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Straightforward and efficient synthesis of 3-benzyloxy-4-bromopicolinate ester and 3-benzyloxy-5-bromopicolinate ester, common building blocks for pharmaceuticals and agrochemicals

Tristan Verdelet [a,b,†], Guillaume Mercey [a,b,†], Nobi Correa [a,b], Ludovic Jean [a,b], Pierre-Yves Renard [a,b,c,*]

[a] Equipe de Chimie Bio-Organique, COBRA-CNRS UMR 6014 & FR 3038, rue Lucien Tesnière, 76131 Mont-Saint-Aignan, France
[b] Université de Rouen, Place Emile Blondel, 76821 Mont-Saint-Aignan, France
[c] Institut Universitaire de France, 103 boulevard Saint Michel, 75005 Paris, France

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ABSTRACT

A practical and rapid preparation of 3-benzyloxy-4-bromo and 3-benzyloxy-5-bromopicolinate esters **10** and **16** was developed in four steps, respectively, in 38% and 31% overall yield. Then their viability as partners for cross-coupling reactions has been evaluated in Suzuki–Miyaura, Hartwig–Buchwald, and Sonogashira reactions to synthesize biologically relevant targets. The preparation of these two highly functionalizable pyridines **10** and **16** has been never described to date in the literature and could be used as common building block for the preparation of several biologically active compounds or agrochemical products.

1. Introduction

3-Alkoxy-6-bromopicolinate esters **1** are building block widely used in the preparation of several biologically active compounds[1–5] and agrochemical products[6] (Fig. 1). While syntheses of **1** are reported in several patents,[1–5] no preparation of 3-alkoxy-4-bromopicolinate esters **2** and 3-alkoxy-5-bromopicolinate esters **3** have been described to date. However, 3-alkoxy-4-bromopicolinate esters **2** and derivatives could be very useful for synthesis of HIF activity modulators,[7] modulators for the treatment of asthma and chronic obstructive pulmonary disease,[8] propyl hydrolase inhibitors[9] and fungicides,[10] and 3-alkoxy-5-bromopicolinate esters **3** could be key intermediates in the preparation of compounds, such as pesticides,[11] HIV integrase inhibitors,[12] antidiabetic drugs,[13] antiulcer agents,[14] and β-secretase inhibitors for the treatment of neurological disorders.[15]

All compounds listed above have been prepared from different pyridine derivatives (e.g., picolinic acid, 3,5-dichloro-2-cyanopyridine, 5-bromo-2-cyano-3-nitropyridine or 3-methoxy-4-nitropyridine *N*-oxide), requiring a new synthetic route for each targeted compound. Therefore, it would be very interesting to develop a practical and rapid synthetic pathway to access to esters **10** and **16**, which could be considered as common building blocks for the drug discovery process and elaboration of new agrochemicals compounds. Herein, the synthesis of **10** and **16** in four steps from 3-hydroxypicolinic acid and 2-amino-3-benzyloxypyridine, respectively, and their evaluation as partner in cross-coupling reactions, in order to access to the scaffold of biologically active compounds, are described.

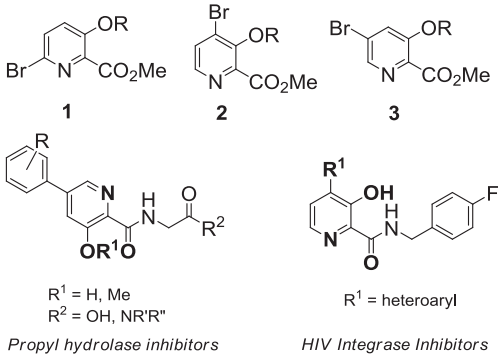

Fig. 1. Structures of 3-alkoxy-bromopicolinates esters and examples of structures of pharmaceuticals products.

* Corresponding author. Tel.: +33 2 35 52 24 14; fax: +33 2 35 52 29 59; e-mail addresses: ludovic.jean@univ-rouen.fr (L. Jean), pierre-yves.renard@univ-rouen.fr (P.-Y. Renard).
† These authors contributed equally to this work.

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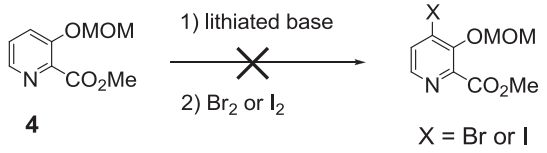
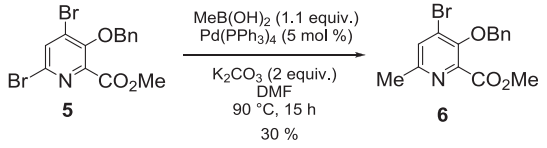
2. Results and discussion

Aiming at the rapid preparation of the desired ester **2**, we firstly evaluated directed *ortho*-lithiation of 3-(methoxymethyl)picolinate ester **4**, followed by a treatment with bromine or iodide, which appeared to be the most expedient way to synthesize this ester. Yet, unexpectedly, whichever lithiated base we used, these attempts led to a mixture of products of degradation or an intermolecular addition of the resulting organolithium on ester function (Scheme 1).



