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Practical Pd/C-Catalysed Suzuki–Miyaura Reactions for the Preparation of 3-Aryl-4-oxypyridin-2(1*H*)-ones, 3-Aryl-2,4-oxypyridines and 3-Aryl-2,4-oxyquinolines as Useful Intermediates for the Synthesis of Biologically Active Compounds

Marc Lamblin,[a] Hugo Bares,[b] Jean Dessolin,[a] Christel Marty,[c] Nathalie Bourgougnon,[c] and François-Xavier Felpin*[d]

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Practical heterogeneous Pd/C-catalysed Suzuki–Miyaura cross-coupling reactions of 3-iodo-4-oxypyridin-2(1*H*)-ones, 3-iodo-2,4-oxypyridines, and 3-iodo-2,4-oxyquinolines with arylboronic acids are described as a useful and efficient alternative to homogeneous conditions. The methodology features ligand-free and environmentally friendly conditions, and tolerates a wide range of boronic acids. The cross-coupled products can be viewed as useful intermediates for the preparation of 3-aryl-4-hydroxypyridin-2(1*H*)-ones, which can be used as new nucleobases for antiherpetic agents.

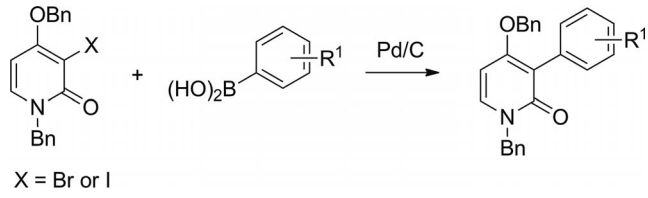
Introduction

The rapid access to structurally relevant skeletons for molecular diversity is an ongoing challenge for synthetic chemists. The development of efficient, practical, and environmentally friendly methodologies directed at the preparation of useful intermediates that can be incorporated into biologically active compounds is highly desired by medicinal chemists. To this end, metal-mediated reactions, and especially palladium-catalysed couplings for carbon–carbon bond formation, have gained a predominant place in the organic chemist's arsenal. The myriad of palladium-catalysed reactions can usually be carried out with high turnover numbers (TONs) and turnover frequencies (TOFs) under mild conditions.[1] However, economic and environmental considerations, as well as the importance of a clean synthesis for biologically active compounds, make the use of easily recoverable palladium catalysts crucial.[2] In this context, heterogeneous cross-coupling reactions using Pd/C as a practical and inexpensive catalyst have proved to be an excellent method,[3] as exemplified by reported industrial applications.[4] In the recent past, we have reported our own contribution to the development of various practical Pd/C-catalysed cross-coupling reactions for the formation of C–C bonds.[5]

In the context of two independent programs of medicinal chemistry, we have been interested in the preparation of 3-aryl-4-hydroxypyridin-2(1*H*)-ones as the central skeleton for anticancer[6] and antiviral compounds.[7] In this paper, we wish to present our results on Pd/C-catalysed Suzuki–Miyaura reactions[8] for the preparation of 3-aryl-4-oxypyridin-2(1*H*)-ones and 3-aryl-2,4-oxypyridines as useful heterocycles.

Results and Discussion

Our initial strategy involved the preparation of 3-halopyridones followed by a Pd^0/C-catalysed Suzuki–Miyaura cross-coupling reaction, as depicted in Scheme 1.[9]



Scheme 1. General strategy for the preparation of 3-aryl-4-hydroxypyridin-2(1*H*)-ones.

[a] Université de Bordeaux, CNRS UMR 5248, CBMN, IECB, 2 rue Robert Escarpit, 33607 Pessac, France
[b] Université de Bordeaux, UMR CNRS 5255, Institut des Sciences Moléculaires, 351 cours de la Libération, 33405 Talence Cedex, France
[c] Université de Bretagne-Sud, PRES Université Européenne de Bretagne, Laboratoire de Biotechnologie et Chimie Marines, Campus de Tohannic, 56017 Vannes, France
[d] Université de Nantes, CNRS UMR 6230, CEISAM, UFR des Sciences et des Techniques, 2 rue de la Houssinière, 44322 Nantes Cedex 3, France
Fax: +33-2-51125402
E-mail: fx.felpin@univ-nantes.fr
Homepage: http://f-x.felpin.voila.net/Index.html
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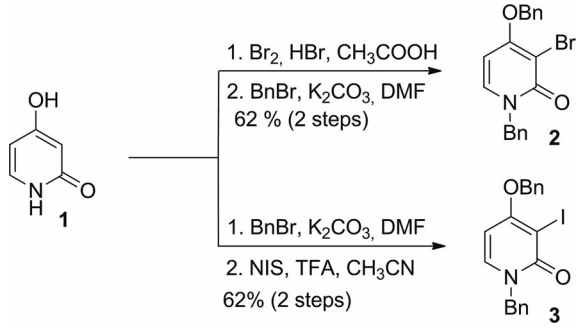
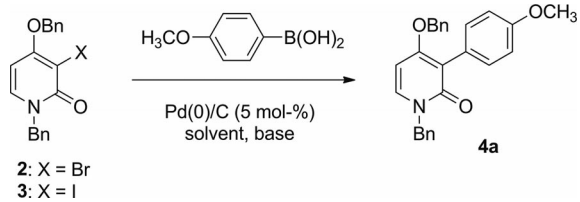
Although the cross-coupling of aryl bromides with boronic acids using Pd^0/C under ligand-free conditions has been well documented,[10] the use of sterically hindered *ortho*-bromo compounds often gave low to moderate yields of cross-coupled products.[11] Moreover, we also noticed in a previous report that the Pd^0/C-catalysed Suzuki–Miyaura reaction of 2-bromocycloenones with arylboronic acids gave only degradation and dehalogenated by-products.[5c] With these issues in mind, we prepared both 3-bromopyridone **2** and 3-iodopyridone **3** with the aim of studying their reactivity. Their preparation was optimised on a multi-gram scale, and pure intermediates were mostly isolated by precipitation or crystallisation, without the need for tedious chromatographic separation. Bromination of commercially available 4-hydroxypyridin-2(1*H*)-one (**1**),[12] followed by benzylation with a combination of K_2CO_3 and benzyl bromide in DMF, gave **2** in good yield over two steps (62%; Scheme 2). Alternatively, initial benzylation of 4-hydroxy-2-pyridone (**1**), and subsequent iodination with NIS, allowed the preparation of iodopyridone **3** in a similar yield (62%). It should be noted that the combination of K_2CO_3 and DMF for the benzylation step proved to be crucial for optimal results. Other combinations of solvents and bases gave inferior results in terms of selectivity (*O*-alkylation vs. *N*-alkylation) and yield. It is important to mention that another useful procedure, under homogeneous conditions, was published by the Balme group a few months after we started this program.[13]



