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Palladium-catalyzed C–H alkylation of 2-phenylpyridines with alkyl iodides†

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Palladium-catalyzed C–H alkylation reaction of 2-phenylpyridines with alkyl iodides has been successfully developed. The palladacycles obtained from 2-phenylpyridines should act as the key intermediates in the alkylation reaction.

Introduction

Transition metal-catalyzed cross-coupling with unactivated alkyl (pseudo)halides remains one of the greatest challenges.[1] However, alkyl (pseudo)halides exhibit high reactivity in some reactions. For instance, in the Catellani reaction, the key palladacycles formed from aryl iodides and norbornene can react with alkyl halides efficiently (Fig. 1a).[2] Recently, our group found that dibenzometallacyclopentadienes exhibited novel reactivity that was distinct from that of other common arylmetal complexes. The palladacycle could selectively react with alkyl halides (Fig. 1b).[3] Inspired by these reactions, we envisioned that palladacycles might be desirable models for the development of Pd-catalyzed alkylation with alkyl halides.

One of the major methods for the formation of palladacylces is the palladation of C–H bonds.[4] In the past few decades, C–H functionalization has experienced noticeable progress. The majority of transition metal-catalyzed C–H functionalization reactions rely on the use of directing groups.[5] The directing groups usually contain heteroatoms such as N and O, so that they can coordinate with transition metals and assist the metalation of C–H bonds. Therefore, the directed C–H metalation often forms metallacycles comprising one chelating heteroatom.[6] In the Catellani reaction and the reactions reported by our group, both palladacycles consist of two metal–carbon bonds. Since metallacycles comprising one chelating heteroatom are ubiquitous, we were curious about the reactivity of the palladacycles of this type towards alkyl halides. Actually, it has been reported that a few palladacycles comprising chelating heteroatoms could react with alkyl halides. A typical example is carboxylate-directed C–H alkylation reported by the Yu group (Fig. 1c).[7] Such a reaction could also be enabled by using a highly acidic amide directing group.[8] Noticeably, pyrroles could act as the directing group in the Pd-catalyzed alkylation of C(sp^2)–H bonds (Fig. 1d).[9] In all

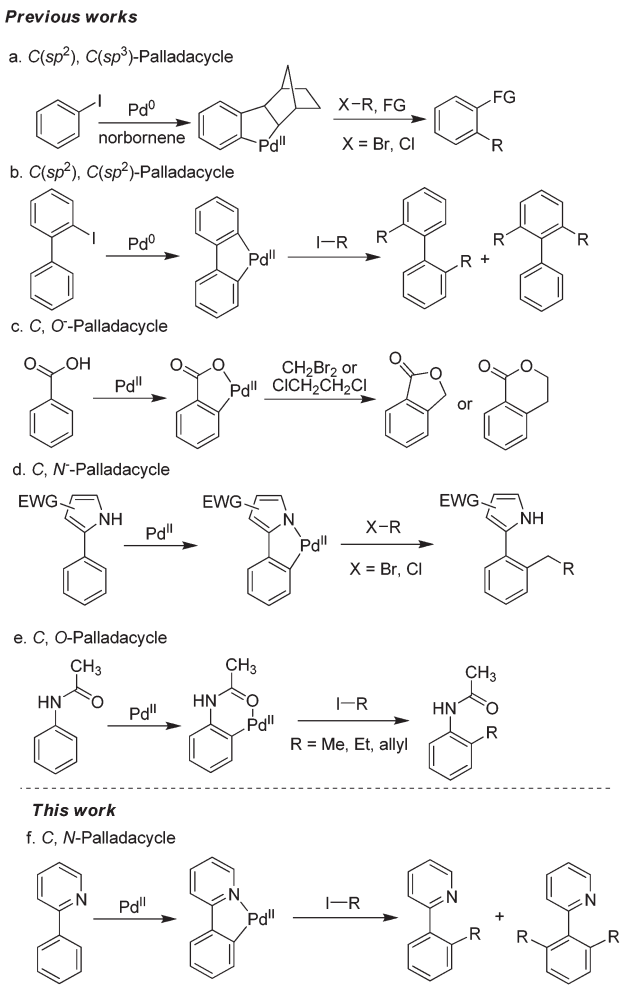

Fig. 1 Alkylation of palladacycles with alkyl halides.

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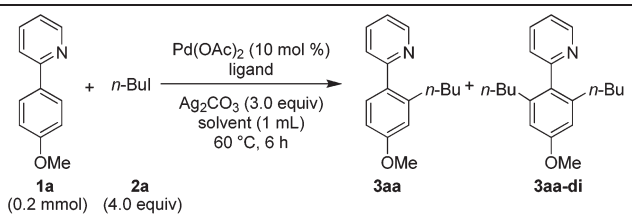
these reactions, an anion, O^- or N^-, bonded with the palladium and formed a *C*,O^-/N^- palladacycle. In addition, it should be mentioned that bidentate directing groups proved to be very effective in Pd-catalyzed C–H alkylation reactions with alkyl halides.[10] In these reactions, tridentate-palladacycles were formed. In summary, in all the above-mentioned reactions, the palladacycles were formed through the chelation of two anions. Reports on the alkylation of palladacycles comprising a carbanion and a neutral chelating heteroatom are very rare. One of the few examples is the alkylation of acetanilides with alkyl iodides (Fig. 1e).[11] In this reaction, a six-membered *C*,*O*-palladacycle was formed and it reacted with alkyl iodides. However, a variety of neutral donors can act as the directing group and form palladacycles comprising one neutral chelating heteroatom. In this context, nitrogen is one of the most important donor atoms. Therefore, we set out to study the alkylation of *C*,*N*-palladacycles, comprising a neutral chelating nitrogen atom, with alkyl halide. Pyridine is one of the most common directing groups in the palladium-catalyzed C–H functionalization reaction.[12] The nitrogen atom of pyridine coordinates to palladium and forms a *C*,*N*-palladacycle; so pyridine-chelated palladacycles are the desirable models for studying the alkylation of *C*,*N*-palladacycles with alkyl halides. It should be mentioned that C–H alkylation reactions with alkyl halides catalyzed by other transition metals such as ruthenium, nickel, copper, and cobalt have been reported.[13] Herein, we report the alkylation of a palladacycle derived from 2-phenylpyridines with alkyl idodides (Fig. 1f).

