1610–1440 (C=C) cm⁻¹. MS (ESI-TOF): *m/z* (%) = 354 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₄H₃₅NO [M + H]⁺ 354.2797; found 354.2811. C₂₄H₃₅NO (353.5): calcd. C 81.53, H 9.98, N 3.96; found C 81.55, H 9.64, N 3.90.

2-Decyl-6-[(4-dimethoxymethyl)phenyl]pyridine (14)

Halogenation: According to general procedure B, 2-DMAE (0.70 mL, 7.56 mmol) in hexane (5 mL), *n*BuLi (2.5 M in hexane, 4.4 mL, 11 mmol), acetal **12** (500 mg, 2.18 mmol) in hexane (5 mL) and C₂Cl₆ (1.81 g, 7.63 mmol) in hexane (10 mL) provided the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 95:5) to give the 2-chloropyridine derivative as a colourless oil (460 mg, 80%). ¹H NMR (500 MHz, CDCl₃): δ = 3.32 (s, 6 H, 2 CH₃O), 5.43 (s, 1 H, OCHO), 7.22 (dd, *J* = 1.0, 7.6 Hz, 1 H, 5-H), 7.53 (br. d, *J* = 8.4 Hz, 2 H, Ar), 7.61 (dd, *J* =

1.0, 7.6 Hz, 1 H, 3-H), 7.66 (t, *J* = 7.6 Hz, 1 H, 4-H), 7.98 (br. d, *J* = 8.4 Hz, 2 H, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 52.7 (q, CH₃O), 102.7 (d, OCHO), 118.8 (d, C-5), 122.7 (d, C-3), 126.9, 127.3, 137.9 (2 d, s, Ar), 139.4 (d, C-4), 139.6 (s, Ar), 151.4 (s, C-2), 157.8 (s, C-6) ppm. MS (ESI-TOF): *m/z* (%) = 286 (7) [M + Na]⁺, 266 (34), 264 (100) [M + H]⁺, 232 (18) [M – CH₃O]⁺. HRMS (ESI-TOF): calcd. for C₁₄H₁₄ClNO₂ [M + H]⁺ 264.0791; found 264.0798.

Grignard Reaction: According to general procedure C, Mg (276 mg, 11.4 mmol), bromodecane (0.60 mL, 2.84 mmol) in dry Et₂O (3 mL), the 2-chloropyridine derivative (300 mg, 1.14 mmol) and Fe(acac)₃ (40 mg, 0.11 mmol) in dry THF/NMP (10 mL/1 mL) afforded after work up the crude product, which was purified by chromatography with silica gel (hexane/EtOAc, 95:5) to give **14** (357 mg, 85%) as a colourless oil. ¹H NMR (500 MHz, CDCl₃): δ = 0.86 (mc, 3 H, CH₃), 1.20–1.40 (m, 14 H, 7 CH₂), 1.78 (m, 2 H, CH₂), 2.85 (t, *J* = 7.7 Hz, 2 H, CH₂), 3.34 (s, 6 H, 2 CH₃O), 5.46 (s, 1 H, OCHO), 7.07 (d, *J* = 7.3 Hz, 1 H, 5-H), 7.52 (br. d, *J* = 7.4 Hz, 1 H, 3-H), 7.54 (br. d, *J* = 8.3 Hz, 2 H, Ar), 7.63 (t, *J* = 7.7 Hz, 1 H, 4-H), 8.00 (br. d, *J* = 8.4 Hz, 2 H, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 14.2 (q, CH₃), 22.7, 29.4, 29.5, 29.6, 29.7, 29.8, 29.9, 32.0, 38.6 (9 t, CH₂), 52.6 (q, CH₃O), 102.9 (d, OCHO), 117.7 (d, C-5), 121.1 (d, C-3), 126.9, 127.2 (2 d, Ar), 136.8 (d, C-4), 138.5, 140.1 (2 s, Ar), 156.5 (s, C-6), 162.6 (s, C-2) ppm. MS (ESI-TOF): *m/z* (%) = 370 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₄H₃₅NO₂ [M + H]⁺ 370.2746; found 370.2760.