Scheme 2. Synthesis of 3-bromo- and 3-iodopyridones.

We next studied the arylation of 3-bromopyridone **2** by means of a Suzuki–Miyaura reaction using Pd^0/C as heterogeneous catalyst. As predicted, compound **2** showed a very low reactivity when aqueous DME or *i*PrOH were used as solvents and Na_2CO_3 was used as a base under ligand-free conditions (Table 1, entries 1–4). Although these results were disappointing, we noticed that the combination of *i*PrOH and water was more efficient than DME. The role of *i*PrOH in the activation of homogeneous palladium complexes has been discussed by Nolan and co-workers,[14] and this role could be extended to heterogeneous catalysis. It should be mentioned that the use of pure water as solvent led to the aggregation of the Pd/C catalyst and irreproducible results. The use of Cs_2CO_3 as a base instead of Na_2CO_3 did not improve the conversion (Table 1, entry 5). We also tested a few additives in order to improve the reactivity of pyridone **2**. While activation of the boronic acid with TBAB or KF (1 equiv.) did not affect the reaction outcome (Table 1, entries 6–7), it appeared that Ph_3P (20 mol-%) considerably improved the conversion and the reaction yield (Table 1, entry 8). However, we next found that 3-iodopyridone **3** was much more reactive, even at temperatures as low as 35 °C (Table 1, entry 9). Nevertheless, the reaction was best carried out at 60 °C to give cross-coupled product **4a** in 94% yield (Table 1, entry 10).

Table 1. Optimisation studies for the cross-coupling of **2** and **3**.



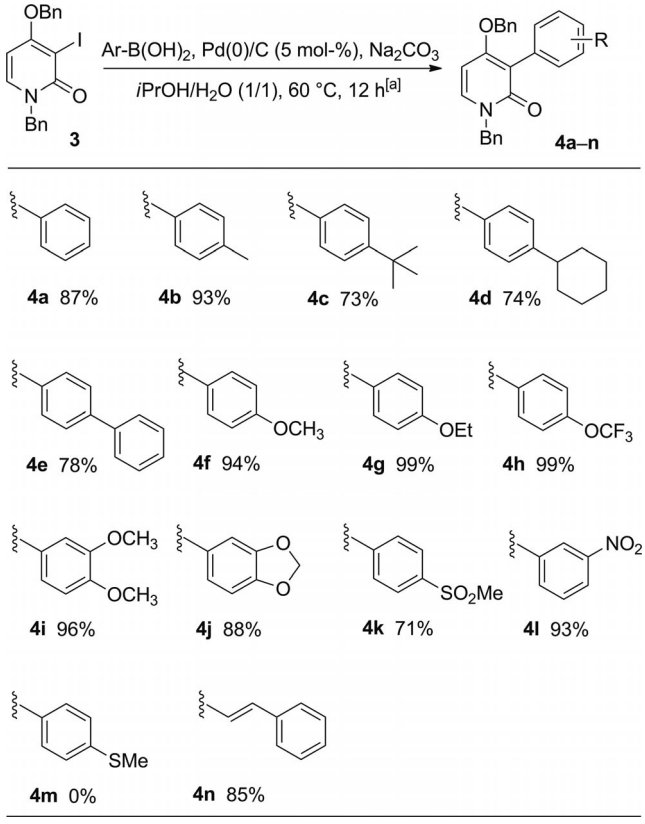
Entry	SM	Solvent, ratio (1:1)	Base	Additive [equiv.]	*T* [°C]	Conv. [%][a]
1	**2**	DME/H_2O	Na_2CO_3	–	35	0
2	**2**	DME/H_2O	Na_2CO_3	–	60	25
3	**2**	*i*PrOH/H_2O	Na_2CO_3	–	35	0
4	**2**	*i*PrOH/H_2O	Na_2CO_3	–	60	44
5	**2**	*i*PrOH/H_2O	Cs_2CO_3	–	60	41
6	**2**	*i*PrOH/H_2O	Na_2CO_3	TBAB (1)	60	35
7	**2**	*i*PrOH/H_2O	Na_2CO_3	KF (1)	60	49
8	**2**	*i*PrOH/H_2O	Na_2CO_3	Ph_3P (0.2)	60	91 (83)
9	**3**	*i*PrOH/H_2O	Na_2CO_3	–	35	82
10	**3**	*i*PrOH/H_2O	Na_2CO_3	–	60	99 (94)

[a] Conversion determined by ^1H NMR spectroscopy. Isolated yields in parentheses.