Scheme 1. Attempts to access 4-halogenopicolinate esters from ester **4**.

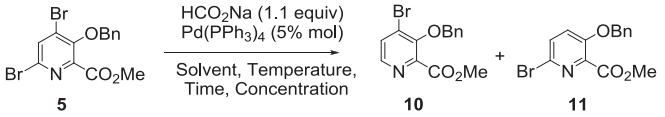
In order to obtain targeted brominated compound **2**, we took advantage of the high selectivities observed for the electrophilic bromination of 3-hydroxypicolinate esters. The first bromination very efficiently takes place at the 6 position, thanks to the directing effect of the phenol then ensuring the easy access to **1** (R=H). Addition of excess bromine cleanly leads to dibrominated product,[6,12] with the second bromination selectively taking place at position 4, which after alkylation with benzyl bromide, gives **5** (we also tested an alternative route to access to the desired 5-bromo-4-chloro-3-methoxypicolinic acid from the maltol,[16] but contrary to the described procedure, we obtained the desired product only in very low yield). From this dibrominated product, we were pleased to observe a regioselective insertion of palladium species into the C–Br bond in position 6 of pyridine **5**. Indeed, a cross-coupling reaction, realized between **5** and methyl boronic acid, gave selectively 3-benzyloxy-4-bromo-6-methylpicolinate ester **6** in 30% isolated yield with only starting material remaining (Scheme 2). Thus, we decided to take advantage of this reactivity in order to prepare **2** from **5** by using a selective Pd-catalyzed dehalogenation.[17]



Scheme 2. Regioselective Suzuki cross-coupling reaction of **5** with methyl boronic acid.

This last step needed optimized conditions to reach a good conversion and to obtain selectively the desired pyridine **10** (benzylated form of **2**) (Table 1). Firstly, the reaction of dehalogenation was carried out in methanol at 65 °C. In a concentration of 0.025 M (Table 1, entries 1–3), the conversion was low (36%) after 2 days refluxing, yet the reaction proved selective, since no trace of bis dehalogenated product neither of the other regioisomer **11** was observed. Eventually, the desired pyridine **10** was obtained in only 35% isolated yield after a reaction time of 72 h and at higher concentration (entry 4). Moreover, increasing the reaction time ended up in the degradation of both substrate and product. Using DMF as solvent, the conversion was dramatically increased (entry 5). However, the selectivity of this dehalogenation reaction was lower, leading to a mixture of **10** and **11** in these conditions. We then investigated the effect of concentration and we were pleased to notice that the selectivity and the conversion were enhanced by increasing the reaction concentration. Indeed, **10** was obtained in 70% isolated yield with a concentration of 50 mg/mL (entry 6). However, at higher concentration (entries 7 and 8), further degradation of products was also observed. Finally, therefore, the best reaction conditions to obtain **10** involves **5** (1 equiv), sodium formate (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %) in DMF heated at 80 °C for 20 h with a concentration of 0.125 M (entry 6).

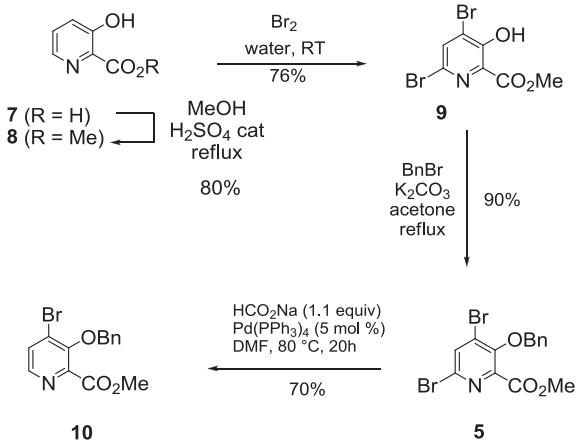
Table 1
Selective dehalogenation of **5**



Entry	Solvent	Time (h)	T (°C)	Concentration[a]	Conversion[b] (%)		
					5	**10**	**11**
1	MeOH	3	65	0.025	97	2	0
2	MeOH	24	65	0.025	70	26	0
3	MeOH	48	65	0.025	40	36	0
4	MeOH	72	65	0.1	30	42 (35)	0
5	DMF	20	80	0.05	13	51	27
6	DMF	20	80	0.125	0	73 (70)	17
7	DMF	20	80	0.25	0	68	14
8	DMF	20	80	0.5	0	50	21

[a] Concentration of **5** in mol/L.
[b] Determined by analysis of ^{1}H NMR spectra of crude material. In parentheses are given the isolated yields.

