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Syntheses of substituted pyridines, quinolines and diazines via palladium-catalyzed cross-coupling of aryl Grignard reagents

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Abstract—The palladium-catalyzed cross-coupling reactions between arylmagnesium halides (phenylmagnesium chloride, mesitylmagnesium bromide, 4-(methoxycarbonyl)phenylmagnesium chloride and 4-cyanophenylmagnesium chloride) and halopyridines allowed the synthesis of substituted pyridines. Owing to the remarkably mild conditions used (often below 0°C), the reaction could be extended to the use of functionalized halopyridines, haloquinolines and halodiazines.

1. Introduction

Interest in azine and diazine natural products and pharmaceuticals, or building blocks for various applications such as material science and supramolecular chemistry, has resulted in extensive efforts on synthesis methodologies.[1] Transition metal-catalyzed cross-couplings have proven to be an important method for preparing a number of complex heterocycles.

Several Negishi,[2,3] Suzuki[2,4] and Stille[2,4c,d,5] cross-coupling reactions have already been reported in the azine and diazine series. The aryl organometallic substrates are usually prepared via their corresponding lithio derivatives.

More reactive organometallics such as organomagnesium derivatives suffer from a moderate functional group tolerance when compared to organozincs, organoboronic acids or organotin derivatives.[6]

The strategy developed uses arylmagnesium reagents. We recently reported an easy access to aryl- and heteroarylmagnesium halides,[7] starting from the corresponding halo derivatives. Thus, we decided to involve functionalized arylmagnesium halides in cross-coupling reactions with functionalized halopyridines and we found that the reaction could be catalyzed with palladium under remarkably soft conditions.[8] Herein, details of our investigations concerning the cross-coupling reactions of various aryl Grignard reagents with pyridine, quinoline and diazine halo substrates (functionalized or not) are recorded.

2. Results and discussion

Initially, phenylmagnesium chloride (PhMgCl) was used in order to optimize reaction conditions for the cross-coupling reactions with various halopyridines. Under nickel-catalysis, such reactions are possible at room temperature (rt);[6] however, the toxicity of nickel salts led us to explore an alternative route. So we turned to palladium-catalyzed cross-coupling reactions.[9] Bis(dibenzylideneacetone)palladium(0) ($Pd(dba)_2$) and 1,1′-bis(diphenylphosphino)ferrocene (dppf) were chosen for this purpose.[10] Under these conditions, 2-, 3- and 4-bromopyridines (**1a–c**) reacted with PhMgCl in tetrahydrofuran (THF) at rt in excellent yields (entries 1–3). Note that both 2-bromo- and 2-chloropyridines could be used. For the halo methylpyridines **1d–e**, no deprotonation of the methyl group was noticed[11] and the coupled products were quantitatively obtained (entries 4–5). Due to the remarkably mild reaction conditions used (−40°C), the ethyl chloronicotinates **1f–g** could also be involved in the reaction (entries 6–7). When 3-halopyridines were used, higher temperatures were required for the cross-coupling. For ethyl 5-bromonicotinate (**1h**), tri(*tert*-butyl)phosphine ($P(t\text{Bu})_3$) was found to be a more convenient ligand[6b,12] than dppf (entry 8) (Scheme 1, Table 1).

Starting from phenyl 6-bromopyridine-2-sulfone (**3**), the cross-coupling reaction could be selectively observed at C6. The phenylpyridine **4** was indeed given when the substrate was treated with PhMgCl at rt in THF, in the presence of catalytic amounts of $Pd(dba)_2$ and dppf. Without

Keywords: palladium catalysis; Grignard reagents; coupling reactions; azines.

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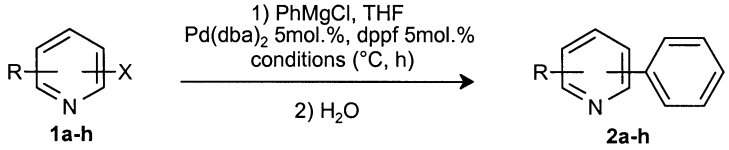
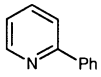
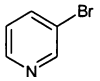
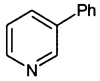
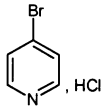
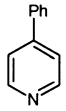
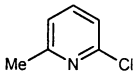
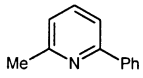
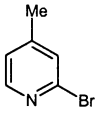
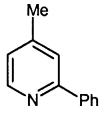
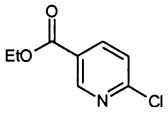
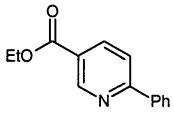
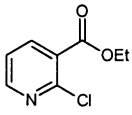
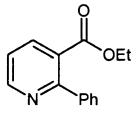
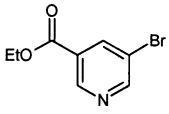
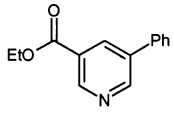
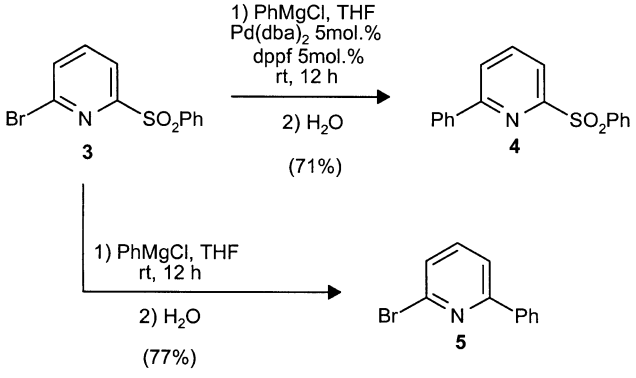


Scheme 1.

Table 1. Cross-coupling reactions of **1a**–**h** with PhMgCl

Entry	Halopyridine	Conditions (°C, h)	Product	Yield%[a]
1	**1a:** 	25, 5	**2a:** 	98[b,c]
2	**1b:** 	25, 5	**2b:** 	95
3	**1c:** 	25, 5	**2c:** 	95[d]
4	**1d:** 	−5, 7	**2d:** 	96
5	**1e:** 	−25, 18	**2e:** 	95
6	**1f:** 	−40, 6	**2f:** 	92[e]
7	**1g:** 	−40, 6	**2g:** 	42
8	**1h:** 	0, 18	**2h:** 	73[f]

[a] Isolated yields based on 1.
[b] 95% at 0°C.
[c] 97% starting from 2-bromopyridine.
[d] 2 equiv. of PhMgCl were used.
[e] 95% starting from ethyl 6-bromonicotinate.
[f] Using P(*t*Bu)$_3$, 10 mol%, instead of dppf.

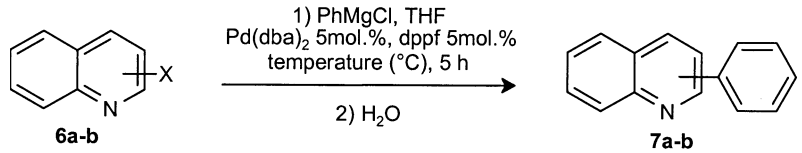


Scheme 2.

catalyst, displacement of the phenylsulfonyl group[13] by the phenyl group of the Grignard reagent was selectively observed to afford the phenylpyridine **5** (Scheme 2).