Results and discussion

We commenced our study by investigating the reaction of 2-(4-methoxyphenyl)pyridine **1a** with *n*-butyl iodide **2a** under palladium catalysis in the presence of Ag_2CO_3. As shown in Table 1, whereas the reaction formed a small amount of the alkylated product in a range of common organic solvents (entries 1–4), **3aa** was obtained in 28% yield when the reaction was carried out in CH_3CN (entry 5). *t*-BuOH was also an effective solvent and 25% product was formed (entry 6). The yield increased slightly to 32% when *t*-AmylOH was used (entry 7). It should be noted that a trace or a small amount of dialkylated product **3aa-di** was observed in all the above-mentioned reactions. The yield was further improved to 38% when the reaction was carried out in a mixture of *t*-AmylOH and CH_3CN (entry 8). Amino acids proved to be powerful ligands in some Pd-catalyzed C–H functionalization reactions.[14] Therefore, we investigated the impact of amino acids on this alkylation reaction. Extensive screening of a range of amino acids revealed that they had little effect on the reaction. For example, the yields of the reaction in the presence of Ac-Gly-OH or Boc-Gly-OH remained almost unchanged (entries 9 and 10). Interestingly, when we added 20 mol% $(BnO)_2PO_2H$ instead of amino acids, the reaction produced 52% of **3aa** as well as 11% of a dialkylated product **3aa-di** (entry 11). The yield was further improved to 64% when 80 mol% $(BnO)_2PO_2H$ was used (entry 12). Finally, the yield decreased at a higher or lower temperature (entries 13 and 14), and no desired alkylated products were

Table 1 Condition survey for Pd-catalyzed C–H *n*-butylation of 2-(4-methoxyphenyl)pyridine with *n*-butyl iodide



Entry	Ligand (equiv.)	Solvent	Yield[a] (%) 3aa	3aa-di	1a
1	—	THF	6	Trace	90
2	—	Toluene	3	Trace	92
3	—	DMSO	7	Trace	90
4	—	1,4-Dioxane	6	Trace	91
5	—	CH_3CN	28	4	64
6	—	*t*-BuOH	25	4	68
7	—	*t*-AmylOH	32	5	60
8	—	*t*-AmylOH : CH_3CN 9 : 1	38	6	53
9	Ac-Gly-OH (0.2)	*t*-AmylOH : CH_3CN 9 : 1	40	5	52
10	Boc-Gly-OH (0.2)	*t*-AmylOH : CH_3CN 9 : 1	39	7	49
11	$(BnO)_2PO_2H$ (0.2)	*t*-AmylOH : CH_3CN 9 : 1	52	11	35
12	**$(BnO)_2PO_2H$ (0.8)**	***t*-AmylOH : CH_3CN 9 : 1**	**64(62)[b]**	**11(10)[b]**	**20**
13[c]	$(BnO)_2PO_2H$ (0.8)	*t*-AmylOH : CH_3CN 9 : 1	26	6	64
14[d]	$(BnO)_2PO_2H$ (0.8)	*t*-AmylOH : CH_3CN 9 : 1	20	4	72
15[e]	$(BnO)_2PO_2H$ (0.8)	*t*-AmylOH : CH_3CN 9 : 1	—	—	100
16[f]	$(BnO)_2PO_2H$ (0.8)	*t*-AmylOH : CH_3CN 9 : 1	—	—	100

[a] The yields were determined by ^1H NMR analysis of the crude reaction mixture using $CHCl_2CHCl_2$ as the internal standard. [b] Isolated yield. [c] 80 °C. [d] 50 °C. [e] *n*-Butyl bromide instead of *n*-butyl iodide. [f] *n*-Butyl chloride instead of *n*-butyl iodide.

observed when *n*-butyl bromide or chloride was used as the alkylating reagent (entries 15 and 16).

The substrate scope was next examined. We first investigated the performance of a range of 2-phenylpyridine derivatives under the optimized reaction conditions. As shown in Fig. 2, the unsubstituted 2-phenylpyridine **1b** underwent the alkylation reaction, forming mono- and dialkylated products (**3ba** and **3ba-di**) in 53% and 11% yield, respectively. The substrates bearing a methyl, *t*-butyl, or phenyl group at the *para* positions of the benzene rings exhibited similar reactivities to **1a**, and the corresponding alkylated products were obtained in moderate yields (**3ca**, **3da**, and **3ea**). It is noted that the chloro group was well-tolerated under the reaction conditions (**3fa**). The substrates bearing electron-withdrawing groups such as acetyl and trifluoromethyl groups were also reactive. However, the reactions were low-yielding (**3ga** and **3ha**).

Next, we examined the performance of substrate containing *meta* arene substituents. In the presence of a *meta*-methyl group, the reaction took place selectively at the less-hindered position and produced a single monoalkylated product (**3ia**). However, a dialkylated product was also isolated. On the contrary, for the substrate with a *meta*-methoxy group on the benzene ring, two monoalkylated products were formed, but the product with an *n*-butyl group at the less-crowded site was still the major one (**3ja** and **3ja-iso**). The reactivities of the disubstituted substrates were also examined. 2-(Naphthalen-2-yl) pyridine was reactive, and the reaction yielded two monoalkylated products as well as the disubstituted one (**3ka** and **3ka-iso**). The reactions of the substrate with two methoxy groups at the *para* and *meta* positions formed one mono-substituted product (**3la**). Interestingly, the substrates containing two substituents, methoxy or methyl groups, at the *meta* positions were also suitable, and mono- and dialkylated products were obtained (**3ma** and **3na**). 2-Phenylpyridines bearing an *ortho*-substituent such as methyl and fluoro could also be alkylated, *albeit* in low yields (**3oa** and **3pa**). Likewise, the reaction of 2-(naphthalen-1-yl)pyridine was also low-yielding (**3qa**).

Finally, the reactions using other nitrogen-containing heterarene as the directing groups were also examined. Pyrazole was an effective directing group, and only the monoalkylated product was formed. Unfortunately, the yield was poor (**3ra**). 2-Phenylpyrimidine was alkylated under the standard conditions, affording mono- and dialkylated products in 19% and 11% yield, respectively (**3sa**).

Next, the compatibility of various alkyl iodides was examined using **1b** as the reactant. As shown in Fig. 3, *n*-heptyl iodide could alkylate **1b** and the corresponding alkylated products were formed in slightly higher yields than those in the reactions of *n*-butyl iodide (**3bb**). The functionalities, benzyl, cyano, and methoxy, at the terminals of the alkyl chains were well tolerated, but a higher loading of the palladium catalyst had to be used (**3bc**, **3bd**, and **3be**). It is noted that only monoalkylated products were isolated in the reaction of 1-iodo-4-methoxybutane and 5-iodopentanenitrile. The more bulky iso-