In summary, 3-benzyloxy-4-dibromopicolinate ester **10** has been synthesized in four steps from commercially available 3-hydropicolinic acid **7** (Scheme 3). The first step consisted in the esterification of carboxylic acid with methanol to afford ester **8** in 80% yield.[18] Then electrophilic bromination in positions 4 and 6 of the pyridine was performed in 76% yield. Phenol **9** was protected using benzyl bromide and K_2CO_3 as a base to give **5** in 90% yield. Finally treatment of **5** with sodium formate in presence of catalytic amount of $Pd(PPh_3)_4$ (5 mol %) gave desired ester **10** in 70% isolated yield.

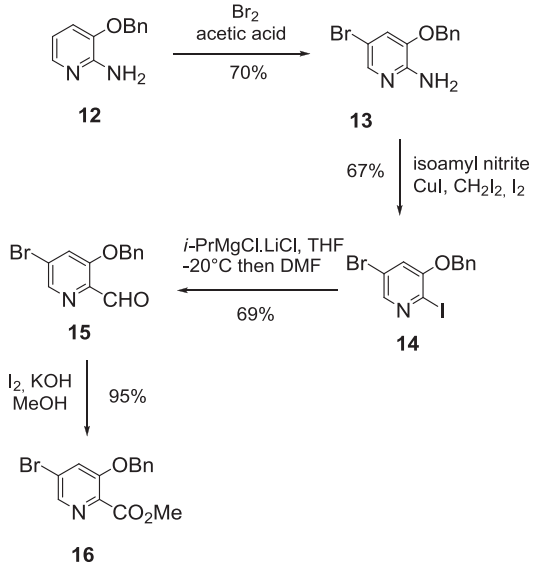


Scheme 3. Synthesis of methyl 4-bromopicolinate ester **10**.

Altogether, **10** was obtained in four steps in 38% overall yield from commercially available 3-hydroxypicolinic acid **7**.

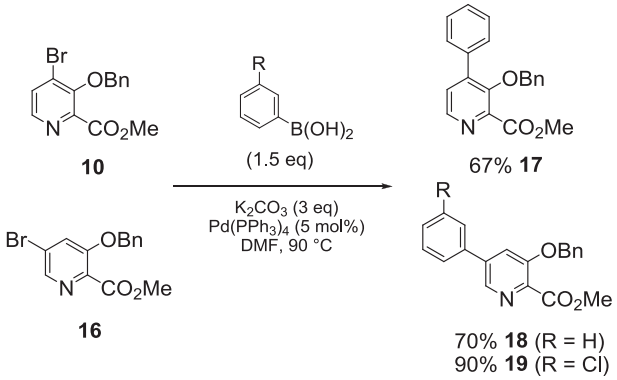
In order to access rapidly and efficiently to the 5-bromopicolinate ester **16**, the regioselectivity of the electrophilic bromination had to be reversed, thus we chose to start from commercially available 2-amino-3-benzyloxypyridine **12** (Scheme 4). The amino function in position 2 was expected to control the electrophilic bromination in position 5. Indeed, electrophilic bromination[19] gave a complete regioselectivity, and brominated derivative **13** was obtained in 70% yield. Treatment of **13** with isoamyl nitrite, iodine, and copper iodide in 1,2-diiodomethane gave desired dihalogenated product **14** in 67% yield. Used as solvent, 1,2-

diiodomethane is quite expensive and we attempted to replace it by 1,2-dichloroethane. Unexpectedly, in the same reaction conditions, a 1/1 mixture of 3-benzyloxy-5-bromo-2-iodopyridine **11** and 3-benzyloxy-5-bromo-2-chloropyridine was obtained. Finally, a straightforward sequence comprising a selective magnesium–halogen exchange,[20] addition of the resulting Grignard reagent to dimethylformamide, and oxidation of the resulting aldehyde **15** with iodide in presence of potassium hydroxide in methanol gave the desired bromopicolinate ester **16** in 65% yield.[21] Attempts to form directly methyl ester **16** by quenching the resulting Grignard reagent with methyl chloroformate or methyl cyanoformate failed.



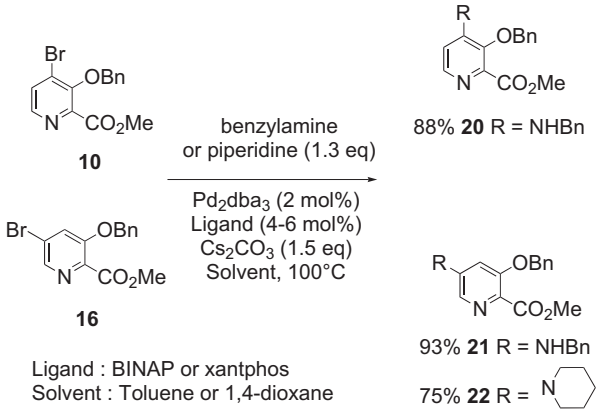
Scheme 4. Synthesis of methyl 5-bromopicolinate **16**.