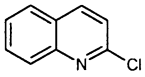
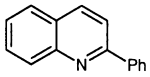
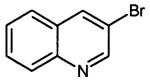
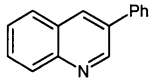
Due to their lower LUMO levels, quinolines and diazines are prone to nucleophilic addition. Nevertheless, under the conditions used, cross-coupling reactions between PhMgCl and the commercial haloquinolines **6a**,**b** could be achieved to give the phenylquinolines **7a**,**b** in good yields (Scheme 3, Table 2).

Moreover, the halodiazines **8a**–**c** could also be involved in the reaction to produce the phenyldiazines **9a**–**c** (Scheme 4, Table 3). Remark that when the reaction of 2-chloropyrimidine (**8a**) was led without catalyst, the 4-phenyl derivative

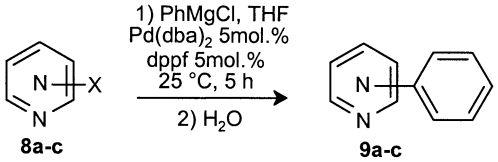


Scheme 3.

Table 2. Cross-coupling reactions of **6a**,**b** with PhMgCl

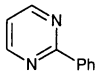
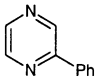
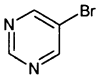
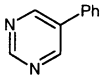
Entry	Haloquinoline	Temperature (°C)	Product	Yield%[a]
1	**6a:** 	−5	**7a:** 	80
2	**6b:** 	25	**7b:** 	75

[a] Isolated yields based on **6**.

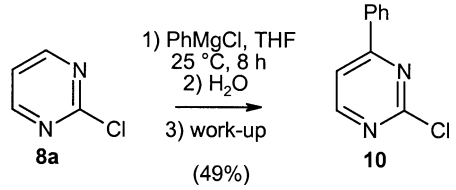


Scheme 4.

Table 3. Cross-coupling reactions of **8a–c** with PhMgCl

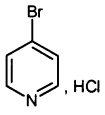
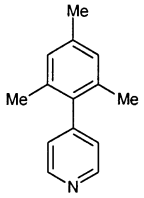
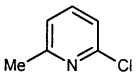
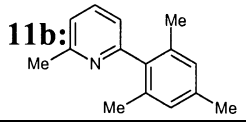
Entry	Halodiazine	Product	Yield%[a]
1	**8a:** 	**9a:** 	80
2	**8b:** 	**9b:** 	91
3	**8c:** 	**9c:** 	40

[a] Isolated yields based on **8**.



Scheme 5.

Table 4. Cross-coupling reactions of **1c**,**d** with mesitylmagnesium bromide

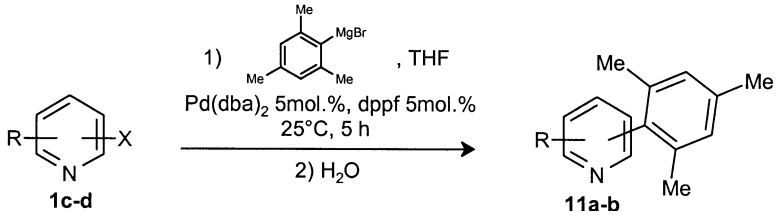
Entry	Halopyridine	Product	Yield%[a]
1	**1c:** 	**11a:** 	62[b]
2	**1d:** 	**11b:** 	51

[a] Isolated yields based on **1**.
[b] 2 equiv. of mesitylmagnesium bromide were used.

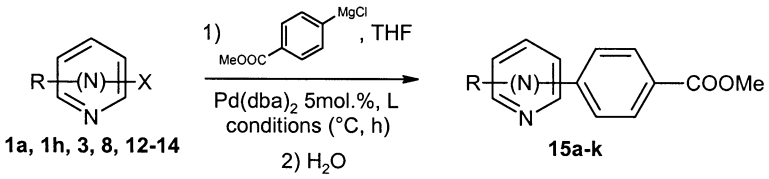
10 was obtained after 1,4-addition of the Grignard reagent to the ring and subsequent oxidation (Scheme 5).

This efficient procedure in hand, we turned to substituted arylmagnesium halides. When the halopyridines **1c**,**d** were treated with commercially available mesitylmagnesium bromide under the same reaction conditions, the corresponding phenylpyridines **11a**,**b** could also be obtained (Scheme 6, Table 4).

Next, functionalized arylmagnesium compounds, such as 4-(methoxycarbonyl)phenylmagnesium chloride[14] or 4-cyanophenylmagnesium chloride,[14] were used. Treating 2-chloropyridine (**1a**) with 4-(methoxycarbonyl)phenylmagnesium chloride at −40°C under the same reaction

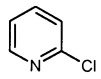
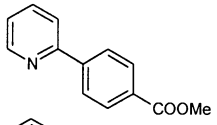
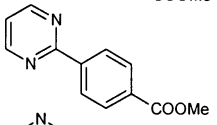
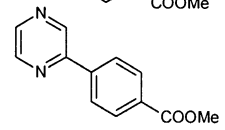
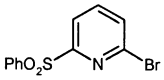
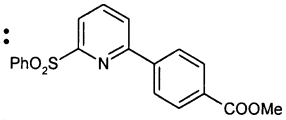
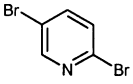
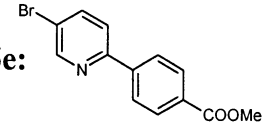
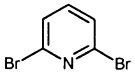
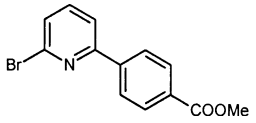
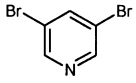
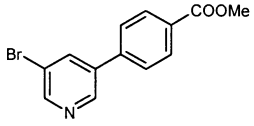
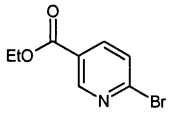
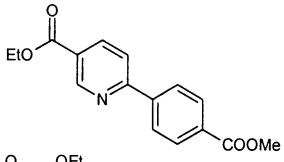
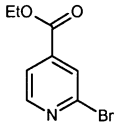
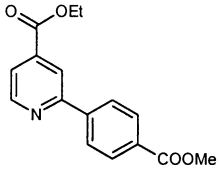
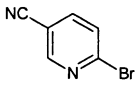
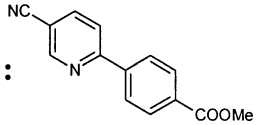
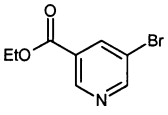
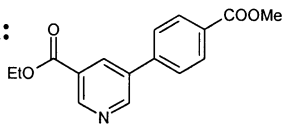


Scheme 6.