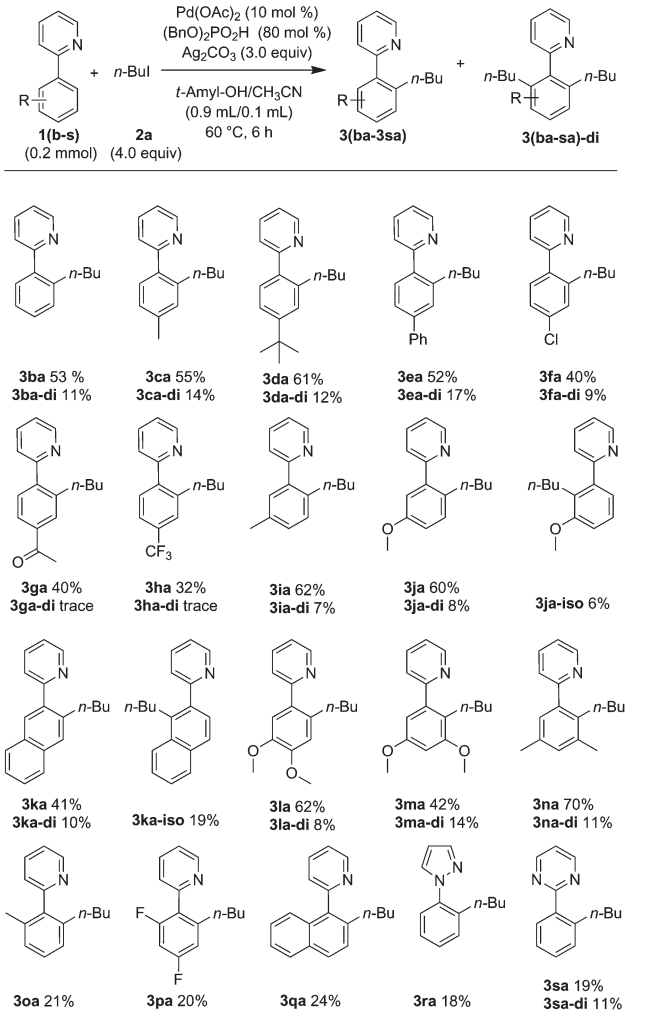


Fig. 2 Substrate scope with respect to 2-phenylpyridine. Isolated yield.

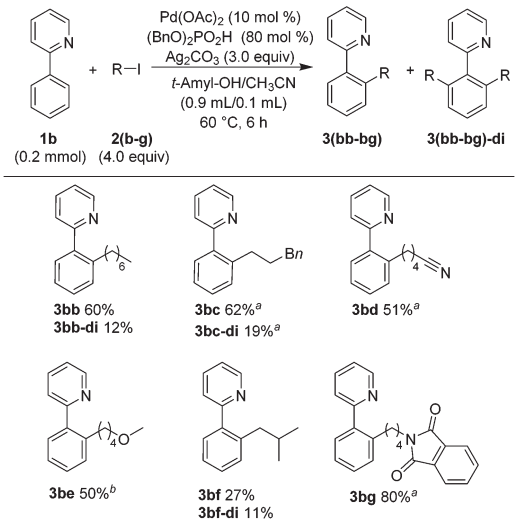
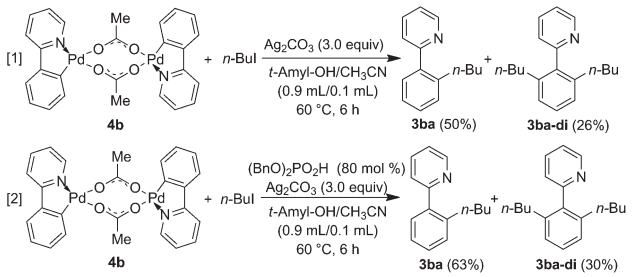


Fig. 3 Substrate scope with respect to alkyl iodide. Isolated yield. [a] $Pd(OAc)_2$ 20%; [b] $Pd(OAc)_2$ 15%.

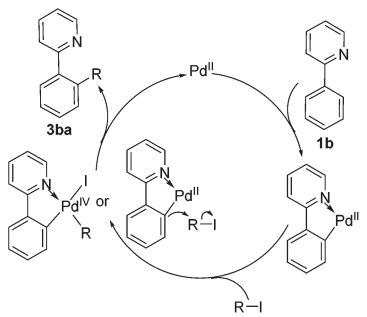


Scheme 1 *n*-Butylation of the palladacycle derived from 2-phenylpyridine with *n*-BuI.

propyl iodide was reactive, but the yields were low (**3bf**). Finally, the phthalimide group was also tolerated. The monoalkylated product was formed in 80% yield, and only a trace amount of the di-alkylated product was observed (**3bg**).

Finally, to investigate if the alkylation reaction proceeded through the palladacycle derived from 2-phenylpyridine as the intermediate, we prepared a complex from 2-phenylpyridine and $Pd(OAc)_2$ (Scheme 1, **4b**). Subsequently, the complex was subjected to the standard alkylation reaction conditions. The corresponding mono- and dialkylated products were formed in 76% overall yield in the absence of $(BnO)_2PO_2H$. In the presence of $(BnO)_2PO_2H$, the complex was alkylated almost quantitatively. These experimental results provide evidence to support palladacycles as the key intermediates in the alkylation reaction. Furthermore, $(BnO)_2PO_2H$ promoted the alkylation of the palladacycle. The mechanism of the promotion remains to be investigated. $(BnO)_2PO_2H$ might act as a ligand.[16]

Based on the experimental results and the previous reports,[3,11,15] a tentative mechanism was proposed as shown in Scheme 2. Therefore, the catalytic cycle was initiated by the pyridine-directed C–H cleavage by a Pd^{II} catalyst, forming the palladacycle. The resulting palladacycle reacts with alkyl iodide, *via* either an oxidative addition or a substitution pathway, to generate the alkylated product and release Pd^{II}. Ag(I) should function as an iodide scavenger.[17] The monoalkylated 2-phenylpyridine undergoes the same catalytic cycle to yield the dialkylated product.



Scheme 2 Proposed mechanism for the Pd-catalyzed C–H alkylation of 2-phenylpyridine with alkyl iodide.

Conclusions

In conclusion, we have successfully developed the Pd-catalyzed C–H alkylation reaction of 2-phenylpyridines with alkyl iodides. The reaction should proceed through a *C*, *N*-palladacycle obtained from 2-phenylpyridine as the key intermediate, this key palladacycle intermediate exhibits great reactivity towards alkyl halides. The reaction may shed light on other Pd-catalyzed alkylation reactions with alkyl halides, and provide inspiration to develop new reactions of this type.

Experimental section

General information

All the solvents were purified by distillation prior to use. Unless otherwise noted, the other commercial chemicals were used without further purification. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker ARX400. High resolution mass spectra were measured on a Bruker Micro TOF II ESI-TOF mass spectrometer. ^{1}H NMR spectra were recorded in $CDCl_3$, and referenced to residual $CHCl_3$ at 7.26 ppm. ^{13}C NMR spectra were referenced to the central peak of $CDCl_3$ at 77.0 ppm. Multiplicities are reported using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad resonance.