Using the optimised reaction conditions, we then screened a variety of boronic acids bearing electron-donating or electron-withdrawing substituents (Table 2). Gratifyingly, cross-coupled products were obtained with excellent yields and purity, even when using β-styrylboronic acid (leading to **4n**). Maximum conversions of 3-iodopyridone **3** to the corresponding products were usually reached within 6–10 h, but we stirred for 12 h for convenience. The use of Pd^0/C greatly simplified the separation of the palladium catalyst from the crude product by allowing the separation to be accomplished by an easy filtration. Indeed, when a homogeneous palladium catalyst [$Pd(PPh_3)_4$] was used during our preliminary studies, it was extremely difficult to remove coloured by-products (assumed to be palladium residues), especially for the highly polar compound **4i**, even after flash chromatography. The only failure encountered in this screening was observed with 4-(methylthio)phenylboronic acid (see compound **4m**). This result suggested that the sulfur atom acts as a poison for the metal centre.

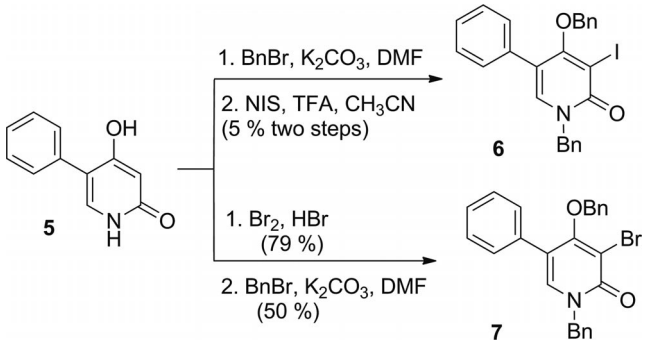
We next investigated the extension of this methodology to the arylation of 4-hydroxy-5-phenylpyridin-2(1*H*)-one **5**. Unfortunately, the protocol previously developed for the formation of **3** from 4-hydroxy-2-pyridone (**1**) failed to give a useful yield of the corresponding iodinated product (i.e., **6**).[15] Indeed, the benzylation–iodination sequence applied to pyridone **5** gave less than 5% overall yield (two steps) of

Table 2. Screening of boronic acids.



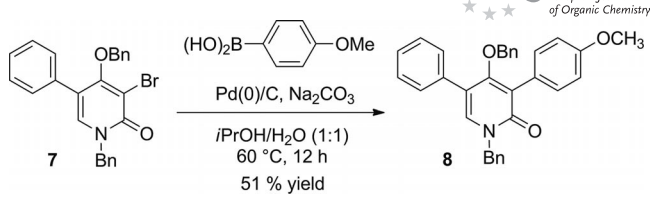
[a] Isolated yields.

target compound **6** (Scheme 3). In contrast, the bromination–benzylation sequence furnished brominated pyridine **7** in acceptable yields (40% overall). However, as expected, the Pd^0/C Suzuki–Miyaura reaction carried out with **7** gave only a moderate yield of cross-coupled product **8** (Scheme 4). This result was consistent with our findings reported in Table 1 with 3-bromopyridone **3**.

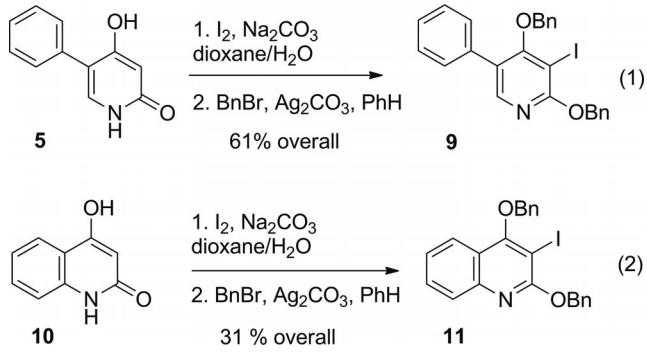


Scheme 3. Synthesis of 3-bromo- and 3-iodopyridones.

With these disappointing results in mind, we reasoned that the benzylation could be carried out after the iodination step. After considerable optimisation studies, we were surprised to find that pyridone **5** was almost exclusively benzylated in its pyridinic tautomer to give 3-iodopyridine **9** [Scheme 5, Equation (1)]. This result was in sharp contrast to the brominated derivative, which was preferentially benzylated in its pyridone form. The reason for such divergent pathways is still unclear at this time. This trend was also observed, albeit to a lesser extent, when starting with 4-hydroxy-2-quinolone **10** [Scheme 5, Equation (2)]. In this case, a lower overall yield of the corresponding iodinated quinoline (i.e., **11**) was obtained, due to competing de-iodination pathways during the benzylation step.



Scheme 4. Example of a Suzuki–Miyaura reaction with pyridone **7**.