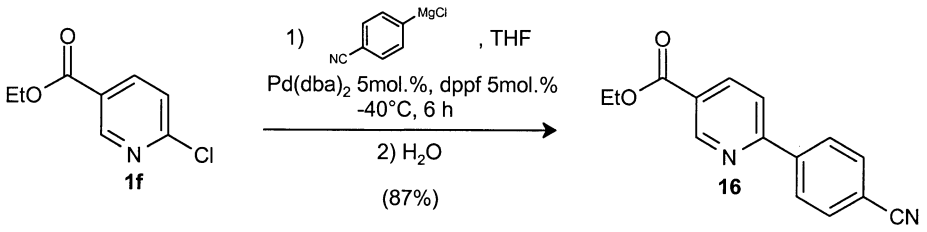


Scheme 7.

Table 5. Cross-coupling reactions of **1a**,**h**, **3**, **8**, **12**–**14** with 4-(methoxycarbonyl)phenylmagnesium chloride

Entry	Halo substrate	Conditions (°C, h)	L	Product	Yield%[a]
1	**1a:** 	−40, 5	dppf 5 mol%	**15a:** 	95[b]
2	**8a:** 	−40, 5	dppf 5 mol%	**15b:** 	36
3	**8b:** 	−40, 5	dppf 5 mol%	**15c:** 	32
4	**3:** 	−5,18	dppf 5 mol%	**15d:** 	32
5	**12a:** 	−15, 7	dppf 5 mol%	**15e:** 	32
6	**12b:** 	−15, 7	dppf 5 mol%	**15f:** 	25
7	**12c:** 	−5, 18	P(*t*Bu)$_3$ 10 mol%	**15g:** 	62
8	**13a:** 	−40, 6	dppf 5 mol%	**15h:** 	95
9	**13b:** 	−20, 4	dppf 5 mol%	**15i:** 	90
10	**14:** 	−40, 6	dppf 5 mol%	**15j:** 	86
11	**1h:** 	0, 18	P(*t*Bu)$_3$ 10 mol%	**15k:** 	63

[a] Isolated yields based on starting halo substrate.
[b] 96% starting from 2-bromopyridine.



Scheme 8.

conditions quantitatively afforded the functionalized phenylpyridine **15a** (entry 1). For the 2-chlorodiazines **8a**,**b** and phenyl 6-bromopyridine-2-sulfone (**3**), moderate yields were observed (entries 2–4). Starting from 2,5-dibromopyridine (**12a**), a good regioselectivity was obtained at C2 (entry 5). A single functionalization was observed from 2,6- and 3,5-dibromopyridines (**12b**,**c**), yields being considerably improved using P(*t*Bu)$_3$ instead of dppf (entries 6–7). From the functionalized 2-bromopyridines **13a**,**b** and **14**, addition of the Grignard reagent to the ester or cyano group could be completely avoided by using lower reaction temperatures (−40 or −20°C). Excellent yields were obtained for the synthesis of the bisfunctionalized phenylpyridines **15h–j** (entries 8–10). In the case of the functionalized 3-bromopyridine **1h**, it has also been advantageous to use P(*t*Bu)$_3$ as ligand instead of dppf (entry 11) (Scheme 7, Table 5).

Treating ethyl 6-chloronicotinate (**1f**) with 4-cyanophenylmagnesium chloride also allowed the synthesis of the bisfunctionalized phenylpyridine **16** (Scheme 8).

3. Conclusion

Using phenylmagnesium chloride, we could find remarkably mild conditions for the cross-coupling reaction with a large range of halopyridines (functionalized or not), haloquinolines or halodiazines. The use of more hindered or functionalized arylmagnesium halides could lead to more elaborated azines and diazines, which are of interest for various pharmaceutical applications.

Extension of this strategy to the use of pyridylmagnesium chlorides is currently under investigation.

4. Experimental

4.1. General

Melting points were measured on a Kofler apparatus. The NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 with a Bruker AM 300 spectrometer (^{1}H at 300 MHz and ^{13}C at 75 MHz). IR spectra were taken on a Perkin–Elmer FT IR 205 spectrometer, and main IR absorptions are given in cm^{-1}. Elemental analyses were performed on a Carlo Erba 1106 apparatus.

4.2. Starting materials

THF was distilled from benzophenone/Na. Reactions were carried out under dry N_2. Silica gel (Geduran Si 60, 0.063–0.200 mm) was purchased from Merck. *i*PrMgCl (2 M) in THF, PhMgCl (2 M) in THF, mesitylmagnesium bromide (1 M) in THF, and BuLi (2.5 M) in hexane were purchased from Aldrich. $Pd(dba)_2$ was supplied by Acros, dppf by Avocado and P(*t*Bu)$_3$ by Aldrich. Petrol refers to petroleum ether (bp 40–60°C).

After the reaction, the aqueous solution was extracted several times with CH_2Cl_2. The organic layer was dried over $MgSO_4$, the solvents were evaporated under reduced pressure, and unless otherwise noted, the crude compound was chromatographed on a silica gel column (eluent is given in the product description).

4.2.1. Ethyl 6-chloronicotinate (1f). A mixture of 6-chloronicotinic acid (6.9 g, 44 mmol), ethanol (100 mL) and conc. sulfuric acid (0.20 mL) was heated at reflux for 2 h (water was distilled off using a Dean–Stark apparatus) and ethanol was evaporated. CH_2Cl_2 (30 mL) was added to the residue and the resulting mixture was poured onto an aqueous saturated solution of Na_2CO_3 (40 mL). Yield of **1f** (eluent: CH_2Cl_2): 46%; pale yellow oil; the ^{1}H NMR data are in accordance with those of the literature;[15] ^{13}C NMR ($CDCl_3$) δ 14.7, 62.1, 121.4, 123.8, 141.2, 151.4, 152.1, 165.1; IR (KBr) ν 2984, 2938, 1724, 1587, 1457, 1368, 1292, 1274, 1128, 1024, 768 cm^{-1}. Anal. Calcd for $C_8H_8ClNO_2$ (185.61): C, 51.77; H, 4.34; N, 7.55. Found: C, 51.86; H, 4.37; N, 7.87%.

4.2.2. Ethyl 6-bromonicotinate (13a). Compound *13a* was prepared by bromine-magnesium exchange from 2,5-dibromopyridine,[6c] using ethyl cyanoformate. Yield of **13a** (eluent: CH_2Cl_2/Et_2O 80:20): 40%; mp <50°C; ^{1}H NMR ($CDCl_3$) δ 1.35 (t, 3H, J=7.9 Hz, CH_3), 4.41 (q, 2H, J=7.9 Hz, CH_2), 7.53 (d, 1H, J=8.2 Hz, H_5), 8.08 (dd, 1H, J=8.2, 1.8 Hz, H_4), 8.97 (d, 1H, J=1.8 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 14.4, 61.9, 125.8, 128.2, 139.3, 146.7, 151.2, 164.5; IR (KBr) ν 2983, 2937, 1725, 1581, 1451, 1369, 1290, 1272, 1116, 1022, 764 cm^{-1}. Anal. Calcd for $C_8H_8BrNO_2$ (230.06): C, 41.77; H, 3.51; N, 6.09. Found: C, 41.82; H, 3.57; N, 6.18%.