General procedure for the C–H alkylation. A 35 mL Schlenk tube equipped with a stir bar was charged with $Pd(OAc)_2$ (4.5 mg, 10 mol%) followed by 2-arylpyridines (0.2 mmol, 1 equiv.), alkyl iodides (0.8 mmol, 4 equiv.), Ag_2CO_3 (165.5 mg, 0.6 mmol, 3 equiv.), $(BnO)_2PO_2H$ (44.5 mg, 1.6 mmol, 0.8 equiv.), and *t*-AmylOH : CH_3CN (9 : 1, 1 mL). The tube was placed into an oil bath at the desired temperature. After the reaction was completed, the reaction mixture was allowed to cool down to room temperature. The reaction mixture was diluted with ethyl acetate and washed with aqueous Na_2S solution (4 mL, once) and brine (4 mL, twice), then filtered through a small pad of Celite. The filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel using petroleum ether and ethyl acetate as the eluent to afford products.

2-(2-Butyl-4-methoxyphenyl)pyridine (3aa). White solid (29.8 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.71 (d, J = 4.2 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.5 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.29–7.22 (m, 1H), 6.93–6.81 (m, 2H), 3.88 (s, 3H), 2.75 (t, J = 8.0 Hz, 2H), 1.54–1.42 (m, 2H), 1.33–1.21 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.12, 159.56, 149.08, 142.43, 136.02, 133.25, 131.08, 124.17, 121.27, 115.27, 110.98, 55.25, 33.41, 32.89, 22.51, 13.83. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{19}NNaO^+$: 264.1359 $(M + Na)^+$, found: 264.1364.

2-(2,6-Dibutyl-4-methoxyphenyl)pyridine (3aa-di). White solid (5.9 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 4.2 Hz, 1H), 7.77 (ddd, J = 7.6, 7.6, 1.7 Hz, 1H), 7.32–7.26 (m, 1H), 6.71 (s, 2H), 3.87 (s, 3H), 2.32 (t, J = 7.9 Hz, 4H), 1.50–1.36 (m, 4H), 1.25–1.13 (m, 4H), 0.77 (t, J = 7.3 Hz, 6H). ^{13}C NMR

(101 MHz, $CDCl_3$): δ 159.68, 149.27, 140.71, 139.87, 135.75, 127.93, 126.52, 125.05, 121.61, 33.32, 33.20, 22.56, 13.79. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{20}H_{27}NNaO^+$: 320.1985 $(M + Na)^+$, found: 320.1983.

2-(2-Butylphenyl)pyridine (3ba). Colorless liquid (22.4 mg, 53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, J = 3.5 Hz, 1H), 7.79 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.40–7.33 (m, 3H), 7.33–7.26 (m, 2H), 1.48 (t, J = 7.9 Hz, 2H), 1.55–1.39 (m, 2H), 1.30–1.21 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.35, 149.12, 140.75, 140.37, 136.09, 129.74, 129.72, 128.28, 125.73, 124.16, 121.63, 33.49, 32.61, 22.51, 13.83. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{15}H_{17}NNa^+$: 234.1253 $(M + Na)^+$, found: 234.1242.

2-(2,6-Dibutylphenyl)pyridine (3ba-di). Colorless liquid (5.9 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 4.0 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.34–7.26 (m, 2H), 7.16 (d, J = 7.6 Hz, 2H), 2.34 (t, J = 8.8 Hz, 4H), 1.53–1.37 (m, 4H), 1.24–1.14 (m, 4H), 0.78 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.68, 149.27, 140.71, 139.87, 135.75, 127.93, 126.52, 125.05, 121.61, 33.32, 33.20, 22.56, 13.79. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{19}H_{25}NNa^+$: 290.1879 $(M + Na)^+$, found: 290.1881.

2-(2-Butyl-4-methylphenyl)pyridine (3ca). Colorless liquid (24.8 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.8 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.30–7.23 (m, 2H), 7.16 (s, 1H), 7.12 (d, J = 7.7 Hz, 1H), 2.73 (t, J = 7.9 Hz, 2H), 2.42 (s, 3H), 1.56–1.42 (m, 2H), 1.33–1.24 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.40, 149.09, 140.61, 137.94, 137.56, 136.03, 130.47, 129.74, 126.50, 124.18, 121.42, 33.61, 32.60, 22.58, 21.29, 13.86. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{16}H_{19}NNa^+$: 248.1410 $(M + Na)^+$, found: 248.1404.

2-(2,6-Dibutyl-4-methylphenyl)pyridine (3ca-di). Colorless liquid (7.9 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 6.8 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.32–7.24 (m, 2H), 6.98 (s, 2H), 2.39 (s, 3H), 2.31 (t, J = 8.0 Hz, 4H), 1.51–1.33 (m, 4H), 1.27–1.14 (m, 4H), 0.78 (t, J = 7.3 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$): δ 159.85, 149.25, 140.62, 137.34, 137.16, 135.66, 127.29, 125.26, 121.46, 33.41, 33.17, 22.62, 21.33, 13.80. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{20}H_{27}NNa^+$: 304.2036 $(M + Na)^+$, found: 304.2034.

2-(4-(*tert*-Butyl)-2-butylphenyl)pyridine (3da). Colorless liquid (32.6 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.2 Hz, 1H), 7.77 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.35 (s, 1H), 7.34 (s, 2H), 7.27 (dd, J = 7.0, 5.4 Hz, 1H), 2.76 (t, J = 7.9 Hz, 2H), 1.54–1.44 (m, 2H), 1.40 (s, 9H), 1.31–1.24 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.41, 151.14, 149.12, 140.24, 137.51, 136.02, 129.50, 126.81, 124.07, 122.79, 121.42, 34.60, 33.76, 33.03, 31.41, 22.64, 13.90. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{19}H_{25}NNa^+$: 290.1879 $(M + Na)^+$, found: 290.1887.

2-(4-(*tert*-Butyl)-2,6-dibutylphenyl)pyridine (3da-di). Colorless liquid (6.4 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, J = 4.8 Hz, 1H), 7.77 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.34–7.31 (m, 1H), 7.30–7.25 (m, 1H), 7.16 (s, 2H), 2.34 (t, J = 7.9 Hz, 4H), 1.38 (s, 9H), 1.36–1.28 (m, 4H), 1.23–1.15 (m, 4H), 0.78 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.91, 150.51, 149.19, 140.16, 137.02, 135.65, 125.12, 123.64, 121.45, 34.51, 33.59, 33.56, 31.44, 22.63, 13.83. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{23}H_{33}NNa^+$: 346.2505 $(M + Na)^+$, found: 346.2519.

2-(3-Butyl-[1,1′-biphenyl]-4-yl)pyridine (3ea). White solid (29.9 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 (d, J = 4.7 Hz, 1H), 7.81 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.70 (d, J = 7.8 Hz, 2H), 7.59 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.50 (dd, J = 15.6, 7.7 Hz, 4H), 7.41 (t, J = 7.3 Hz, 1H), 7.34–7.28 (m, 1H), 2.84 (t, J = 7.8 Hz, 2H), 1.60–1.50 (m, 2H), 1.36–1.25 (m, 2H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.05, 149.23, 141.24, 141.13, 141.07, 139.34, 136.16, 130.32, 128.78, 128.64, 127.35, 127.23, 124.58, 124.16, 121.68, 33.60, 32.84, 22.59, 13.88. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{21}H_{21}NNa^+$: 310.1566 $(M + Na)^+$, found: 310.1560.