4-(6-Decylpyridin-2-yl)benzaldehyde (15): TFA (10.6 mL, 138 mmol) was added at room temperature to a solution of **14** (850 mg, 2.30 mmol) in CH₂Cl₂ (50 mL). The resulting orange solution was stirred at room temperature for 45 min (TLC control) and neutralized with saturated aqueous NaHCO₃ solution. After washing with saturated NaHCO₃ solution and extraction with CH₂Cl₂, the combined organic layer was dried with MgSO₄, filtered and concentrated to afford **15** (716 mg, 96%) as a colourless solid, which was analytically pure. M.p. 37–39 °C. ¹H NMR (500 MHz, CDCl₃): δ = 0.87 (t, *J* = 7.4 Hz, 3 H, CH₃), 1.25–1.41 (m, 14 H, 7 CH₂), 1.79 (quint., *J* = 7.7 Hz, 2 H, CH₂), 2.86 (t, *J* = 7.7 Hz, 2 H, CH₂), 7.15 (d, *J* = 7.7 Hz, 1 H, 3-H), 7.59 (d, *J* = 7.7 Hz, 1 H, 5-H), 7.69 (t, *J* = 7.7 Hz, 1 H, 4-H), 7.97 (br. d, *J* = 8.4 Hz, 2 H, Ar), 8.18 (br. d, *J* = 8.4 Hz, 2 H, Ar), 10.05 (s, 1 H, CHO) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 14.1 (q, CH₃), 22.7, 29.3, 29.4, 29.5, 29.6, 29.6, 29.7, 31.9, 38.4 (9 t, CH₂), 118.4 (d, C-3), 122.1 (d, C-5), 127.5, 130.1, 136.2 (2 d, s, Ar), 137.1 (d, C-4), 145.3 (s, Ar), 155.1 (s, C-2), 162.9 (s, C-6), 192.0 (d, CHO) ppm. IR (KBr): ν̄ = 3060–2725 (CH), 1700 (C=O), 1610–1570 (C=C) cm⁻¹. MS (ESI-TOF): *m/z* (%) = 324 (100) [M + H]⁺, 197 (11) [M – C₉H₁₉]⁺. HRMS (ESI-TOF): calcd. for C₂₂H₃₀NO [M + H]⁺ 324.2322; found 324.2317. C₂₂H₂₉NO (323.5): calcd. C 81.69, H 9.04, N 4.33; found C 81.48, H 9.21, N 4.35.

4-(6-Decylpyridin-2-yl)benzoic Acid (16): A solution of NaClO₂ (36 mg, 0.40 mmol) in pH 3.5 buffer (3 mL NaH₂PO₄) was added dropwise to a rapidly stirred solution of aldehyde **15** (100 mg, 0.31 mmol) and 2-methyl-2-butene (0.30 mL, 3.10 mmol) in *t*BuOH (15 mL). The solution was stirred at room temperature overnight, basified with NaOH (1 M, to pH 10) and *t*BuOH was removed under vacuum. After addition of water, the solution was extracted with hexane, the aqueous layer was acidified with HCl (2%, to pH 4) and extracted with Et₂O. The combined organic layer was dried with MgSO₄, filtered and concentrated to afford **16** as a colourless solid, which was washed with pentane (80 mg, 76%). M.p. 146–148 °C. ¹H NMR (500 MHz, CDCl₃): δ = 0.88 (t, *J* = 7.0 Hz, 3 H, CH₃), 1.26–1.42 (m, 14 H, 7 CH₂), 1.81 (quint., *J* = 7.7 Hz, 2 H,