4.2.3. Ethyl 2-chloronicotinate (1g). A mixture of 2-chloronicotinic acid (1.6 g, 10 mmol) and $SOCl_2$ (25 mL) was heated at reflux for 3 h. The excess of $SOCl_2$ was evaporated and the residue was treated with ethanol (30 mL) at 0°C with stirring. After 15 h, ethanol was evaporated, CH_2Cl_2 (30 mL) was added to the residue and the resulting mixture was poured onto an aqueous saturated solution of Na_2CO_3 (40 mL). Yield of **1g** (eluent: CH_2Cl_2): 90%; pale yellow oil; the ^{1}H NMR data are in accordance with those of the

literature;[16] IR (KBr) ν 3416, 2992, 1727, 1580, 1275, 1172, 1022, 763 cm^{-1}. Anal. Calcd for $C_8H_8ClNO_2$ (185.61): C, 51.77; H, 4.34; N, 7.55. Found: C, 51.96; H, 4.48; N, 7.38%.

4.2.4. Ethyl 5-bromonicotinate (1h). A mixture of 5-bromonicotinic acid (2.1 g, 10 mmol) and $SOCl_2$ (25 mL) was heated at reflux for 3 h. The excess of $SOCl_2$ was evaporated and the residue was treated with ethanol (30 mL) at 0°C with stirring. After 15 h, ethanol was evaporated, CH_2Cl_2 (30 mL) was added to the residue and the resulting mixture was poured onto an aqueous saturated solution of Na_2CO_3 (40 mL). Yield of **1h** (eluent: CH_2Cl_2): 94%; mp <50°C; the spectral data are in accordance with those of the literature;[17] Anal. Calcd for $C_8H_8BrNO_2$ (230.06): C, 41.77; H, 3.51; N, 6.09. Found: C, 42.51; H, 3.49; N, 6.17%.

4.3. Phenyl 6-bromopyridine-2-sulfone (3)

4.3.1. 6-Bromo-2-(phenylthio)pyridine. To a solution of 2,6-dibromopyridine (2.4 g, 10 mmol) in THF (20 mL) at −75°C was added a solution of BuLi (11 mmol) in hexane (4.4 mL). After 1 h at this temperature, PhSSPh (2.4 g, 11 mmol) was added and the mixture was stirred for 2 h at −50°C before hydrolysis with water (10 mL). Yield (eluent: CH_2Cl_2/Et_2O 90:10): 54%; mp <50°C; ^1H NMR ($CDCl_3$) δ 6.60 (d, 1H, J=7.9 Hz, H_5), 6.72 (t, 1 H, J=7.9 Hz, H_4), 7.13 (d, 1H, J=7.9 Hz, H_3), 7.29 (m, 3H, Ph), 7.41 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 117.4, 119.9, 124.1, 130.2 (2C), 130.4 (2C), 135.6, 141.7, 163.6, 130.7; IR (KBr) ν 3060, 1561, 1536, 1409, 1161, 1142, 776, 751, 610 cm^{-1}. Anal. Calcd for $C_{11}H_8BrNS$ (266.16): C, 49.64; H, 3.03; N, 5.26; S, 12.05. Found: C, 49.69; H, 3.17; N, 5.12; S, 12.16%.

4.3.2. Phenyl 6-bromopyridine-2-sulfone (3). A solution of 6-bromo-2-(phenylthio)pyridine (2.4 g, 11 mmol) in THF (30 mL) was treated at −5°C with a solution of 3-chloroperbenzoic acid (7.4 g, 43 mmol) in THF (40 mL). After stirring for 6 h, $Na_2S_2O_4$ (7.5 g, 43 mmol) was added to the mixture and the solvent was evaporated. Water (20 mL) was added to the residue and the pH of the resulting solution was adjusted to 7–8 with $NaHCO_3$. Yield of **3** (eluent: petrol/CH_2Cl_2 50:50): 42%; mp 129–131°C; ^1H NMR ($CDCl_3$) δ 7.42 (d, 1H, J=7.5 Hz, H_5), 7.51 (t, 1H, J=7.5 Hz, H_4), 7.69 (d, 1H, J=7.5 Hz, H_3), 7.92 (m, 3H, Ph), 8.03 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 121.5, 129.4 (2C), 129.8 (2C), 132.4, 134.6, 138.6, 140.7, 143.0, 159.3. Anal. Calcd for $C_{11}H_8BrNO_2S$ (298.16): C, 44.31; H, 2.70; N, 4.70; S, 10.75. Found: C, 44.42; H, 2.88; N, 4.74; S, 10.67%.

4.4. Ethyl 2-bromoisonicotinate (13b)

4.4.1. 2-Bromo-4-methylpyridine. To 2-amino-4-methylpyridine (15 g, 0.14 mol) were successively added dropwise at 0°C a 48% solution of HBr (120 mL) and Br_2 (21 mL). A solution of $NaNO_2$ (24 g) in water (35 mL) was then introduced dropwise at 0°C to the mixture. After 3 h, 50% aqueous KOH (200 mL) and Na_2SO_3 (18 g) were successively added. 2-Bromo-4-methylpyridine was distillated with water. Yield (eluent: CH_2Cl_2): 94%; colorless oil; the ^1H and ^{13}C NMR data are in accordance with those of the literature;[18] IR (KBr) ν 3053, 2920, 1592, 1464, 1374, 1119, 1079, 986, 849, 823, 700 cm^{-1}. Anal. Calcd for C_6H_6BrN (172.03): C, 41.89; H, 3.52; N, 8.14. Found: C, 41.59; H, 3.58; N, 8.25%.

4.4.2. 2-Bromoisonicotinic acid. 2-Bromo-4-methylpyridine (18 g, 0.11 mol) was dissolved in water (1 L) and treated with a solution of $KMnO_4$ (33 g, 0.22 mol) in water (500 mL). After 5 h at reflux, the mixture was filtrated. The filtrate was concentrated to 500 mL and acidified with conc. HCl to reach pH 3. The precipitate was filtrated and dried under vacuum. Yield: 31%; mp 240–244°C (lit.[19] mp 245–246°C); the ^1H and ^{13}C NMR data are in accordance with those of the literature;[18] IR (KBr) ν 3102, 2774, 2477, 1852, 1714, 1545, 1454, 1366, 1284, 1228, 1008, 765 cm^{-1}. Anal. Calcd for $C_6H_4BrNO_2$ (202.01): C, 35.68; H, 2.00; N, 6.93. Found: C, 35.38; H, 2.03; N, 6.76%.