In order to evaluate the functionalization of 3-benzyloxy-4-bromo and 3-benzyloxy-5-bromopicolinate esters **10** and **16**, the scopes and limitations of cross-coupling reactions using these brominated pyridines have been evaluated. Firstly, Suzuki–Miyaura reactions between bromo-pyridines **10** and **16** and arylboronic acids have been carried out in good yields and allowed to access to the scaffold of propyl hydrolase inhibitors (Scheme 5).[9]



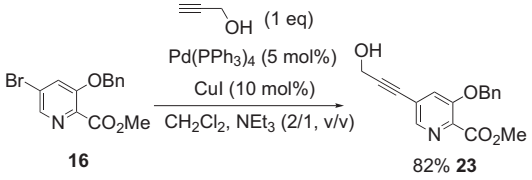
Scheme 5. Suzuki–Miyaura reactions.

The 4-amino-3-hydroxypicolinic acid and derivatives are also very useful for the preparation agrochemical (e.g., fungicides[10]) or pharmaceutical (e.g., modulators of CXCR-2 receptor for the treatment of asthma[8]), whereas 5-amino-3-hydroxypicolinic acid and derivatives are monoamine oxidase (MAO-B) inhibitors for the treatment of obesity.[22] Therefore, bromo-pyridines **10** and **16** have also been evaluated as partner in Hartwig–Buchwald reactions (Scheme 6). The cross-coupling reaction with benzylamine gave different results depending on the catalyst and solvent used. Concerning the amination with a primary amine, after optimization, synthesis of **20** was obtained in 88% yield using Pd_2dba_3/xantphos in toluene, whereas **21** was obtained in 93% yield using Pd_2dba_3/BINAP in 1,4-dioxane. For amination reactions with a secondary amine (e.g., piperidine), the results were dependent on the bromopyridine used. The reaction with **16** using Pd_2dba_3/xantphos in toluene gave **22** in a satisfactory 75% yield, while the cross-coupling reaction with **10** was carried out in low yield (less than 25%) whatever the conditions used, probably due to a problem of steric hindrance.



Scheme 6. Pd-catalyzed aminations.

Finally, bromo-pyridines **10** and **16** have been tested as partner in Sonogashira reaction with propargyl alcohol. The reaction with **16** gave the desired product **23** in 82% yield (Scheme 7), while the reaction with **10** failed even using harsher conditions (DMF, 60 °C).



Scheme 7. Sonogashira reaction.

3. Conclusion

We described a practical and efficient preparation of methyl 3-(benzyloxy)-4-bromopiconinate ester **10** in four steps in 38% overall yield and methyl 3-(benzyloxy)-5-bromopiconinate ester **16** in four steps in 31% overall yield. As reported above, the preparation of these pyridines **10** and **16** have been never described to date in the literature and we have demonstrated that these compounds are highly functionalizable using cross-coupling reactions and are useful for the preparation of several biologically active compounds or agrochemical products.

4. Experimental section

4.1. General

Column chromatography purifications were performed on silica gel (40–63 μm) from Merck. Thin-layer chromatography (TLC) was carried out on Merck DC Kieselgel 60 F_{254} aluminum sheets.

Compounds were visualized by one of the two following methods: (1) illumination with a short wavelength UV lamp (λ=254 nm) or (2) staining with a 3.5% (w/v) phosphomolybdic acid solution in absolute ethanol. All commercially available reagents and solvents were purchased and used without further purification, except THF, which was dried by distillation over Na/benzophenone.

Melting points were recorded on a LEICA VMHB Kofler system at atmospheric pressure and were uncorrected. Microanalyses were carried out on Carlo-Erba 1106. Infrared spectra were recorded as KBr pellets using a Perkin–Elmer FT-IR Paragon 500 spectrometer with frequencies given in reciprocal centimeters (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX 300 spectrometer (Bruker, Wissembourg, France). Chemical shifts are expressed in parts per million (ppm) from $CDCl_3$ (δ_H=7.26, δ_C=77.16).[23] *J* values are expressed in hertz. Mass spectra were obtained with a Finnigan LCQ Advantage MAX (ion trap) apparatus equipped with an electrospray source. All analyses were performed in the positive mode.