CH₂), 2.87 (t, J = 7.7 Hz, 2 H, CH₂), 7.15 (d, J = 7.7 Hz, 1 H, 3-H), 7.60 (d, J = 7.7 Hz, 1 H, 5-H), 7.69 (t, J = 7.7 Hz, 1 H, 4-H), 8.12, 8.20 (2 d, J = 8.4 Hz, 2 H each, Ar) ppm. No signal detected for CO₂H. ¹³C NMR (126 MHz, CDCl₃): δ = 14.1 (q, CH₃), 22.7, 29.3, 29.4, 29.5, 29.6*, 29.7, 31.9, 38.5 (8 t, CH₂), 118.2 (d, C-3), 122.0 (d, C-5), 127.0, 129.1, 130.6 (d, s, d, Ar), 137.0 (d, C-4), 144.8 (s, Ar), 155.4 (s, C-2), 162.8 (s, C-6), 171.0 (s, CO₂H) ppm. *Higher intensity. IR (KBr): $\tilde{\nu}$ = 3065–2845 (CH), 2720–2550 (O–H), 1675 (C=O), 1610–1510 (C=C), 1290 (C–O) cm^{−1}. MS (ESI-TOF): m/z (%) = 340 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₂H₃₀NO₂ [M + H]⁺ 340.2277; found 340.2269. C₂₂H₂₉NO₂ (339.5) + 1/2 H₂O: calcd. C 75.83, H 8.68, N 4.02; found C 75.76, H 8.53, N 4.04.

4-(6-Decylpyridin-2-yl)benzaldehyde Oxime (17): Hydroxylamine hydrochloride (172 mg, 2.47 mmol) was added to a solution of aldehyde **15** (400 mg, 1.24 mmol) and K₂CO₃ (171 mg, 1.24 mmol) in a mixture of MeOH/H₂O (15 mL/1.5 mL). The resulting solution was heated at reflux for 2 h. At room temperature H₂O was added, and the aqueous layer was extracted with Et₂O. The combined organic layer was dried with MgSO₄, filtered and concentrated to give oxime **17** as a colourless solid (402 mg, 96%), which was used without any further purification. M.p. 69–71 °C. ¹H NMR (500 MHz, CDCl₃): δ = 0.87 (t, J = 7.0 Hz, 3 H, CH₃), 1.25–1.42 (m, 14 H, 7 CH₂), 1.79 (quint., J = 7.7 Hz, 2 H, CH₂), 2.86 (t, J = 7.7 Hz, 2 H, CH₂), 7.11 (d, J = 7.7 Hz, 1 H, 3-H), 7.54 (d, J = 7.7 Hz, 1 H, 5-H), 7.64–7.68 (m, 3 H, 4-H, Ar), 8.02 (br. d, J = 8.4 Hz, 2 H, Ar), 8.19 (s, 1 H, CHN), 8.20 (br. s, 1 H, OH) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 14.1 (q, CH₃), 22.7, 29.3, 29.4, 29.5, 29.6, 29.6, 29.8, 31.9, 38.5 (9 t, CH₂), 117.8 (d, C-3), 121.4 (d, C-5), 127.3, 127.4, 132.3 (2 d, s, Ar), 136.9 (d, C-4), 141.2 (s, Ar), 150.0 (d, CHN), 155.9 (s, C-2), 162.7 (s, C-6) ppm. MS (ESI-TOF): m/z (%) = 339 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₂H₃₀N₂O [M + H]⁺ 339.2436; found 339.2433.