4.4.3. Ethyl 2-bromoisonicotinate (13b).[18] A mixture of 2-bromoisonicotinic acid (1.5 g, 7.4 mmol), ethanol (25 mL) and conc. sulfuric acid (0.20 mL) was heated at reflux for 3 h (water was distilled off using a Dean–Stark apparatus) and ethanol was evaporated. CH_2Cl_2 (30 mL) was added to the residue and the resulting mixture was poured onto an aqueous saturated solution of Na_2CO_3 (40 mL). Yield of **13b** (eluent: CH_2Cl_2): 55%; colorless oil; ^1H NMR ($CDCl_3$) δ 1.29 (t, 3H, J=7.2 Hz, CH_3), 4.30 (q, 2H, J=7.2 Hz, CH_2), 7.68 (d, 1H, J=4.9 Hz, H_5), 7.85 (s, 1H, H_3), 8.38 (d, 1H, J=4.9 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 14.4, 62.5, 122.2, 127.9, 140.4, 143.0, 151.1, 163.8; IR (KBr) ν 2983, 1731, 1588, 1549, 1362, 1295, 1261, 1141, 1101, 761, 730 cm^{-1}. Anal. Calcd for $C_8H_8BrNO_2$ (230.06): C, 41.77; H, 3.51; N, 6.09. Found: C, 41.74; H, 3.69; N, 6.35%.

4.4.4. 2-Bromo-5-cyanopyridine (14). Compound **14** was prepared by bromine–magnesium exchange from 2,5-dibromopyridine,[6c] using tosyl cyanide. Yield of **14** (eluent: CH_2Cl_2/Et_2O 80:20): 52%; mp 116–118°C (lit.[20] mp 116–118°C); the ^1H and ^{13}C NMR data are in accordance with those of the literature;[20] Anal. Calcd for $C_6H_3BrN_2$ (183.01): C, 39.38; H, 1.65; N, 15.31. Found: C, 39.22; H, 1.82; N, 15.17%.

4.5. General procedure 1: preparation of phenyl derivatives 2a–h, 4, 5, 7a,b, 9a–c, 10 and 11a,b

$Pd(dba)_2$ (29 mg, 0.050 mmol), dppf (27 mg, 0.050 mmol) and, 10 min later, the halo derivative (1.0 mmol) were added to THF (3 mL). After stirring for 30 min at rt, a solution of PhMgCl (1.2 mmol) in THF (0.60 mL) was added dropwise at −40°C. After stirring under the conditions described in the product description, the mixture was quenched with an aqueous saturated NH_4Cl solution (5 mL).

4.5.1. 2-Phenylpyridine (2a). The general procedure 1 (5 h at rt), starting from **1a**, gave **2a** (eluent: CH_2Cl_2/Et_2O 90:10). Yield: 98%. The physical and spectral data are analogous to those obtained for a commercial sample.

4.5.2. 3-Phenylpyridine (2b). The general procedure 1 (5 h at rt), starting from **1b**, gave **2b** (eluent: CH_2Cl_2/Et_2O 90:10). Yield: 95%. The physical and spectral data are analogous to those obtained for a commercial sample.

4.5.3. 4-Phenylpyridine (2c). The general procedure 1 (5 h at rt), starting from **1c** and using 2.2 mmol of PhMgCl, gave **2c** (eluent: CH_2Cl_2/Et_2O 90:10). Yield: 95%. The physical and spectral data are analogous to those obtained for a commercial sample.

4.5.4. 2-Methyl-6-phenylpyridine (2d). The general procedure 1 (7 h at −5°C), starting from **1d**, gave **2d** (eluent: CH_2Cl_2/Et_2O 90:10). Yield: 96%; pale yellow oil; the ^1H NMR data are in accordance with those of the literature;[21] ^{13}C NMR ($CDCl_3$) δ 24.9, 118.7, 122.3, 129.1 (2C), 129.2, 132.1 (2C), 137.2, 150.3, 157.4, 158.8; IR (KBr) ν 3061, 2957, 2923, 1592, 1573, 1458, 1239, 757, 694 cm^{-1}. Anal. Calcd for $C_{12}H_{11}N$ (169.23): C, 85.17; H, 6.55; N, 8.28. Found: C, 84.79; H, 6.74; N, 8.06%.

4.5.5. 4-Methyl-2-phenylpyridine (2e). The general procedure 1 (18 h at −25°C), starting from **1e**, gave 95% (eluent: CH_2Cl_2/Et_2O 90:10) of **2e**: mp <50°C; the ^1H and ^{13}C NMR data are in accordance with those of the literature;[22] IR (KBr) ν 3057, 1605, 1558, 1446, 827, 776, 736, 695, 590 cm^{-1}. Anal. Calcd for $C_{12}H_{11}N$ (169.23): C, 85.17; H, 6.55; N, 8.28. Found: C, 85.48; H, 6.18; N, 8.04%.

4.5.6. Ethyl 6-phenylnicotinate (2f). The general procedure 1 (6 h at −40°C), starting from **1f**, gave 92% (eluent: CH_2Cl_2/Et_2O 90:10) of **2f**: mp 48–50°C (lit.[23] mp 51–53°C); the ^1H and ^{13}C NMR data are in accordance with those of the literature;[23] IR (KBr) ν 3051, 2982, 1712, 1598, 1284, 1262, 1125, 1017, 748, 691 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_2$ (227.27): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.54; H, 5.76; N, 6.08%.

4.5.7. Ethyl 2-phenylnicotinate (2g). The general procedure 1 (6 h at −40°C), starting from **1g**, gave **2g** (eluent: CH_2Cl_2/Et_2O 90:10). Yield: 42%; pale yellow oil; the ^1H and ^{13}C NMR data are in accordance with those of the literature;[24] IR (KBr) ν 2982, 2937, 1714, 1583, 1562, 1429, 1305, 1283, 1098, 756, 699 cm^{-1}. Anal. Calcd for $C_{14}H_{13}NO_2$ (227.27): C, 73.99; H, 5.77; N, 6.16. Found: C, 73.59; H, 5.66; N, 6.19%.

4.5.8. Ethyl 5-phenylnicotinate (2h). The general procedure 1 (18 h at 0°C and $P(tBu)_3$ (20 mg, 0.10 mmol) instead of dppf), starting from 1 h, gave 73% (eluent: CH_2Cl_2/Et_2O 90:10) of 2 h: mp 68–70°C (lit.[25] mp 68°C); the ^1H NMR and IR data are in accordance with those of the literature;[25] ^{13}C NMR ($CDCl_3$) δ 15.6, 62.0, 128.1 (2C), 128.2, 129.0, 129.6 (2C), 135.6, 146.1, 149.4, 149.6, 151.9, 165.6. Anal. Calcd for $C_{14}H_{13}NO_2$ (227.27): C, 73.99; H, 5.77; N, 6.16. Found: C, 74.13; H, 5.42; N, 6.12%.

4.5.9. Phenyl 6-phenylpyridine-2-sulfone (4). The general procedure 1 (12 h at rt), starting from **3**, gave 71% (eluent: CH_2Cl_2/Et_2O 90:10) of **4**: mp 172–174°C; ^1H NMR ($CDCl_3$) δ 7.36 (m, 2H, $H_{3,5}$), 7.48 (m, 3H, Ph), 7.75 (t, 1H, J=7.7 Hz, H_4), 7.84 (m, 4H, Ph), 8.03 (m, 3H, Ph); ^{13}C NMR ($CDCl_3$) δ 120.2, 123.5, 127.4 (2C), 129.3 (2C), 129.4 (2C), 129.6 (2C), 130.4, 134.1, 137.5, 139.1, 139.3, 158.4, 159.1; IR (KBr) ν 3064, 1582, 1546, 1447, 1322, 1158, 1130, 1087, 765, 729, 692 cm^{-1}. Anal. Calcd for $C_{17}H_{13}NO_2S$ (295.36): C, 69.13; H, 4.44; N, 4.74; S, 10.86. Found: C, 68.86; H, 4.36; N, 4.69; S, 10.69%.