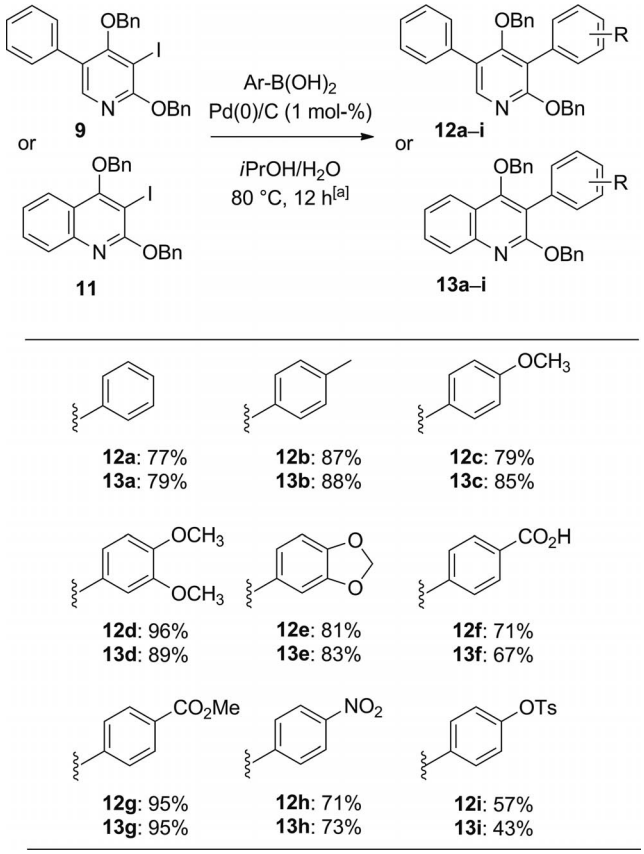


Scheme 5. Preparation of 3-iodopyridine **9** and 3-iodoquinoline **11**.

From these unexpected results, we found an opportunity to develop an unprecedented Pd^0/C-catalysed Suzuki–Miyaura cross-coupling reaction of highly substituted 2,4-alkoxypyridines and 2,4-alkoxyquinolines. To this end, we tested the cross-coupling reactins of **9** and **11** with boronic acids under the optimised reaction conditions described above. Although reactions run under these conditions proceeded smoothly, we later found that a slight increase in temperature, from 60 to 80 °C, allowed the use of only 1 mol-% of the heterogeneous catalyst. We screened a variety of boronic acids bearing electron-donating and electron-withdrawing groups (Table 3). Whatever the electronic nature of the substituent borne by the boronic acid, we consistently isolated the targeted cross-coupling products in high yields. The only exception to this trend was found with the *O*-tosylated products (i.e., **12i** and **13i**). In general, we did not observe a significant difference in reactivity between pyridine **9** and quinoline **11** in the cross-coupling reactions. This result could be easily explained by the closely related electronic structures of these two heterocycles.

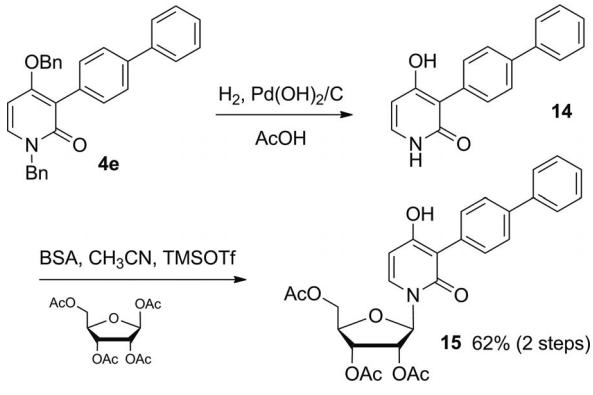
These methodologies were optimised for use in two medicinal chemistry projects. For instance, we used this strategy for the construction of unnatural C-3-arylated nucleobases (Scheme 6). As an example, debenzylation of arylated pyridone **4e** under reductive conditions gave free pyridone

Table 3. Screening of boronic acids.



[a] Yields of isolated products.

14, which was then treated, without purification, with tetra-*O*-acetyl-D-ribose under Vorbrüggen conditions[16] to yield the corresponding acetylated nucleoside (i.e., **15**).



Scheme 6. Preparation of an antiviral nucleoside.

Compound **15** was tested for its antiherpetic activity against HSV-1 on the Vero cell-line by cell viability, and showed an EC_{50} value of 33 μM, while an EC_{50} value of 22 μM was found for the commercially available drug Zovirax® (acyclovir) at MOI 0.01 ID_{50}/cells. It should be also mentioned that no cytotoxic side-effects were detected on Vero, HeLa and HL-60 cell-lines. Additional biological assays will be reported shortly on a library of 3-arylated deazauridines.

Conclusions

We have developed new applications of the Pd/C-catalysed Suzuki–Miyaura reactions for the synthesis of 4-oxy-3-arylpyridin-2(1*H*)-ones and 2,4-oxy-3-arylpyridines. This work extends the scope of Pd/C catalysis for C–C bond formation with nitrogen-containing heterocycles. The optimum conditions use inexpensive reagents and solvents with low toxicities, which makes the method environmentally benign, very practical, and scalable. A preliminary application of the methodology in the preparation of promising new antiherpetic nucleosides has been disclosed. Extensive biological studies are still ongoing, and the results will be reported in due course.

Experimental Section

General Methods: Chemical shifts from proton and carbon NMR spectra are reported in ppm relative to tetramethylsilane, using residual solvent peaks [$CDCl_3$: δ = 7.26 ppm (^{1}H) or 77.0 ppm (^{13}C); [D_6]DMSO: δ = 2.50 ppm (1*H*) or 39.5 ppm (^{13}C)] as internal references. Infrared (IR) spectra were recorded as neat samples on NaCl plates or with KBr pellets. Yields refer to isolated material determined to be pure by NMR spectroscopy and thin layer chromatography (TLC), unless specified otherwise in the text. The 10% Pd/C used in this study was commercially available from Sigma–Aldrich.