2-(3,5-Dibutyl-[1,1′-biphenyl]-4-yl)pyridine (3ea-di). White solid (11.6 mg, 17%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 4.7 Hz, 1H), 7.88–7.76 (m, 1H), 7.68 (d, J = 7.5 Hz, 2H), 7.50 (t, J = 7.6 Hz, 2H), 7.43–7.31 (m, 5H), 2.42 (t, J = 7.7 Hz, 4H), 1.54–1.42 (m, 4H), 1.28–1.17 (m, 4H), 0.80 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.52, 149.39, 141.52, 141.25, 140.77, 139.00, 135.80, 128.69, 127.25, 127.15, 125.52, 125.13, 121.69, 33.39, 22.62, 13.82. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{25}H_{29}NNa^+$: 366.2192 $(M + Na)^+$, found: 366.2196.

2-(2-Butyl-4-chlorophenyl)pyridine (3fa). Colorless liquid (19.6 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.7 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 2.0 Hz, 1H), 7.32–7.24 (m, 3H), 2.72 (t, J = 7.9 Hz, 2H), 1.53–1.41 (m, 2H), 1.29–1.20 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.21, 149.29, 142.83, 138.81, 136.28, 134.04, 131.13, 129.61, 125.89, 124.11, 121.93, 33.21, 32.53, 22.45, 13.81. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{15}H_{16}ClNNa^+$: 268.0863 $(M + Na)^+$, found: 268.0867.

2-(2,6-Dibutyl-4-chlorophenyl)pyridine (3fa-di). Colorless liquid (5.4 mg, 9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 4.4 Hz, 1H), 7.79 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H), 7.35–7.31 (m, 1H), 7.26 (d, J = 7.7 Hz, 1H), 7.15 (s, 2H), 2.30 (t, J = 8.9 Hz, 4H), 1.49–1.33 (m, 4H), 1.24–1.11 (m, 4H), 0.78 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.64, 149.49, 142.81, 138.39, 135.94, 133.45, 126.40, 125.07, 121.91, 33.05, 33.00, 22.47, 13.75. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{19}H_{24}ClNNa^+$: 324.1489 $(M + Na)^+$, found: 324.1492.

1-(3-Butyl-4-(pyridin-2-yl)phenyl)ethan-1-one (3ga). White solid (20.2 mg, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 4.1 Hz, 1H), 7.95 (d, J = 1.4 Hz, 1H), 7.88 (dd, J = 7.9, 1.7 Hz, 1H), 7.82 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.34 (ddd, J = 7.5, 4.9, 1.0 Hz, 1H), 2.79 (t, J = 8.2 Hz, 2H), 2.68 (s, 3H), 1.56–1.43 (m, 2H), 1.32–1.19 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 198.21, 159.21, 149.34, 144.83, 141.44, 136.81, 136.32, 130.12, 129.67, 125.86, 124.03, 122.22, 33.36, 32.65, 26.79, 22.49, 13.78. HRMS (ESI-TOF) *m*/*z*: calcd for $C_{17}H_{19}NNaO^+$: 276.1359 $(M + Na)^+$, found: 276.1359.

2-(2-Butyl-4-(trifluoromethyl)phenyl)pyridine (3ha). White solid (17.8 mg, 32%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (d, J = 4.3 Hz, 1H), 7.82 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.60 (s, 1H),

7.56 (d, J = 8.1 Hz, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.38–7.32 (m, 1H), 2.78 (t, J = 7.9 Hz, 2H), 1.55–1.45 (m, 2H), 1.32–1.23 (m, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.97, 149.37, 143.67, 141.80, 136.35, 130.36 (q, J = 32.0 Hz), 130.17, 126.47 (q, J = 3.7 Hz), 124.26 (q, J = 272.3 Hz), 124.01, 122.55 (q, J = 3.8 Hz), 122.25, 33.20, 32.61, 22.45, 13.73. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{16}F_3NNa^+$: 302.1127 $(M + Na)^+$, found: 320.1153.

2-(2-Butyl-5-methylphenyl)pyridine (3ia). Colorless liquid (27.9 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, J = 4.5 Hz, 1H), 7.77 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.32–7.26 (m, 1H), 7.26–7.16 (m, 3H), 2.70 (t, J = 8.29 Hz, 2H), 2.40 (s, 3H), 1.53–1.38 (m, 2H), 1.32–1.19 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.39, 149.20, 140.20, 137.59, 136.00, 135.18, 130.42, 129.68, 128.95, 124.14, 121.56, 33.65, 32.19, 22.52, 20.98, 13.88. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{19}NNa^+$: 248.1410 $(M + Na)^+$, found: 248.1404.

2-(2,6-Dibutyl-3-methylphenyl)pyridine (3ia-di). Colorless liquid (3.1 mg, 7%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 3.6 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H), 7.34–7.26 (m, 2H), 7.17 (d, J = 7.8 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 2.37 (s, 3H), 2.34–2.19 (m, 4H), 1.50–1.33 (m, 4H), 1.24–1.08 (m, 4H), 0.82–0.69 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.27, 149.19, 140.21, 139.06, 138.38, 135.63, 133.49, 130.04, 126.31, 125.04, 121.53, 33.37, 33.10, 31.98, 30.23, 23.07, 22.59, 19.51, 13.83, 13.61. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{19}NNa^+$: 304.2046 $(M + Na)^+$, found: 304.2046.

2-(2-Butyl-5-methoxyphenyl)pyridine (3ja). White solid (28.5 mg, 60%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, J = 4.1 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.32–7.21 (m, 2H), 6.93 (dd, J = 5.4, 2.7 Hz, 2H), 3.85 (s, 3H), 2.66 (t, J = 7.9 Hz, 2H), 1.50–1.37 (m, 2H), 1.30–1.15 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.16, 157.47, 149.19, 141.23, 136.09, 132.87, 130.78, 124.09, 121.73, 114.71, 114.36, 55.38, 33.72, 31.78, 22.44, 13.86. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{19}NNaO^+$: 264.1359 $(M + Na)^+$, found: 264.1364.

2-(2,6-Dibutyl-3-methoxyphenyl)pyridine (3ja-di). White solid (2.3 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 4.6 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H), 7.31 (s, 1H), 7.28 (s, 1H), 7.11 (d, J = 8.4 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 3.87 (s, 3H), 2.37–2.19 (m, 4H), 1.49–1.28 (m, 4H), 1.23–1.09 (m, 4H), 0.81–0.62 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.65, 155.67, 149.19, 141.08, 135.64, 132.77, 129.67, 126.90, 124.95, 121.60, 110.26, 55.64, 33.50, 32.62, 32.07, 27.16, 22.94, 22.53, 13.83, 13.75. HRMS (ESI-TOF) m/z: calcd for $C_{20}H_{27}NNaO^+$: 320.1985 $(M + Na)^+$, found: 320.1996.