4.5.10. 2-Bromo-6-phenylpyridine (5).[26] The general procedure 1 (12 h at rt and without catalyst), starting from **3**, gave 77% (eluent: CH_2Cl_2/Et_2O 90:10) of **5**: mp 50–52°C; ^1H NMR ($CDCl_3$) δ 7.29 (dd, 1H, J=6.0, 1.1 Hz, H_5), 7.38 (m, 3H, Ph), 7.50 (t, 1H, J=6.0 Hz, H_4), 7.59 (d, 1H, J=6.0, 1.1 Hz, H_3), 7.98 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 119.0, 127.4 (2C), 129.1 (2C), 129.4, 137.9, 139.9, 140.5, 141.3, 157.2. Anal. Calcd for $C_{11}H_8BrN$ (234.10): C, 56.44; H, 3.44; N, 5.98. Found: C, 56.36; H, 3.61; N, 5.69.

4.5.11. 2-Phenylquinoline (7a). The general procedure 1 (5 h at −5°C), starting from **6a**, gave 80% (eluent: CH_2Cl_2/Et_2O 90:10) of **7a**. The physical and spectral data are analogous to those obtained for a commercial sample.

4.5.12. 3-Phenylquinoline (7b). The general procedure 1 (5 h at rt), starting from **6b**, gave 75% (eluent: CH_2Cl_2/Et_2O 90:10) of **7b**. The ^1H and ^{13}C NMR data are in accordance with those of the literature.[27]

4.5.13. 2-Phenylpyrimidine (9a). The general procedure 1 (5 h at rt), starting from **8a**, gave 80% (eluent: CH_2Cl_2/Et_2O 90:10) of **9a**: mp <50°C; the ^1H and ^{13}C NMR data are in accordance with those described in the literature;[28] IR (KBr) ν 3066, 2928, 1567, 1556, 1418, 745, 889 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2$ (156.19): C, 76.90; H, 5.16; N, 17.94. Found: C, 76.63; H, 5.42; N, 17.58%.

4.5.14. 2-Phenylpyrazine (9b). The general procedure 1 (5 h at rt), starting from **8b**, gave 91% (eluent: CH_2Cl_2/Et_2O 90:10) of **9b**: mp 76°C (lit.[29] mp 73°C); the ^1H and ^{13}C NMR data are in accordance with those of the literature;[30] IR (KBr) ν 3050, 1474, 1447, 1409, 1082, 1010, 772, 744, 692 cm^{-1}. Anal. Calcd for $C_{10}H_8N_2$ (156.19): C, 76.90; H, 5.16; N, 17.94. Found: C, 76.78; H, 5.26; N, 18.02%.

4.5.15. 5-Phenylpyrimidine (9c).[31] The general procedure 1 (5 h at rt), starting from **8c**, gave 40% (eluent: CH_2Cl_2/Et_2O 90:10) of **9c**: mp 39–41°C; ^1H NMR ($CDCl_3$) δ 7.08 (m, 3H, Ph), 7.17 (m, 2H, Ph), 7.32 (s, 1H, H_4), 7.41 (s, 1H, H_6), 7.62 (s, 1H, H_2). Anal. Calcd for $C_{10}H_8N_2$ (156.19): C, 76.90; H, 5.16; N, 17.94. Found: C, 76.75; H, 5.20; N, 17.83%.

4.5.16. 2-Chloro-4-phenylpyrimidine (10). The general procedure 1 (8 h at rt, without catalyst and using 5 mmol of PhMgCl), starting from **8**, gave 49% (eluent: CH_2Cl_2) of **10**: mp 88°C (lit.[32] mp 87–89°C); the ^1H and ^{13}C NMR, and IR data are in accordance with those of the literature;[32] Anal. Calcd for $C_{10}H_7ClN_2$ (190.63): C, 63.01; H, 3.70; N, 14.69. Found: C, 63.41; H, 3.55; N, 14.38%.

4.5.17. 4-(2,4,6-Trimethylphenyl)pyridine (11a).[33] The general procedure 1 (5 h at rt), using mesitylmagnesium bromide (2.2 mmol) instead of PhMgCl and starting from **1c**, gave 62% (eluent: CH_2Cl_2/Et_2O 90:10) of **11a**: mp 78–80°C.

4.5.18. 2-Methyl-6-(2,4,6-trimethylphenyl)pyridine (11b). The general procedure 1 (5 h at rt), using mesitylmagnesium bromide instead of PhMgCl and starting from **1d**, gave 51% (eluent: CH_2Cl_2/Et_2O 90:10) of **11b**: mp <50°C; ^1H NMR

($CDCl_3$) δ 1.93 (s, 6H, $2CH_3$), 2.20 (s, 3H, CH_3), 2.50 (s, 3H, CH_3), 6.82 (s, 2H, Ph), 6.94 (d, 1H, J=7.5 Hz, H_3), 7.01 (d, 1H, J=7.5 Hz, H_5), 7.54 (t, 1H, J=7.5 Hz, H_4); ^{13}C NMR ($CDCl_3$) δ 19.1 (2C), 20.0, 23.5, 119.9, 120.5, 127.2 (2C), 134.6, 135.4 (2C), 136.2, 136.9, 157.1, 158.3; IR (KBr) ν 2953, 2921, 2857, 1613, 1587, 1574, 1455, 849, 800, 753 cm^{-1}. Anal. Calcd for $C_{15}H_{17}N$ (211.31): C, 85.26; H, 8.11; N, 6.63. Found: C, 84.97; H, 8.21; N, 6.72%.

4.6. General procedure 2: preparation of phenyl derivatives 15a–k

In a first flask, a solution of *i*PrMgCl (1.2 mmol) in THF (0.6 mL) was added at −40°C to a solution of methyl 4-iodobenzoate (0.31 g, 1.2 mmol) in THF (5 mL). After 40 min at this temperature, 4-(methoxycarbonyl)phenylmagnesium chloride is formed. In a second flask, $Pd(dba)_2$ (29 mg, 0.050 mmol), dppf (27 mg, 0.050 mmol) and, 10 min later, the halo derivative (1.0 mmol) were added to THF (3 mL). After stirring for 30 min at rt, the solution of 4-(methoxycarbonyl)phenylmagnesium chloride was added dropwise at −40°C. After stirring under the conditions described in the product description, the mixture was quenched with an aqueous saturated NH_4Cl solution (5 mL).