3-Bromo-2,4-dihydroxypyridine: A solution of Br_2 (447 μL, 8.71 mmol) in AcOH (4 mL) was slowly added to a solution of 2,4-dihydroxypyridine **1** (1 g, 9 mmol) in 48% aqueous HBr (3.5 mL) at 0 °C over 20 min. After 10 min of stirring, the ice-bath was removed, and the solution was diluted with cold water (40 mL). The white solid was filtered, washed with cold Et_2O, and dried under vacuum at 60 °C for 12 h to give 3-bromo-2,4-dihydroxypyridine (1.64 g, 96%), m.p. 263 °C [lit.[17] 261–262 °C]. IR (KBr): $\tilde{\nu}$ = 1636, 2845, 3004, 3102 cm^{-1}. ^{1}H NMR (250 MHz, [D_6]DMSO): δ = 6.00 (d, J = 7 Hz, 1 H), 7.25 (d, J = 7 Hz, 1 H), 11.33 (br. s, 1 H), 11.46 (br. s, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 95.3, 98.6, 134.1, 160.3, 163.9 ppm.

3-Bromo-1-benzyl-4-benzyloxypyridin-2(1*H*)-one (2): A solution of 3-bromo-2,4-dihydroxypyridine (1.64 g, 8.63 mmol) in DMF (35 mL) was treated with K_2CO_3 (6.22 g, 45 mmol) and benzyl bromide (4.2 mL, 36 mmol) at room temperature. The resulting mixture was stirred for 24 h, and then water (30 mL) was added. The white powder was filtered, washed with cold Et_2O (3×) and dried under vacuum at 60 °C for 12 h to give **2** (2.16 g, 65%), m.p. 168 °C. IR (KBr): $\tilde{\nu}$ = 1603, 1644, 1662, 2933, 2960, 3033 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.15 (s, 2 H), 5.21 (s, 2 H), 6.05 (d, J = 7.9 Hz, 1 H), 7.22 (d, J = 7.9 Hz, 1 H), 7.26–7.41 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.7, 71.0, 96.0, 99.8, 126.8, 128.2, 128.3, 128.4, 128.8, 128.9, 135.3, 135.9, 136.3, 160.0, 163.1 ppm. HRMS (LSIMS): calcd. for $C_{19}H_{16}BrNO_2$ $[M]^+$ 370.0443; found 370.0440.

1-Benzyl-4-benzyloxypyridin-2(1*H*)-one: K_2CO_3 (3.73 g, 27.03 mmol) and benzyl bromide (2.52 mL, 21.62 mmol) were added to a solution of 2,4-dihydroxypyridine **1** (600 mg, 5.41 mmol) in DMF (20 mL) at room temperature. After being

stirred for 24 h, cold water (60 mL) was added, and the white solid was filtered and washed twice with cold Et_2O. The filtrate was concentrated, diluted with Et_2O and stored in the freezer (–20 °C) for 5 h to give a further amount of a white solid. The combined solids were dried under vacuum at 60 °C for 12 h to give the title compound (1.05 g, 67%), m.p. 130 °C. IR (KBr): $\tilde{\nu}$ = 1603, 1659, 2974, 3032 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 4.99 (s, 2 H), 5.09 (s, 2 H), 5.95 (dd, J = 2.7, 7.6 Hz, 1 H), 6.04 (d, J = 2.8 Hz, 1 H), 7.12 (d, J = 7.3 Hz, 1 H), 7.26–7.41 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.0, 70.2, 98.4, 101.4, 127.7, 127.9, 128.0, 128.5, 128.7, 128.8, 135.3, 136.7, 137.1, 164.1, 167.0 ppm. HRMS (ESI): calcd. for $C_{19}H_{18}NO_2$ $[M + H]^+$ 292.1332; found 292.1341.

1-Benzyl-4-benzyloxy-3-iodopyridin-2(1*H*)-one (3): A solution of the previously obtained benzylated pyridone **2** (500 mg, 1.72 mmol) in CH_3CN (15 mL) was stirred with NIS (425 mg, 1.89 mmol) and TFA (40 μL, 0.52 mmol) at room temperature for 4 h. The mixture was diluted with CH_2Cl_2 (50 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (50 mL). The aqueous phase was extracted with CH_2Cl_2 (3×). The collected organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (50% EtOAc/petroleum ether) gave **3** (659 mg, 92%) as a white solid, m.p. 127 °C. IR (KBr): $\tilde{\nu}$ = 1599, 1639, 1654, 1700, 3031 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 5.15 (s, 2 H), 5.20 (s, 2 H), 5.97 (d, J = 7.6 Hz, 1 H), 7.23 (d, J = 7.6 Hz, 1 H), 7.26–7.41 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.0, 71.1, 95.7, 126.7, 128.1, 128.3, 128.4, 128.7, 128.9, 135.3, 136.0, 137.7, 161.1, 166.4 ppm. HRMS (ESI): calcd. for $C_{19}H_{17}NO_2I$ $[M + H]^+$ 418.0298; found 418.0312.

General Procedure for the Suzuki–Miyaura Coupling of Iodopyridone 3: Na_2CO_3 (229 mg, 2.16 mmol), $ArB(OH)_2$ (1.08 mmol), and Pd/C (38 mg, 5 mol-%) were added to a solution of iodopyridone **3** (300 mg, 0.719 mmol) in *i*PrOH (2 mL) and H_2O (2 mL). The resulting mixture was stirred for 12 h at 60 °C and then filtered. The catalyst was washed with H_2O (3 mL) and CH_2Cl_2 (5 mL). The aqueous phase was extracted twice with CH_2Cl_2. The collected organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude compound was purified by flash chromatography to give the cross-coupled product.