2-(2-Butyl-3-methoxyphenyl)pyridine (3ja-iso). White solid (2.9 mg, 6%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.3 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.27 (dd, J = 9.2, 6.8 Hz, 2H), 6.97 (dd, J = 10.2, 8.2 Hz, 2H), 3.89 (d, J = 14.3 Hz, 3H), 2.75–2.59 (m, 2H), 1.51–1.40 (m, 2H), 1.27–1.16 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.34, 157.89, 149.07, 141.85, 135.94, 129.82, 126.28, 124.21, 122.00, 121.64, 110.33, 55.68, 32.16, 26.29, 22.84, 13.82. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{19}NNaO^+$: 264.1359 $(M + Na)^+$, found: 264.1365.

2-(3-Butylnaphthalen-2-yl)pyridine (3ka). White solid (21.4 mg, 41%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.78 (d, J = 4.5 Hz, 1H), 7.93–7.76 (m, 5H), 7.59–7.45 (m, 3H), 7.34 (dd, J = 6.9, 5.4 Hz, 1H), 2.94 (t, J = 7.9 Hz, 2H), 1.56–1.42 (m, 2H), 1.35–1.22 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.32, 149.12, 139.30, 138.79, 136.30, 133.40, 131.79, 129.10, 127.95, 127.87, 127.16, 126.26, 125.47, 124.34, 121.80, 33.19, 33.04, 22.53, 13.90. HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{19}NNa^+$: 284.1410 $(M + Na)^+$, found: 284.1420.

2-(1,3-Dibutylnaphthalen-2-yl)pyridine (3ka-di). White solid (6.3 mg, 10%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.80 (d, J = 3.6 Hz, 1H), 8.06 (dd, J = 13.9, 8.1 Hz, 1H), 7.92–7.77 (m, 2H), 7.65 (s, 1H), 7.59–7.48 (m, 2H), 7.35 (d, J = 7.7 Hz, 2H), 2.76 (t, J = 7.9 Hz, 2H), 2.50–2.40 (m, 2H), 1.72–1.60 (m, 1H), 1.59–1.41 (m, 3H), 1.36–1.18 (m, 4H). 0.81 (t, J = 7.3 Hz, 6H).^{13}C NMR (101 MHz, $CDCl_3$): δ 160.19, 149.35, 138.55, 138.45, 136.85, 135.82, 133.75, 130.43, 128.19, 125.57, 125.24, 125.17, 124.43, 121.78, 121.35, 33.71, 33.18, 32.89, 29.65, 23.18, 22.61, 13.86, 13.73. HRMS (ESI-TOF) m/z: calcd for $C_{23}H_{27}NNa^+$: 340.2036 $(M + Na)^+$, found: 340.2047.

2-(1-Butylnaphthalen-2-yl)pyridine (3ka-iso). White solid (9.9 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.79 (d, J = 4.3 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.84 (dd, J = 13.3, 5.1 Hz, 2H), 7.61 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.4 Hz, 1H), 7.50 (t, J = 7.4 Hz, 2H), 7.35 (dd, J = 7.0, 5.4 Hz, 1H), 3.12 (t, J = 8.13 Hz, 2H), 1.79–1.63 (m, 2H), 1.42–1.29 (m, 2H), 0.92–0.77 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.99, 149.28, 137.61, 136.80, 136.06, 133.68, 132.15, 128.73, 127.54, 126.23, 126.13, 125.70, 124.80, 124.61, 121.70, 33.48, 28.79, 23.03, 13.82. HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{19}NNa^+$: 284.1410 $(M + Na)^+$, found: 284.1420.

2-(2-Butyl-3,4-dimethoxyphenyl)pyridine (3la). White solid (33.6 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 4.6 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.30–7.24 (m, 1H), 7.10 (d, J = 8.4 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 3.94 (s, 3H), 3.90 (s, 3H), 2.77 (t, J = 8.1 Hz, 2H), 1.38 (dd, J = 15.3, 8.0 Hz, 2H), 1.27–1.16 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.18, 152.74, 149.00, 147.36, 136.09, 135.48, 125.48, 124.21, 121.43, 109.55, 100.22, 60.76, 55.72, 32.89, 26.39, 22.81, 13.75. HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{21}NNaO_2^+$: 294.1465 $(M + Na)^+$, found: 294.1466.

2-(2,6-Dibutyl-3,4-dimethoxyphenyl)pyridine (3la-di). White solid (4.3 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, J = 3.8 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.31–7.24 (m, 2H), 6.72 (s, 1H), 3.93 (s, 3H), 3.87 (s, 3H), 2.43–2.32 (m, 2H), 2.31–2.23 (m, 2H), 1.51–1.33 (m, 4H), 1.24–1.10 (m, 4H), 0.78 (t, J = 7.3 Hz, 3H), 0.72 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.41, 152.11, 149.16, 145.05, 136.61, 135.75, 135.09, 133.23, 125.53, 121.59, 110.61, 60.74, 55.70, 33.52, 33.33, 32.82, 27.32, 22.92, 22.60, 13.85, 13.58. HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{29}NNaO_2^+$: 350.2091 $(M + Na)^+$, found: 350.2094.

2-(2-Butyl-3,5-dimethoxyphenyl)pyridine (3ma). White solid (22.8 mg, 42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.1 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.38 (t, J = 14.0 Hz, 1H),

7.29 (d, J = 9.9 Hz, 1H), 6.53 (d, J = 10.3 Hz, 2H), 3.88 (s, 3H), 3.85 (s, 3H), 2.56 (t, J = 7.9 Hz 2H), 1.50–1.35 (m, 2H), 1.26–1.13 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.40, 158.90, 158.17, 149.12, 142.05, 135.89, 124.15, 122.42, 121.72, 105.36, 98.87, 55.65, 55.42, 32.42, 25.81, 22.68, 13.81. HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{21}NNaO_2^+$: 294.1465 $(M + Na)^+$, found: 294.1469.

2-(2,6-Dibutyl-3,5-dimethoxyphenyl)pyridine (3ma-di). White solid (9.1 mg, 14%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.4 Hz, 1H), 7.76 (t, J = 7.6 Hz, 1H), 7.28 (d, J = 7.6 Hz, 2H), 6.56 (s, 1H), 3.89 (s, 6H), 2.34–2.12 (m, 4H), 1.46–1.32 (m, 2H), 1.31–1.22 (m, 2H), 1.19–1.08 (m, 4H), 0.73 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.69, 156.26, 149.04, 141.90, 135.47, 124.89, 121.85, 121.54, 95.72, 55.85, 32.39, 26.64, 22.86, 13.72. HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{29}NNaO_2^+$: 350.2091 $(M + Na)^+$, found: 350.2098.