4.6.1. Methyl 4-(2-pyridyl)benzoate (15a). The general procedure 2 (5 h at −40°C), starting from **1a**, gave 95% (eluent: CH_2Cl_2/Et_2O 90:10) of **15a**: mp 99–100°C (lit.[34] mp 98°C); the ^1H NMR data are in accordance with those of the literature;[34] ^{13}C NMR ($CDCl_3$) δ 52.6, 121.5, 123.3, 126.8 (2C), 130.4 (2C), 133.3, 137.4, 143.8, 150.2, 156.6, 167.3. Anal. Calcd for $C_{13}H_{11}NO_2$ (213.24): C, 73.23; H, 5.20; N, 6.57. Found: C, 73.49; H, 5.46; N, 6.36%.

4.6.2. Methyl 4-(2-pyrimidyl)benzoate (15b). The general procedure 2 (5 h at −40°C), starting from **8a**, gave 36% (eluent: CH_2Cl_2/Et_2O 90:10) of **15b**: mp 146–148°C; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H, CH_3), 7.16 (t, 1H, J=4.9 Hz, $H_{5'}$), 8.07 (d, 2H, J=8.6 Hz, $H_{2,6}$), 8.44 (d, 2H, J=8.6 Hz, $H_{3,5}$), 8.76 (d, 2H, J=4.9 Hz, $H_{4',6'}$); ^{13}C NMR ($CDCl_3$) δ 52.6, 120.1, 128.5 (2C), 130.2 (2C), 132.3, 142.0, 157.7 (2C), 164.1, 167.2; IR (KBr) ν 2949, 1723, 1563, 1532, 1418, 1114, 817, 758, 698 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_2$ (214.23): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.38; H, 4.75; N, 13.14%.

4.6.3. Methyl 4-(2-pyrazyl)benzoate (15c). The general procedure 2 (5 h at −40°C), starting from **8b**, gave 32% (eluent: CH_2Cl_2/Et_2O 90:10) of **15c**: mp 144–146°C; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H, CH_3), 8.03 (d, 2H, J=8.7 Hz, $H_{2,6}$), 8.10 (d, 2H, J=8.7 Hz, $H_{3,5}$), 8.51 (dd, 1H, J=2.6, 1.5 Hz, $H_{5'}$), 8.60 (d, 1H, J=2.6 Hz, $H_{6'}$), 9.01 (d, 1H, J=1.5 Hz, $H_{3'}$); ^{13}C NMR ($CDCl_3$) δ 53.5, 126.9 (2C), 130.3 (2C), 131.8, 140.4, 142.4, 143.6, 144.4, 151.7, 167.2; IR (KBr) ν 2963, 1720, 1262, 1099, 1017, 700 cm^{-1}. Anal. Calcd for $C_{12}H_{10}N_2O_2$ (214.23): C, 67.28; H, 4.71; N, 13.08. Found: C, 67.54; H, 4.47; N, 12.93%.

4.6.4. Phenyl 6-((4-methoxycarbonyl)phenyl)pyridine-2-sulfone (15d). The general procedure 2 (18 h at −5°C), starting from **3**, gave 32% (eluent: CH_2Cl_2/Et_2O 90:10) of **15d**: mp 180°C; ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H, CH_3), 7.46 (m, 3H, $H_{3,5}$, Ph), 7.78 (t, 1H, J=7.9 Hz, H_4), 7.87 (m, 3H, Ph), 7.98 (m, 3H, Ph), 8.04 (m, 2H, Ph); ^{13}C NMR ($CDCl_3$) δ 51.2, 119.5, 122.6, 126.0, 128.1, 128.2, 129.0, 130.2, 132.9, 137.6, 138.1, 139.9, 155.6, 157.7, 165.5; IR (KBr) ν 3072, 1716, 1585, 1440, 1278, 1120, 771, 688, 594 cm^{-1}. Anal. Calcd for $C_{19}H_{15}NO_4S$ (353.40): C, 64.58; H, 4.28; N, 3.96; S, 9.07. Found: C, 64.89; H, 3.95; N, 3.94; S, 8.80%.

4.6.5. Methyl 4-(5-bromo-2-pyridyl)benzoate (15e). The general procedure 2 (7 h at −15°C), starting from **12a**, gave 32% (eluent: CH_2Cl_2/Et_2O 90:10) of **15e**: mp 158°C; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H, CH_3), 7.62 (d, 1H, J=8.4 Hz, $H_{3'}$), 7.84 (dd, 1H, J=8.4, 2.5 Hz, $H_{4'}$), 8.00 (2d, 4H, J=6.9 Hz, Ph), 8.66 (d, 1H, J=2.5 Hz, $H_{6'}$); ^{13}C NMR ($CDCl_3$) δ 25.3, 120.6, 122.4, 127.1 (2C), 130.5 (2C), 134.6, 141.4, 142.7, 151.3, 155.0, 167.1; IR (KBr) ν 2943, 1719, 1437, 1281, 1110, 1098, 1004, 828, 779, 741 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrNO_2$ (292.13): C, 53.45; H, 3.45; N, 4.79. Found: C, 53.42; H, 3.44; N, 4.49%.

4.6.6. Methyl 4-(6-bromo-2-pyridyl)benzoate (15f). The general procedure 2 (7 h at −15°C), starting from **12b**, gave 25% (eluent: CH_2Cl_2/Et_2O 90:10) of **15f**: mp 145–150°C; ^1H NMR ($CDCl_3$) δ 3.86 (s, 3H, CH_3), 7.37 (d, 1H, J=7.5 Hz, $H_{3'}$), 7.54 (t, 1H, J=7.5 Hz, $H_{4'}$), 7.65 (d, 1H, J=7.5 Hz, $H_{5'}$), 8.01 (2d, 4H, J=8.6 Hz, Ph); ^{13}C NMR ($CDCl_3$) δ 52.6, 119.9, 127.6, 128.6 (2C), 130.4 (2C), 131.8, 139.5, 142.0, 142.7, 157.6, 167.1; IR (KBr) ν 2958, 2928, 1722, 1579, 1550, 1431, 1280, 1109, 768 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrNO_2$ (292.13): C, 53.45; H, 3.45; N, 4.79. Found: C, 53.75; H, 3.79; N, 4.49%.

4.6.7. Methyl 4-(5-bromo-3-pyridyl)benzoate (15g). The general procedure 2 (18 h at −5°C and $P(tBu)_3$ (20 mg, 0.10 mmol) instead of dppf), starting from **12c**, gave 62% (eluent: CH_2Cl_2/Et_2O 90:10) of **15g**: mp 260–262°C; ^1H NMR ($CDCl_3$) δ 3.96 (s, 3H, CH_3), 7.74 (d, 2H, J=7.9 Hz, Ph), 8.16 (s, 1H, $H_{4'}$), 8.25 (d, 2H, J=7.9 Hz, Ph), 8.96 (s, 1H, $H_{2'}$), 8.97 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$) δ 52.7, 121.1, 125.7, 128.1 (2C), 130.1 (2C), 131.1, 138.8, 142.5, 151.4, 160.0, 166.8; IR (KBr) ν 3015, 2958, 1721, 1608, 1433, 1283, 1192, 1109, 856, 770, 703 cm^{-1}. Anal. Calcd for $C_{13}H_{10}BrNO_2$ (292.13): C, 53.45; H, 3.45; N, 4.79. Found: C, 53.48; H, 3.59; N, 4.82%.