1-Benzyl-4-benzyloxy-3-phenylpyridin-2(1*H*)-one (4a): Purification by flash chromatography (50% EtOAc/petroleum ether) gave **4a** (230 mg, 87%) as a white solid, m.p. 161 °C. IR (KBr): $\tilde{\nu}$ = 1593, 1643, 2920, 3021, 3062, 3085 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 5.09 (s, 2 H), 5.14 (s, 2 H), 6.13 (d, J = 7.6 Hz, 1 H), 7.24 (d, J = 7.9 Hz, 1 H), 7.29–7.43 (m, 13 H), 7.51–7.55 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0, 70.3, 96.6, 115.7, 126.5, 127.0, 127.6, 127.9, 128.4, 128.5, 128.8, 130.8, 133.1 136.1, 136.6, 136.6, 162.3, 162.6 ppm. HRMS (ESI): calcd. for $C_{25}H_{22}NO_2$ $[M + H]^+$ 368.1645; found 368.1658.

1-Benzyl-4-benzyloxy-3-tolylpyridin-2(1*H*)-one (4b): Purification by flash chromatography (40% EtOAc/petroleum ether) gave **4b** (255 mg, 93%) as a white solid, m.p. 168 °C. IR (KBr): $\tilde{\nu}$ = 1642, 2919, 3029, 3061, 3083 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 2.37 (s, 3 H), 5.09 (s, 2 H), 5.14 (s, 2 H), 6.10 (d, J = 7.6 Hz, 1 H), 7.20–7.44 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.3, 51.9, 70.3, 96.6, 115.6, 126.5, 127.9, 128.4, 128.4, 128.5, 128.7, 130.0, 130.6, 136.2, 136.3, 136.5, 136.6, 162.1, 162.7 ppm. HRMS (ESI): calcd. for $C_{26}H_{24}NO_2$ $[M + H]^+$ 382.1801; found 382.1815.

1-Benzyl-4-benzyloxy-3-(4-*tert*-butylphenyl)pyridin-2(1*H*)-one (4c): Purification by flash chromatography (40% EtOAc/petroleum ether) gave **4c** (222 mg, 73%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 1651, 2962, 3033, 3064, 3087 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 9 H), 5.13 (s, 2 H), 5.18 (s, 2 H), 6.16 (d, J = 7.7 Hz, 1 H), 7.27–7.53 (m, 15 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.3, 34.5, 52.1, 70.3, 96.9, 115.7, 124.6, 126.4, 127.9, 127.9, 128.4, 128.5, 128.7, 129.8, 130.3, 136.2, 136.4, 136.5, 149.6, 162.3, 162.7 ppm. HRMS (ESI): calcd. for $C_{29}H_{30}NO_2$ $[M + H]^+$ 424.2271; found 424.2277.

1-Benzyl-4-benzyloxy-3-(4-cyclohexylphenyl)pyridin-2(1*H*)-one (4d): Purification by flash chromatography (40% EtOAc/petroleum ether) gave **4d** (239 mg, 74%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 1643, 2923, 3031, 3062 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28–1.56 (m, 5 H), 1.78–1.97 (m, 5 H), 2.52–2.60 (m, 1 H), 5.09 (s, 2 H), 5.15 (s, 2 H), 6.12 (d, J = 7.7 Hz, 1 H), 7.23 (d, J = 7.7 Hz, 1 H), 7.27–7.37 (m, 12 H), 7.50 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.1, 26.8, 34.2, 44.3, 51.9, 70.2, 96.6, 115.6, 126.0, 126.4, 127.8, 128.3, 128.4, 128.6, 130.2, 130.5, 136.1, 136.3, 136.6, 146.5, 162.1, 162.6 ppm. HRMS (ESI): calcd. for $C_{31}H_{32}NO_2$ $[M + H]^+$ 450.2427; found 450.2449.

1-Benzyl-4-benzyloxy-3-biphenylpyridin-2(1*H*)-one (4e): Purification by flash chromatography (40% EtOAc/petroleum ether) gave **4e** (248 mg, 78%) as a white solid. IR (KBr): $\tilde{\nu}$ = 1643, 3028 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.11 (s, 2 H), 5.16 (s, 2 H), 6.14 (d, J = 7.7 Hz, 1 H), 7.25 (d, J = 7.7 Hz, 1 H), 7.28–7.40 (m, 11 H), 7.48 (tm, J = 8.6 Hz, 2 H), 7.67–7.70 (m, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0, 70.3, 96.5, 115.0, 126.3, 126.5, 126.9, 127.0, 127.8, 127.9, 128.3, 128.5, 128.6, 128.7, 131.2, 132.1, 136.0, 136.5, 136.7, 139.5, 141.2, 162.3, 162.5 ppm. HRMS (ESI): calcd. for $C_{31}H_{26}NO_2$ $[M + H]^+$ 444.1958; found 444.1959.

1-Benzyl-4-benzyloxy-3-(4-methoxyphenyl)pyridin-2(1*H*)-one (4f): Purification by flash chromatography (50% EtOAc/petroleum ether) gave **4f** (268 mg, 94%) as a white solid, m.p. 128 °C. IR (KBr): $\tilde{\nu}$ = 1591, 1645, 2922, 2946, 3028, 3060 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 5.11 (s, 2 H), 5.16 (s, 2 H), 6.14 (d, J = 7.8 Hz, 1 H), 6.97 (dm, J = 8.9 Hz, 1 H), 7.24 (d, J = 7.8 Hz, 2 H), 7.28–7.42 (m, 10 H), 7.51 (dm, J = 8.9 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0, 55.1, 70.3, 96.7, 113.1, 115.3, 125.3, 126.5, 127.8, 127.9, 128.3, 128.5, 128.7, 131.9, 136.2, 136.6, 158.4, 162.1, 162.8 ppm. HRMS (LSIMS): calcd. for $C_{26}H_{24}NO_3$ $[M + H]^+$ 398.1756; found 398.1755.