4.1.1. Methyl 3-benzyloxy-4-bromo-6-methylpicolinate ***6***. To a degassed solution of **5** (0.60 g, 1.5 mmol) in DMF (10 mL) were added successively $MeB(OH)_2$ (200 mg, 2.2 equiv) and $Pd(PPh_3)_4$ (87 mg, 0.05 equiv). The mixture was stirred for 20 h at 90 °C. DMF was removed in vacuum and the resulting mixture was absorbed on silica gel and purified by flash chromatography (cyclohexane/EtOAc 8/2, v/v) to give **6** (152 mg, 30%) as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 2.57 (s, 3H), 3.92 (s, 3H), 5.11 (s, 2H), 7.32–7.42 (m, 3H), 7.50–7.56 (m, 2H), 7.57 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.7, 53.1, 76.7, 127.0, 127.6, 128.6, 129.9, 130.8, 126.0, 144.6, 150.0, 154.9, 164.8. MS (ESI^+) *m*/*z*: 338 (90), 336 (100). HRMS (ESI^+): calcd for $C_{15}H_{15}BrNO_3$ 336.0235; found 336.0233.

4.1.2. Methyl 3-hydroxypicolinate ***8***. H_2SO_4 (1.8 mL, 3 equiv) was added dropwise to a suspension of 3-hydroxypicolinic acid **7** (1.5 g, 10.5 mmol) in MeOH (24 mL). The mixture was refluxed for 24 h. Then, the mixture was basified with a solution of K_2CO_3 (pH 8.5). The aqueous layer was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to give desired methyl ester **8** (1.28 g, 80%) as a white solid. ^1H and ^{13}C NMR data were in agreement with those given in the literature.[18]

4.1.3. Methyl 4,6-dibromo-3-hydroxypicolinate ***9***. At room temperature, Br_2 (2.7 mL, 3 equiv) was added to a suspension of methyl ester **8** (2.7 g, 6.5 mmol) in water (200 mL). The mixture was stirred for 20 h at room temperature. The solution was extracted with dichloromethane, and the organic layer was washed with an aqueous solution of sodium thiosulfate, with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give desired compound **9** (4.0 g, 76%) as a white powder. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 4.06 (s, 3H), 7.86 (s, 1H), 11.35 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.9, 124.7, 129.9, 130.2, 136.9, 156.0, 168.8. MS (ESI^-) *m*/*z*: 312 (40), 310 (100), 308 (45).

4.1.4. Methyl 3-benzyloxy-4,6-dibromobenzylpicolinate ***5***. Benzyl bromide (1.2 mL, 3 equiv) was slowly added to a mixture of **9** (1.0 g, 3.2 mmol) and K_2CO_3 (2.0 g, 4.5 equiv) in acetone (40 mL). The reaction mixture was refluxed for 18 h. The resulting mixture was filtered and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/EtOAc 9/1, v/v) gave **5** (1.2 g, 90%) as a white solid. Mp 74 °C. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.92 (s, 3H), 5.13 (s, 2H), 7.35–7.44 (m, 3H), 7.49–7.53 (m, 2H), 7.88 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.3, 77.0, 128.6, 128.7, 128.8, 131.9, 134.9, 135.4, 135.5, 145.3, 151.9, 163.3. MS (ESI^+) *m*/*z* (%): 404 (65), 402 (100), 400 (60). Anal. Calcd for $C_{14}H_{11}Br_2NO_3$: C, 41.93; H, 2.76; N, 3.49. Found: C, 41.95; H, 2.81; N, 3.21.

4.1.5. Methyl 3-benzyloxy-4-bromobenzylpicolinate ***10***. $Pd(PPh_3)_4$ (140 mg, 0.05 equiv) was added to a degassed solution of **5** (1.0 g, 2.5 mmol) and sodium formate (190 mg, 1.1 equiv) in DMF (20 mL, 50 g/L). The mixture was stirred for 20 h at 80 °C. DMF was removed under vacuum and the crude mixture was directly absorbed on silica gel and purified by flash chromatography (cyclohexane/EtOAc 7/3, v/v) to give **10** (560 mg, 70%) as a beige solid. R_f=0.3 (cyclohexane/EtOAc 7/3, v/v). Mp 78 °C. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.95 (s, 3H), 5.16 (s, 2H), 7.36–7.45 (m, 3H), 7.53–7.56 (m, 2H), 7.71 (d, *J*=5.1 Hz, 1H), 8.27 (d, *J*=5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.1, 76.8, 128.5, 128.6, 128.7, 130.1, 131.3, 135.9, 145.3, 145.4, 152.5, 164.4. MS (ESI^+) *m*/*z* (%): 324 (95), 322 (100). Anal. Calcd for $C_{14}H_{12}BrNO_3$: C, 52.20; H, 3.75; N, 4.35. Found: C, 52.33; H, 3.89; N, 3.81.