4.6.8. Ethyl 6-(4-(methoxycarbonyl)phenyl)nicotinate (15h). The general procedure 2 (6 h at −40°C), starting from **13a**, gave 95% (eluent: CH_2Cl_2/Et_2O 90:10) of **15h**: mp 116–117°C; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, J=7.1 Hz, CH_3), 3.91 (s, 3H, OCH_3), 4.40 (q, 2H, J=7.1 Hz, CH_2), 7.79 (d, 1H, J=7.9 Hz, H_5), 8.08 (s, 4H, Ph), 8.32 (d, 1H, J=7.9 Hz, H_4), 9.95 (s, 1H, H_2); ^{13}C NMR ($CDCl_3$) δ 14.9, 52.9, 62.1, 121.1, 125.7, 128.1 (2C), 130.1 (2C), 131.1, 138.8, 142.5, 151.4, 160.0, 166.8, 167.1; IR (KBr) ν 2982, 2981, 1731, 1710, 1595, 1439, 1371, 1284, 1117, 756 cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_4$ (285.30): C, 67.36; H, 5.30; N, 4.91. Found: C, 67.79; H, 5.41; N, 4.86%.

4.6.9. Ethyl 2-(4-(methoxycarbonyl)phenyl)isonicotinate (15i). The general procedure 2 (4 h at −20°C), starting from **13b**, gave 90% (eluent: CH_2Cl_2/Et_2O 90:10) of **15i**: mp 66°C; ^1H NMR ($CDCl_3$) δ 1.35 (t, 3H, J=7.2 Hz, CH_3), 3.93 (s, 3H, OCH_3), 4.38 (q, 2H, J=7.2 Hz, CH_2), 7.73 (d, 1H, J=4.9 Hz, H_5), 8.06 (s, 4H, Ph), 8.25 (s, 1H, H_3), 8.78

(d, 1H, J=4.9 Hz, H_6); ^{13}C NMR ($CDCl_3$) δ 14.6, 52.6, 62.4, 120.5, 122.3, 127.3 (2C), 130.5 (2C), 131.1, 139.1, 142.9, 150.9, 157.5, 165.4, 167.1; IR (KBr) ν 3063, 1726, 1599, 1390, 1292, 1275, 1111 cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_4$ (285.30): C, 67.36; H, 5.30; N, 4.91. Found: C, 67.33; H, 5.27; N, 4.71%.

4.6.10. Methyl 4-(5-cyano-2-pyridyl)benzoate (15j). The general procedure 2 (6 h at −40°C), starting from **14**, gave 86% (eluent: CH_2Cl_2/Et_2O 90:10) of **15j**: mp 162°C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H, CH_3), 7.92 (d, 1H, J= 7.8 Hz, $H_{3'}$), 8.07 (d, 1H, J=7.8 Hz, $H_{4'}$), 8.16 (m, 4H, Ph), 9.00 (s, 1H, $H_{6'}$); ^{13}C NMR ($CDCl_3$) δ 52.8, 116.2, 120.9, 127.7 (2C), 128.4, 130.6 (2C), 132.7, 138.7, 140.5, 152.9, 157.3, 163.8; IR (KBr) ν 3015, 2959, 2240, 1720, 1438, 1274, 1112, 1108, 835, 749 cm^{-1}. Anal. Calcd for $C_{14}H_{10}N_2O_2$ (238.25): C, 70.58; H, 4.23; N, 11.76. Found: C, 70.27; H, 4.67; N, 11.49%.

4.6.11. Ethyl 5-(4-(methoxycarbonyl)phenyl)nicotinate (15k). The general procedure 2 (18 h at 0°C and P(tBu)$_3$ (20 mg, 0.10 mmol) instead of dppf), starting from **1h**, gave 63% (eluent: CH_2Cl_2/Et_2O 90:10) of **15k**: mp 98–100°C; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 3H, J=7.2 Hz, CH_3), 3.89 (s, 3H, OCH_3), 4.40 (q, 2H, J=7.2 Hz, CH_2), 7.69 (m, 2H, Ph), 8.10 (m, 2H, Ph), 8.44 (t, 1H, J=1.9 Hz, H_4), 8.96 (d, 1H, J=1.9 Hz, H_6), 9.17 (d, 1H, J=1.9 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 13.3, 51.3, 60.9, 125.4, 126.2 (2C), 129.2, 129.4 (2C), 134.4, 140.0, 142.3, 149.1, 150.7, 164.1, 165.6; IR (KBr) ν 3036, 2956, 1933, 1720,1718, 1439, 1276, 1255, 1171, 854, 762 cm^{-1}. Anal. Calcd for $C_{16}H_{15}NO_4$ (285.30): C, 67.36; H, 5.30; N, 4.91. Found: C, 67.77; H, 5.67; N, 4.81%.

4.7. General procedure 3: preparation of phenyl derivatives 16

In a first flask, a solution of iPrMgCl (1.2 mmol) in THF (0.6 mL) was added at −40°C to a solution of 1-cyano-4-iodobenzene (0.27 g, 1.2 mmol) in THF (5 mL). After 1 h at this temperature, 4-cyanophenylmagnesium chloride is formed. In a second flask, Pd(dba)$_2$ (29 mg, 0.050 mmol), dppf (27 mg, 0.050 mmol) and, 10 min later, the halo derivative (1.0 mmol) were added to THF (3 mL). After stirring for 30 min at rt, the solution of 4-cyanophenylmagnesium chloride was added dropwise at −40°C. After 6 h at −40°C, the mixture was quenched with an aqueous saturated NH_4Cl solution (5 mL).

4.7.1. Ethyl 6-(4-cyanophenyl)nicotinate (16). The general procedure 3, starting from **1f**, gave 87% (eluent: CH_2Cl_2/Et_2O 90:10) of **16**: mp 120–124°C; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, 3H, J=7.2 Hz, CH_3), 4.38 (q, 2H, J=7.2 Hz, CH_2), 7.73 (d, 2H, J=6.1 Hz, $H_{2',6'}$), 7.79 (d, 1H, J=7.4 Hz, H_5), 8.12 (d, 2H, J=6.1 Hz, $H_{3',5'}$), 8.33 (dd, 1H, J=7.4, 2.1 Hz, H_4), 9.24 (d, 1H, J=2.1 Hz, H_2); ^{13}C NMR ($CDCl_3$) δ 13.3, 60.6, 112.3, 117.3, 119.3, 124.6, 126.9 (2C), 131.7 (2C), 137.2, 141.3, 150.2, 157.4, 164.0; IR (KBr) ν 2963, 2223, 1713, 1593, 1287, 1264, 1120, 1023, 782 cm^{-1}. Anal. Calcd for $C_{15}H_{12}N_2O_2$ (252.28): C, 71.42; H, 4.79; N, 11.10. Found: C, 71.25; H, 4.88; N, 10.98%.

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