4-(6-Decylpyridin-2-yl)benzonitrile (18): To a solution of oxime **17** (380 mg, 1.12 mmol) in CH₂Cl₂ (15 mL) was added SOCl₂ (1.00 mL, 11.3 mmol). The mixture was stirred at room temperature overnight. After evaporation of the solvent, the residue was dissolved in EtOAc and washed with saturated aqueous NaHCO₃ solution. The combined organic layer was dried with MgSO₄, filtered and concentrated. The crude oil was then purified by chromatography with silica gel (hexane/EtOAc, 95:5) to give **18** (345 mg, 96%) as a colourless solid. M.p. 39–40 °C. ¹H NMR (500 MHz, CDCl₃): δ = 0.88 (t, J = 7.0 Hz, 3 H, CH₃), 1.20–1.40 (m, 14 H, 7 CH₂), 1.79 (quint., J = 7.7 Hz, 2 H, CH₂), 2.85 (t, J = 7.7 Hz, 2 H, CH₂), 7.16 (d, J = 7.7 Hz, 1 H, 3-H), 7.56 (d, J = 7.7 Hz, 1 H, 5-H), 7.69 (t, J = 7.7 Hz, 1 H, 4-H), 7.74, 8.13 (2 dt, J = 1.8, 8.6 Hz, 2 H each, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 14.1 (q, CH₃), 22.7, 29.3, 29.4, 29.5, 29.5, 29.6, 29.7, 31.9, 38.5 (9 t, CH₂), 112.1 (s, Ar), 118.0 (s, CN), 118.9 (d, C-3), 122.3 (d, C-5), 127.5, 132.4 (2 d, Ar), 137.1 (d, C-4), 143.9 (s, Ar), 154.4 (s, C-2), 163.0 (s, C-6) ppm. IR (KBr): $\tilde{\nu}$ = 3080–2850 (CH), 2230 (C≡N), 1610–1570 (C=C) cm^{−1}. MS (ESI-TOF): m/z (%) = 321 (100) [M + H]⁺. HRMS (ESI-TOF): calcd. for C₂₂H₂₉N₂ [M + H]⁺ 321.2325; found 321.2327. C₂₂H₂₈N₂ (320.5): calcd. C 82.45, H 8.81, N 8.74; found C 82.17, H 8.64, N 8.61.

2-(3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10-Heptafluorodecyl)-6-phenylpyridine (19): To a suspension of Zn powder (200 mg, 3.50 mmol) in dry THF (1 mL) was added 1,2-dibromoethane (0.02 mL, 0.18 mmol). The mixture was heated at reflux to initiate the reaction and cooled to room temperature. Then, Me₃SiCl (0.01 mL, 0.07 mmol) was added. After 10 min, a solution of ICH₂CH₂C₈F₁₇ **20** (500 mg, 0.88 mmol) in THF (1 mL) was added dropwise. The

mixture was stirred for 15 min and then added to a mixture of bromopyridine derivative **8b** (82 mg, 0.35 mmol) and *trans*-PdCl₂(PPh₃)₂ (12 mg, 0.02 mmol). The resulting mixture was stirred at 65 °C for 5 h and after cooling to room temperature Et₂O was added. After washing with saturated aqueous NH₄Cl solution, the organic layer was dried with MgSO₄, filtered and concentrated. The crude oil was purified by chromatography with silica gel (hexane/EtOAc: 98:2) to give **19** (160 mg, 76%) as a yellow solid. M.p. 54–55 °C. ¹H NMR (500 MHz, CDCl₃): δ = 2.73 (m_c, 2 H, CH₂), 3.15 (m_c, 2 H, CH₂), 7.12 (d, J = 7.6 Hz, 1 H, 3-H), 7.42 (tt, J = 1.6, 7.3 Hz, 1 H, Ar), 7.48 (br. t, J = 7.3 Hz, 2 H, Ar), 7.60 (d, J = 7.7 Hz, 1 H, 5-H), 7.68 (t, J = 7.7 Hz, 1 H, 4-H), 8.02 (dt, J = 1.6, 7.3 Hz, 2 H, Ar) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 28.7 (t, CH₂), 30.3 (t, $J_{C,F}$ = 22 Hz, CH₂), 118.4 (d, C-5), 121.3 (d, C-3), 126.9, 128.8, 129.1 (3 d, Ar), 137.3 (d, C-4), 139.3 (s, Ar), 157.0 (s, C-6), 158.4 (s, C-2) ppm. IR (KBr): $\tilde{\nu}$ = 3095–2870 (CH), 1595–1575 (C=C), 1315–1090 (C–F) cm^{−1}. MS (EI): m/z (%) = 601 (100) [M]⁺, 231 (62) [M – C₇F₁₅]⁺, 181 (27) [M – C₈F₁₇]⁺. HRMS: calcd. for C₂₁H₁₂F₁₇N [M]⁺ 601.06928; found: 601.06929. C₂₁H₁₂F₁₇N (601.3): calcd. C 41.95, H 2.01, N 2.33, F 53.71; found C 42.37, H 2.13, N 2.36, F 53.0.

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