4.1.6. 3-Benzyloxy-5-bromopyridin-2-ylamine ***13***. Sulfuric acid (10%, 160 mL) was introduced in a three necked flask equipped with mechanical stirrer. 3-Benzyloxypyridi-2-ylamine **12** (8 g, 40 mmol) was added at room temperature under efficient stirring. The reaction mixture was cooled at 0 °C, where a mixture of Br_2 (7.68 g, 48.1 mmol) in acetic acid (25 mL) was added dropwise over a period of 35 min. The resulting mixture was stirred for 3 h at 0 °C. Then, ice water (160 mL) was added and the solution was basified by addition of 30% aqueous ammonia solution. The aqueous phase was extracted with CH_2Cl_2 (thrice). Combined organic layers were washed with water, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cyclohexane/EtOAc 8/2, v/v) afforded **13** (8 g, 70%) as a yellow/orange solid. ^1H NMR (300 MHz, $CDCl_3$) δ 4.71 (br s, 2H), 5.05 (s, 2H), 7.08 (d, *J*=1.87 Hz, 1H), 7.37–7.42 (m, 5H), 7.73 (d, *J*=1.87 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.7, 107.0, 119.6, 127.8, 128.7, 128.9, 135.6, 135.6, 139.3, 141.9, 149.1. MS (ESI^+) *m*/*z* (%): 281 (98), 279 (100).

4.1.7. 3-Benzyloxy-5-bromo-2-iodopyridine ***14***. To a solution of 3-benzyloxy-5-bromopyridin-2-amine **13** (3 g, 10.4 mmol), CuI (2 g, 10.4 mmol), and I_2 (2.65 g, 10.4 mmol) in CH_2I_2 (50 mL), isoamyl nitrite (4.3 mL, 31.2 mmol) was added at 85 °C. The resulting mixture was stirred at 85 °C for 10 min. After cooling, the reaction mixture was absorbed on silica gel and purified by flash chromatography (cyclohexane/EtOAc 100/0 to 90/10, v/v) to afford the desired product **14** as a white solid (2.73 g, 67%). Mp 112–113 °C ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (s, 2H), 7.15 (d, *J*=2.00 Hz, 1H), 7.34–7.49 (m, 5H), 8.10 (d, *J*=2.00 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.4, 110.1, 120.4, 121.5, 127.2, 128.6, 129.0, 134.9, 143.7, 154.8. MS (ESI^+) *m*/*z* (%): 392 (98), 390 (100). Anal. Calcd for $C_{12}H_9BrINO$: C, 36.95; H, 2.33; N, 3.59. Found: C, 36.88; H, 2.24; N, 3.33.

4.1.8. 3-Benzyloxy-5-bromopicolinaldehyde ***15***. To a solution of **14** (2.7 g, 6.94 mmol) in dry THF (70 mL) *i*-PrMgCl·LiCl (5.6 mL, 1.3 M in THF, 7.30 mmol) was added dropwise at −20 °C. The resulting mixture was stirred at −20 °C for 1 h and dry DMF (800 μL, 10.40 mmol) was added dropwise. After stirring for additional 30 min at −20 °C, the cool bath was removed and the reaction mixture was allowed to warm at room temperature. The reaction was quenched with a saturated aqueous solution of NH_4Cl. The phases were separated, the aqueous layer was extracted with EtOAc (twice) and the organic layer was washed with brine. The combined organic layers were dried over $MgSO_4$, and concentrated under reduced pressure. Purification by flash chromatography on silica gel (cylclohexane/EtOAc 9/1, v/v) afforded aldehyde **15** as an yellow solid (1.4 g, 69%). ^1H NMR (300 MHz, $CDCl_3$) δ 5.22 (s, 2H), 7.36–7.47 (m, 5H), 7.63 (d, *J*=1.70 Hz, 1H), 8.44 (d, *J*=1.70 Hz, 1H), 10.35 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.1, 124.6, 126.1, 127.3, 128.8, 129, 134.7,

139.8, 143.6, 157.0, 189.2. MS (ESI^+) *m/z* (%): 294 (98), 292 (100). HRMS (ESI^+): calcd for $C_{13}H_{11}BrNO_2$ 291.9973; found 291.9969.

4.1.9. Methyl 3-benzyloxy-5-bromopicolinate ***16***. To a solution of aldehyde **15** (0.81 g, 2.76 mmol) in methanol (15 mL) at 0 °C a methanolic solution of potassium hydroxide (0.53 g, 9.38 mmol, 5 mL) and iodine (1.19 g, 4.69 mmol, 10 mL) was added dropwise. The reaction mixture was stirred at 0 °C and monitored by ^1H NMR spectroscopy for completion. Then the reaction was quenched with a 30% aqueous sodium bisulfite solution until the brown color disappeared. The product was extracted twice with CH_2Cl_2, the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (cyclohexane/EtOAc 9/1, v/v) to afford **16** as a white solid (0.846 g, 95%). Mp 110–111 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 3H), 5.18 (s, 2H), 7.33–7.47 (m, 5H), 7.53 (d, *J*=1.75 Hz, 1H), 8.33 (d, *J*=1.75 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.8, 71.1, 123.9, 124.6, 127.0, 128.4, 128.9, 135.1, 137.3, 142.3, 155.0, 164.5. MS (ESI^+) *m/z* (%): 324 (99), 322 (100). Anal. Calcd for $C_{14}H_{12}BrNO_3$: C, 52.20; H, 3.75; N, 4.35. Found: C, 52.18; H, 3.73; N, 4.38.