2-(2-Butyl-3,5-dimethylphenyl)pyridine (3na). Colorless liquid (33.6 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.7 Hz, 1H), 7.77 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.28 (ddd, J = 7.4, 5.4, 2.5 Hz, 1H), 7.08 (s, 1H), 7.01 (s, 1H), 2.65 (t, J = 7.9 Hz, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 1.47–1.33 (m, 2H), 1.28–1.16 (m, 2H), 0.80 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 161.24, 148.90, 140.91, 136.58, 136.12, 135.96, 134.73, 131.29, 128.24, 124.21, 121.48, 32.40, 28.90, 22.89, 20.85, 19.78, 13.72. HRMS (ESI-TOF) m/z: calcd for $C_{17}H_{21}NNa^+$: 262.1566 $(M + Na)^+$, found: 262.1564.

2-(2,6-Dibutyl-3,5-dimethylphenyl)pyridine (3na-di). Colorless liquid (6.4 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (d, J = 4.2 Hz, 1H), 7.76 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.33–7.28 (m, 2H), 7.04 (s, 1H), 2.33 (s, 6H), 2.27–2.16 (m, 4H), 1.47–1.34 (m, 2H), 1.34–1.21 (m, 2H), 1.19–1.08 (m, 4H), 0.73 (t, J = 7.3 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.85, 149.05, 140.60, 136.76, 135.46, 133.28, 132.25, 125.04, 121.43, 32.10, 30.15, 23.04, 19.29, 13.58. HRMS (ESI-TOF) m/z: calcd for $C_{21}H_{29}NNa^+$: 318.2192 $(M + Na)^+$, found: 318.2205.

2-(2-Butyl-6-methylphenyl)pyridine (3oa). Colorless liquid (9.5 mg, 21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 4.4 Hz, 1H), 7.86–7.76 (m, 1H), 7.35–7.26 (m, 3H), 7.21–7.11 (m, 2H), 2.37 (t, J = 7.9 Hz, 2H), 2.06 (s, 3H), 1.43 (d, J = 7.4 Hz, 2H), 1.25–1.12 (m, 2H), 0.78 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.85, 149.50, 140.65, 140.20, 136.05, 135.86, 127.91, 127.46, 126.64, 124.72, 121.64, 33.33, 33.11, 22.52, 20.34, 13.79. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{19}NNa^+$: 248.1410 $(M + Na)^+$, found: 248.1413.

2-(2-Butyl-4,6-difluorophenyl)pyridine (3pa). Colorless liquid (9.9 mg, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 4.2 Hz, 1H), 7.82 (td, J = 7.7, 1.8 Hz, 1H), 7.43–7.31 (m, 2H), 6.88 (d, J = 9.5 Hz, 1H), 6.78 (td, J = 9.3, 2.4 Hz, 1H), 2.63–2.50 (m, 2H), 1.43 (dt, J = 15.3, 7.5 Hz, 2H), 1.22 (dq, J = 14.5, 7.3 Hz, 2H), 0.80 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.54, 149.60, 145.61 (t, J_{CF} = 5.36 Hz), 136.19, 125.81, 122.45, 111.96 (d, J_{CF} = 3.32 Hz), 111.78 (d, J_{CF} = 3.36 Hz), 101.54, 101.28, 101.02, 32.70, 32.56, 22.30, 13.71. HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{15}F_2NNa^+$: 270.1065 $(M + Na)^+$, found: 270.1057.

2-(2-Butylnaphthalen-1-yl)pyridine (3qa). Colorless liquid (12.5 mg, 24%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.86 (d, J = 4.1 Hz, 1H), 7.88 (t, J = 7.5 Hz, 3H), 7.51–7.47 (m, 1H), 7.46–7.34 (m, 4H), 7.28 (s, 1H), 2.57 (t, J = 7.9 Hz, 2H), 1.56 (dtd, J = 20.7, 13.4, 7.2 Hz, 2H), 1.25 (dt, J = 14.5, 7.3 Hz, 2H), 0.83 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 158.94, 149.73, 138.35, 136.48, 136.04, 132.57, 132.02, 128.24, 127.83, 127.75, 126.05, 125.85, 125.64, 124.91, 121.99, 33.57, 33.31, 22.61, 13.85. HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{11}NNa^+$: 288.0784 $(M + Na)^+$, found: 288.0781.

1-(2-Butylphenyl)-1*H*-pyrazole (3ra). Colorless liquid (7.2 mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 1.2 Hz, 1H), 7.62 (d, J = 2.2 Hz, 1H), 7.44–7.36 (m, 2H), 7.35–7.29 (m, 2H), 6.48 (t, J = 1.8 Hz, 1H), 2.67–2.53 (m, 2H), 1.51–1.39 (m, 2H), 1.34–1.22 (m, 3H), 0.86 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 140.16, 139.70, 139.01, 130.76, 130.30, 128.63, 126.70, 126.44, 106.09, 32.79, 30.99, 22.50, 13.81. HRMS (ESI-TOF) m/z: calcd for $C_{13}H_{16}N_2Na^+$: 223.1206 $(M + Na)^+$, found: 223.1205.

2-(2-Butylphenyl)pyrimidine (3sa). Colorless liquid (8.1 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.88 (t, J = 7.6 Hz, 1H), 7.75 (d, J = 7.3 Hz, 1H), 7.46–7.38 (m, 1H), 7.38–7.32 (m, 1H), 7.27 (t, J = 4.8 Hz, 1H), 3.05–2.87 (m, 1H), 1.58–1.43 (m, 1H), 1.35–1.21 (m, 2H), 0.86 (t, J = 7.3 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.08, 156.90, 141.97, 138.04, 130.50, 130.39, 129.38, 125.88, 118.59, 33.73, 33.08, 22.60, 13.89. HRMS (ESI-TOF) m/z: calcd for $C_{14}H_{16}N_2Na^+$: 235.1206 $(M + Na)^+$, found: 235.1209.

2-(2,6-Dibutylphenyl)pyrimidine (3sa-di). Colorless liquid (5.9 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (d, J = 4.9 Hz, 1H), 7.37–7.29 (m, 1H), 7.16 (d, J = 7.6 Hz, 1H), 2.49–2.27 (m, 2H), 1.53–1.37 (m, 2H), 1.26–1.11 (m, 2H), 0.78 (t, J = 7.3 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.64, 156.79, 140.28, 138.54, 128.43, 126.72, 118.83, 33.15, 33.07, 22.54, 13.79. HRMS (ESI-TOF) m/z: calcd for $C_{18}H_{24}N_2Na^+$: 291.1832 $(M + Na)^+$, found: 291.1832.