1-Benzyl-4-benzyloxy-3-(4-ethoxyphenyl)pyridin-2(1*H*)-one (4g): Purification by flash chromatography (50% EtOAc/petroleum ether) gave **4g** (308 mg, 99%) as a colourless oil. IR (KBr): $\tilde{\nu}$ = 1642, 2928, 2982, 3036, 3065 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (t, J = 7.0 Hz, 3 H), 4.06 (q, J = 7.0 Hz, 2 H), 5.08 (s, 2 H), 5.14 (s, 2 H), 6.12 (d, J = 7.7 Hz, 1 H), 6.93 (d, J = 8.7 Hz, 2 H), 7.20–7.33 (m, 11 H), 7.45 (d, J = 8.7 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 52.0, 63.3, 70.4, 96.8, 113.8, 115.4, 125.0, 126.5, 127.9, 128.4, 128.6, 128.8, 131.9, 136.1, 136.2, 136.6, 157.9, 162.1, 162.9, 179.9 ppm. HRMS (ESI): calcd. for $C_{27}H_{26}NO_3Na$ $[M + Na]^+$ 435.1804; found 435.1802.

1-Benzyl-4-benzyloxy-3-(4-trifluoromethoxyphenyl)pyridin-2(1*H*)-one (4h): Purification by flash chromatography (40% EtOAc/petroleum ether) gave **4h** (321 mg, 99%) as a white solid, m.p. 95 °C. IR (KBr): $\tilde{\nu}$ = 1644, 2937, 3037, 3068 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 5.08 (s, 2 H), 5.13 (s, 2 H), 6.14 (d, J = 7.9 Hz, 1 H), 7.20–7.34 (m, 13 H), 7.54 (dm, J = 8.3 Hz, 2 H) ppm. HRMS (ESI): calcd. for $C_{26}H_{20}NO_3F_3Na$ $[M + Na]^+$ 474.1287; found 474.1285.

1-Benzyl-4-benzyloxy-3-(3,4-dimethoxyphenyl)pyridin-2(1*H*)-one (4i): Purification by flash chromatography (20% EtOAc/CH_2Cl_2) gave **4i** (295 mg, 96%) as a white solid, m.p. 60 °C. IR (KBr): $\tilde{\nu}$ = 1641, 2933, 3030 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 3.89 (s, 3 H), 5.08 (s, 2 H), 5.15 (s, 2 H), 6.14 (d, J = 7.9 Hz, 1 H), 6.91 (d, J = 8.2 Hz, 1 H), 7.07 (d, J = 1.9 Hz, 1 H), 7.13 (dd,

J = 2.2, 8.6 Hz, 1 H), 7.24 (d, J = 7.6 Hz, 1 H), 7.24–7.37 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.0, 55.7, 55.8, 70.5, 96.7, 110.7, 114.3, 115.4, 123.5, 125.5, 126.7, 127.9, 128.0, 128.4, 128.6, 128.8, 136.1, 136.3, 136.6, 148.0, 148.1, 162.2, 162.8 ppm. HRMS (ESI): calcd. for $C_{27}H_{26}NO_4$ $[M + H]^+$ 428.1856; found 428.1860.

1-Benzyl-4-benzyloxy-3-(3,4-methylenedioxyphenyl)pyridin-2(1*H*)-one (4j): Purification by flash chromatography (50% EtOAc/petroleum ether) gave **4j** (260 mg, 88%) as a white solid, m.p. 165 °C. IR (KBr): $\tilde{\nu}$ = 1591, 1646, 2923, 3028, 3063 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.09 (s, 2 H), 5.13 (s, 2 H), 5.94 (s, 2 H), 6.10 (d, J = 7.9 Hz, 1 H), 6.86 (dd, J = 1.2, 7.6 Hz, 1 H), 6.99 (dd, J = 1.8, 7.6 Hz, 1 H), 7.00 (s, 1 H), 7.22 (d, J = 7.6 Hz, 1 H), 7.24–7.39 (m, 10 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.1, 70.4, 96.6, 100.7, 107.8, 111.4, 115.4, 124.4, 126.5, 127.9, 128.0, 128.4, 128.6, 128.8, 136.1, 136.4, 136.6, 146.4, 147.0, 162.3, 162.7 ppm. HRMS (ESI): calcd. for $C_{26}H_{22}NO_4$ $[M + H]^+$ 412.1543; found 412.1558.

1-Benzyl-4-benzyloxy-3-(4-methylsulfonylphenyl)pyridin-2(1*H*)-one (4k): Purification by flash chromatography (20% EtOAc/petroleum ether) gave **4k** (227 mg, 71%) as a colourless oil. IR (neat): $\tilde{\nu}$ = 1645, 2923, 3002, 3033 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.03 (s, 3 H), 5.11 (s, 2 H), 5.14 (s, 2 H), 6.19 (d, J = 7.7 Hz, 1 H), 7.20–7.36 (m, 11 H), 7.73 (d, J = 8.6 Hz, 2 H), 7.92 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.6, 52.2, 70.7, 96.3, 113.3, 126.5, 126.7, 128.1, 128.3, 128.7, 128.9, 131.9, 135.4, 136.1, 137.9, 138.3, 139.3, 162.1, 162.9 ppm. HRMS (ESI): calcd. for $C_{26}H_{23}NO_4NaS$ $[M + Na]^+$ 468.1240; found 468.1233.