4.1.10. Methyl 3-benzyloxy-4-phenylpicolinate ***17***. $Pd(PPh_3)_4$ (16 mg, 5 mol %) was added to a degassed solution of **10** (90 mg, 0.28 mmol), phenylboronic acid (51 mg, 1.5 equiv), and K_2CO_3 (116 mg, 3 equiv) in DMF (2 mL). The mixture was stirred for 20 h at 90 °C. DMF was removed under vacuum and the crude mixture was directly absorbed on silica gel and purified by flash chromatography (cyclohexane/EtOAc 7/3, v/v) to give **17** (60 mg, 67%) as a white solid. R_f=0.3 (cyclohexane/EtOAc 7/3, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 3.87 (s, 3H), 4.54 (s, 2H), 7.01–7.56 (m, 11H), 8.41 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.9, 79.4, 127.7, 128.4, 128.8, 128.9, 129.0, 129.2, 135.1, 135.7, 135.9, 145.0, 145.2, 145.3, 152.0, 165.7. MS (ESI^+) *m/z* (%): 639 $[2M+H]^+$ (10), 320 $[M+H]^+$ (100). HRMS (ESI^+): calcd for $C_{20}H_{18}NO_3$ 320.1287; found 320.1297.

4.1.11. Methyl 3-benzyloxy-5-phenylpicolinate ***18***. $Pd(PPh_3)_4$ (12 mg, 5 mol %) was added to a degassed solution of **16** (66 mg, 0.21 mmol), phenylboronic acid (75 mg, 3 equiv), and K_2CO_3 (85 mg, 3 equiv) in DMF (2 mL). The mixture was stirred for 20 h at 90 °C. DMF was removed under vacuum and the crude mixture was directly absorbed on silica gel and purified by flash chromatography (cyclohexane/EtOAc 7/3, v/v) to give **18** (46 mg, 70%) as a white solid. R_f=0.3 (cyclohexane/EtOAc 7/3, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 4.01 (s, 3H), 5.29 (s, 2H), 7.33–7.55 (m, 11H), 8.51 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7, 70.9, 120.3, 127.1, 127.5, 128.3, 128.9, 129.1, 129.3, 135.9, 136.7, 137.4, 140.0, 140.7, 155.1, 165.0. MS (ESI^+) *m/z* (%): 342 $[M+Na]^+$ (15), 320 $[M+H]^+$ (100). HRMS (ESI^+): calcd for $C_{20}H_{18}NO_3$ 320.1287; found 320.1283.

4.1.12. Methyl 3-benzyloxy-5-(3-chlorophenyl)picolinate ***19***. $Pd(PPh_3)_4$ (9 mg, 5 mol %) was added to a degassed solution of **16** (50 mg, 0.16 mmol), 3-chlorophenylboronic acid (36 mg, 1.5 equiv), and K_2CO_3 (64 mg, 3 equiv) in DMF (2 mL). The mixture was stirred for 20 h at 90 °C. DMF was removed under vacuum and the crude mixture was directly absorbed on silica gel and purified by flash chromatography (cyclohexane/EtOAc 7/3, v/v) to give **19** (51 mg, 90%) as a light brown solid. R_f=0.7 (cyclohexane/EtOAc 1/1, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 5.19 (s, 2H), 7.22–7.35 (m, 6H), 7.40–7.42 (m, 4H), 8.38 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7, 71.0, 120.3, 125.6, 127.1, 127.5, 128.3, 128.8, 129.0, 130.5, 135.2, 135.6, 138.0, 138.4, 139.2, 139.6, 154.9, 164.9. MS (ESI^+) *m/z* (%): 354 $[M+H]^+$ (100). HRMS (ESI^+): calcd for $C_{20}H_{17}ClNO_3$ 354.0897; found 354.0901.