2-(2-Heptylphenyl)pyridine (3bb). Colorless liquid (30.4 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.73 (dd, J = 4.8, 0.7 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.40–7.34 (m, 3H), 7.30 (ddd, J = 7.5, 6.7, 4.9 Hz, 2H), 2.74 (t, J = 7.9 Hz, 2H), 1.56–1.43 (m, 2H), 1.29–1.16 (m, 8H), 0.88 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.36, 149.12, 140.82, 140.34, 136.10, 129.75, 129.73, 128.30, 125.74, 124.15, 121.63, 32.96, 31.72, 31.30, 29.42, 28.98, 22.66, 14.12. HRMS (ESI-TOF) m/z: calcd for $C_{18}H_{23}NNa^+$: 276.1723 $(M + Na)^+$, found: 276.1729.

2-(2,6-Diheptylphenyl)pyridine (3bb-di). Colorless liquid (8.4 mg, 12%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.75 (dd, J = 5.9, 1.6 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.30 (d, J = 6.5 Hz, 3H), 7.15 (d, J = 7.6 Hz, 2H), 2.41–2.27 (m, 4H), 1.53–1.35 (m, 4H), 1.28–1.22 (m, 4H), 1.16 (s, 12H), 0.87 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.69, 149.28, 140.78, 139.83, 135.73, 127.94, 126.51, 125.03, 121.60, 33.57, 31.67, 31.12, 29.50, 28.92, 22.64, 14.10. HRMS (ESI-TOF) m/z: calcd for $C_{25}H_{37}NNa^+$: 374.2818 $(M + Na)^+$, found: 374.2818.

2-(2-(3-Phenylpropyl)phenyl)pyridine (3bc). White solid (33.8 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.2 Hz, 1H), 7.75 (t, J = 7.7 Hz, 1H), 7.40 (t, J = 17.2 Hz, 5H),

7.32–7.25 (m, 3H), 7.25–7.17 (m, 1H), 7.13 (d, J = 7.4 Hz, 2H), 2.84 (t, J = 7.6 Hz, 2H), 2.59 (t, J = 7.5 Hz, 2H), 1.92–1.80 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.26, 149.23, 142.31, 140.48, 140.35, 136.19, 129.91, 128.45, 128.28, 126.02, 125.68, 124.10, 121.69, 35.77, 32.87, 32.72. HRMS (ESI-TOF) m/z: calcd for $C_{20}H_{19}NNa^+$: 296.1410 $(M + Na)^+$, found: 296.1409.

2-(2,6-Bis(3-phenylpropyl)phenyl)pyridine (3bc-di). White solid (14.86 mg, 19%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 4.3 Hz, 1H), 7.75–7.64 (m, 1H), 7.34–7.21 (m, 7H), 7.18 (dd, J = 7.3, 5.4 Hz, 4H), 7.07 (d, J = 7.2 Hz, 4H), 2.50 (t, J = 7.6 Hz, 4H), 2.40 (t, J = 8.0 Hz, 4H), 1.88–1.67 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.33, 149.35, 142.20, 140.30, 140.04, 135.75, 128.33, 128.17, 128.06, 126.75, 125.55, 124.85, 121.67, 35.75, 33.22, 32.55. HRMS (ESI-TOF) m/z: calcd for $C_{29}H_{29}NNa^+$: 414.2192 $(M + Na)^+$, found: 414.2192.

5-(2-(Pyridin-2-yl)phenyl)pentanenitrile (3bd). Colorless liquid (24.0 mg, 51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.7 Hz, 1H), 7.80 (t, J = 7.0 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.37 (d, J = 4.9 Hz, 2H), 7.31 (dd, J = 11.8, 5.9 Hz, 3H), 2.80 (t, J = 7.5 Hz, 2H), 2.23 (t, J = 6.9 Hz, 2H), 1.73–1.62 (m, 2H), 1.62–1.52 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.12, 149.12, 140.36, 139.36, 136.47, 129.95, 129.79, 128.50, 126.25, 124.12, 121.87, 119.70, 31.94, 30.08, 24.98, 16.83. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{16}N_2Na^+$: 259.1206 $(M + Na)^+$, found: 259.1202.

2-(2-(4-Methoxybutyl)phenyl)pyridine (3be). White solid (24.0 mg, 50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.6 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.39–7.33 (m, 3H), 7.32–7.25 (m, 2H), 3.32–3.26 (m, 5H), 2.77 (t, J = 7.2 Hz, 2H), 1.63–1.45 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.27, 149.11, 140.33, 140.32, 136.19, 129.79, 129.73, 128.34, 125.88, 124.16, 121.67, 72.54, 58.49, 32.64, 29.35, 27.76. HRMS (ESI-TOF) m/z: calcd for $C_{16}H_{19}NNaO^+$: 264.1359 $(M + Na)^+$, found: 264.1361.

2-(2-Isobutylphenyl)pyridine (3bf). Colorless liquid (11.4 mg, 27%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.3 Hz, 1H), 7.78 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H), 7.48–7.22 (m, 6H), 2.68 (d, J = 7.2 Hz, 2H), 1.70–1.58 (m, 1H), 0.76 (d, J = 6.6 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 160.58, 149.08, 140.74, 139.58, 136.09, 130.56, 129.79, 128.03, 125.84, 124.29, 121.57, 42.05, 29.81, 22.43. HRMS (ESI-TOF) m/z: calcd for $C_{15}H_{17}NNa^+$: 234.1253 $(M + Na)^+$, found: 234.1250.

2-(2,6-Diisobutylphenyl)pyridine (3bf-di). Colorless liquid (5.9 mg, 11%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.74 (d, J = 4.7 Hz, 1H), 7.77 (t, J = 8.1 Hz, 1H), 7.27 (d, J = 7.7 Hz, 3H), 7.13 (d, J = 7.6 Hz, 2H), 2.35–2.17 (m, 4H), 1.68–1.58 (m, 2H), 0.83–0.68 (m, 12H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.75, 149.14, 140.58, 139.52, 135.59, 127.54, 127.33, 125.50, 121.51, 42.78, 29.41, 22.68, 22.43. HRMS (ESI-TOF) m/z: calcd for $C_{19}H_{25}NNa^+$: 290.1879 $(M + Na)^+$, found: 290.1880.

2-(4-(2-(Pyridin-2-yl)phenyl)butyl)isoindoline-1,3-dione (3bg). White solid (56.9 mg, 80%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 4.5 Hz, 1H), 7.92–7.78 (m, 2H), 7.71 (dd, J = 7.8, 6.1 Hz, 3H), 7.42–7.28 (m, 5H), 7.25–7.19 (m, 1H), 3.61 (t, J = 6.9 Hz, 2H), 2.80 (t, J = 7.3 Hz, 2H), 1.67–1.57 (m, 2H), 1.57–1.47 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.35, 160.17, 149.09, 140.29, 139.96, 136.22, 133.86, 132.13, 129.81, 128.38, 125.99, 124.04, 123.14, 121.69, 37.78, 32.53, 28.36, 28.35. HRMS (ESI-TOF) m/z: calcd for $C_{23}H_{20}N_2NaO_2^+$: 379.1417 $(M + Na)^+$, found: 379.1403.

Conflict of interest

The authors declare no competing financial interest.

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