4.1.13. Methyl 4-benzylamino-3-(benzyloxy)picolinate ***20***. Pd_2dba_3 (5.1 mg, 2 mol %), xantphos (9.7 mg, 6% mol), and benzylamine (40 μL, 1.3 equiv) were added to a degassed solution of **10** (90 mg, 0.28 mmol) and Cs_2CO_3 (137 mg, 1.5 equiv) in toluene (3 mL). The mixture was stirred for 20 h at 100 °C. Solvent was removed and the residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 1/1, v/v) to give **20** (86 mg, 88%) as a light brown solid. R_f=0.5 (cyclohexane/EtOAc 3/7, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 4.19 (d, *J*=5.7 Hz, 2H), 4.96 (s, 2H), 5.16 (t, *J*=5.7 Hz, 1H), 6.45 (d, *J*=5.1 Hz, 1H), 7.06–7.34 (m, 10H), 8.01 (d, *J*=5.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 46.8, 52.7, 76.8, 107.8, 127.0, 127.7, 128.6, 128.7, 128.8, 128.9, 136.7, 137.3, 140.3, 143.6, 145.9, 148.5, 165.6. MS (ESI^+) *m/z* (%): 349 $[M+H]^+$ (100). HRMS (ESI^+): calcd for $C_{21}H_{21}N_2O_3$ 349.1552; found 349.1541.

4.1.14. Methyl 5-benzylamino-3-(benzyloxy)picolinate ***21***. Pd_2dba_3 (2.3 mg, 2 mol %), BINAP (3.1 mg, 4 mol %), and benzylamine (20 μL, 1.5 equiv) were added to a degassed solution of **16** (40 mg, 0.12 mmol) and Cs_2CO_3 (60 mg, 1.5 equiv) in 1,4-dioxane (0.5 mL). The mixture was stirred for 20 h at 100 °C. Solvent was removed and the residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 3/7, v/v) to give **21** (39 mg, 93%) as a colorless oil. R_f=0.6 (EtOAc). ^1H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.33 (d, *J*=5.1 Hz, 2H), 4.68 (t, *J*=5.1 Hz, 1H), 5.10 (s, 2H), 6.41 (d, *J*=1.5 Hz, 1H), 7.26–7.44 (m, 10H), 7.76 (d, *J*=1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 47.5, 52.0, 70.5, 103.0, 126.2, 126.8, 127.4, 127.9, 127.9, 128.5, 128.7, 129.0, 136.1, 137.3, 147.7, 157.7, 164.7. MS (ESI^+) *m/z* (%): 349 $[M+H]^+$ (100). HRMS (ESI^+): calcd for $C_{21}H_{21}N_2O_3$ 349.1552; found 349.1548.

4.1.15. Methyl 3-benzyloxy-5-(piperidin-1-yl)picolinate ***22***. Pd_2dba_3 (3 mg, 2 mol %), xantphos (5.6 mg, 6 mol %), and piperidine (21 μL, 1.3 equiv) were added to a degassed solution of **16** (50 mg, 0.16 mmol) and Cs_2CO_3 (78 mg, 1.5 equiv) in toluene (2 mL). The mixture was stirred for 20 h at 90 °C. Solvent was removed and the residue was purified by flash chromatography on silica gel (cyclohexane/EtOAc 3/7, v/v) to give **21** (39 mg, 75%) as a white solid. R_f=0.6 (EtOAc). ^1H NMR (300 MHz, $CDCl_3$) δ 1.50–1.60 (m, 6H), 3.20–3.25 (m, 4H), 3.86 (s, 3H), 5.11 (s, 2H), 6.57 (d, *J*=2.4 Hz, 1H), 7.20–7.34 (m, 3H), 7.40–7.45 (m, 2H), 7.89 (d, *J*=2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.1, 25.1, 48.4, 52.0, 70.7, 105.8, 126.1, 126.9, 127.9, 128.6, 129.4, 136.3, 150.1, 157.3, 164.7. MS (ESI^+) *m/z* (%): 327 $[M+H]^+$ (100). HRMS (ESI^+): calcd for $C_{19}H_{23}N_2O_3$ 327.1709; found 327.1716.

4.1.16. Methyl 3-(benzyloxy)-5-(3-hydroxyprop-1-ynyl)picolinate ***23***. $Pd(PPh_3)_4$ (9 mg, 5 mol %) and CuI (3 mg, 10 mol %) were added to a degassed solution of **16** (50 mg, 0.16 mmol) and propargyl alcohol (9 μL, 1 equiv) in a mixture of dichloromethane (2 mL) and triethylamine (1 mL). The mixture was stirred for 20 h at room temperature. Solvents were removed under vacuum and the crude mixture was directly absorbed on silica gel and purified by flash chromatography (cyclohexane/EtOAc 1/1, v/v) to give **23** (39 mg, 82%) as a light brown solid. R_f=0.2 (cyclohexane/EtOAc 1/1, v/v). ^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (br s, 1H), 3.96 (s, 3H), 4.49 (s, 2H), 5.17 (s, 2H), 7.25–7.46 (m, 6H), 8.33 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 51.1, 52.8, 70.8, 81.0, 93.8, 123.5, 124.1, 128.3, 135.3, 137.8, 143.5, 154.1, 164.6. MS (ESI^+) *m/z* (%): 298 $[M+H]^+$ (100). HRMS (ESI^+): calcd for $C_{17}H_{16}NO_4$ 298.1079; found 298.1068.

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