1-Benzyl-4-benzyloxy-3-(3-nitrophenyl)pyridin-2(1*H*)-one (4l): Purification by flash chromatography (5% EtOAc/CH_2Cl_2) gave **4l** (276 mg, 93%) as a yellow solid, m.p. 134 °C. IR (KBr): $\tilde{\nu}$ = 1594, 1646, 2928, 3032 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.12 (s, 2 H), 5.16 (s, 2 H), 6.21 (d, J = 7.9 Hz, 1 H), 7.26–7.37 (m, 11 H), 7.51 (app t, J = 7.9 Hz, 1 H), 7.91 (dm, J = 7.9 Hz, 1 H), 8.11 (dm, J = 8.3 Hz, 1 H), 8.45 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.1, 70.7, 96.1, 112.7, 121.8, 126.2, 126.8, 128.1, 128.3, 128.7, 128.9, 134.8, 135.3, 136.1, 137.3, 137.9, 147.7, 162.0, 162.9 ppm. HRMS (ESI): calcd. for $C_{25}H_{20}N_2O_4Na$ $[M + Na]^+$ 435.1315; found 435.1335.

1-Benzyl-4-benzyloxy-3-styrylpyridin-2(1*H*)-one (4n): Purification by flash chromatography (40% EtOAc/petroleum ether) gave **4n** (240 mg, 85%) as a white solid, m.p. 133 °C. IR (KBr): $\tilde{\nu}$ = 1593, 1640, 2942, 3026, 3053 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.16 (s, 2 H), 5.20 (s, 2 H), 6.11 (d, J = 7.6 Hz, 1 H), 7.17 (d, J = 7.6 Hz, 1 H), 7.19–7.52 (m, 15 H), 7.55 (d, J = 16.5 Hz, 1 H), 8.10 (d, J = 16.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.8, 70.7, 96.0, 111.6, 119.5, 126.5, 126.9, 127.0, 127.9, 128.0, 128.3, 128.4, 128.7, 128.8, 131.8, 135.6, 135.8, 136.5, 139.2, 162.2, 162.8 ppm. HRMS (ESI): calcd. for $C_{27}H_{24}NO_2$ $[M + H]^+$ 394.1801; found 394.1796.

4-Hydroxy-5-phenylpyridin-2(1*H*)-one (5): Malonyl dichloride (6 mL, 62 mmol) and phenylacetonitrile (3.6 mL, 31 mmol) were stirred without solvent under an atmosphere of argon at room temperature for 5 d. The resulting gum was triturated with Et_2O (20 mL) to give a brown powder. After filtration, the powder was transferred into a flask and stirred for 30 min with EtOAc (20 mL) and then filtered. This operation was repeated twice. The collected buff solid was diluted in EtOH (120 mL), and treated with $Pd(OH)_2/C$ (20 mol-%). The resulting mixture was heated for 12 h at reflux, and then filtered to give a white solid (4.75 g, 82% over two steps), m.p. 175 °C. IR (KBr): $\tilde{\nu}$ = 1645, 2957, 3072, 3391 cm^{-1}. ^{1}H NMR (300 MHz, [D$_4$]-methanol): δ = 6.60 (s, 1 H), 7.38–7.54 (m, 5 H) 7.95 (s, 1 H) ppm. HRMS (ESI): calcd. for $C_{11}H_{10}NO_2$ $[M + H]^+$ 188.0706; found 188.0700.

3-Bromo-5-phenylpyridin-2(1*H*)-one (7): Br_2 (0.40 mL, 7.70 mmol) was added to a solution of 4-hydroxy-5-phenyl-2(1*H*)-pyridone (**5**) (1.2 g, 6.42 mmol) in HBr (48%, 9.6 mL) and AcOH (2.4 mL), and the mixture was stirred for 1 h. The resulting mixture was diluted with water (60 mL) and filtered, and the solid was washed with pentane (25 mL) to give a pale yellow solid (1.35 g, 79%), m.p. 243 °C. IR (KBr): $\tilde{\nu}$ = 1645, 2943, 3393 cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 7.30–7.46 (m, 6 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]-DMSO): δ = 97.6, 113.4, 127.0, 128.1, 129.1, 133.1, 134.1, 159.3, 161.4 ppm. HRMS (ESI): calcd. for $C_{11}H_8NO_2NaBr$ $[M + Na]^+$ (for ^{79}Br) 287.9630; found 287.9639.

A solution of the 3-bromo-4-hydroxy-5-phenyl-2(1*H*)-pyridone (1 g, 3.76 mmol) in DMF (19 mL) was treated with K_2CO_3 (2.59 g, 18.8 mmol) and BnBr (1.75 mL, 15.04 mmol). The resulting mixture was stirred at 25 °C for 12 h, and then diluted with H_2O (19 mL). After 10 min of stirring, the white precipitate was filtered, and washed with cold Et_2O (3×) to give **7** (830 mg, 50%) as a white solid, m.p. 158 °C. IR (KBr): $\tilde{\nu}$ = 1647, 2958, 3036 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.64 (s, 2 H), 5.24 (s, 2 H), 7.14 (br. s, 2 H), 7.27–7.39 (m, 14 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 53.1, 74.5, 109.0, 118.4, 128.0, 128.3, 128.3, 128.4, 128.5, 128.6, 128.7, 129.0, 133.7, 135.3, 135.5, 135.8, 159.9, 163.0 ppm. HRMS (ESI): calcd. for $C_{25}H_{20}NO_2NaBr$ $[M + Na]^+$ (for ^{79}Br) 468.0569; found 468.0575.

1-Benzyl-4-benzyloxy-3-(4-methoxyphenyl)-5-phenylpyridin-2(1*H*)-one (8): Na_2CO_3 (159 mg, 1.5 mmol), $ArB(OH)_2$ (114 mg, 0.75 mmol), and Pd/C (26.5 mg, 5 mol-%) were added to a solution of bromopyridone (**7**) (223 mg, 0.5 mmol) in *i*PrOH (1.5 mL) and H_2O (1.5 mL). The resulting mixture was stirred at 60 °C for 12 h and then filtered. The catalyst was washed with H_2O (3 mL) and CH_2Cl_2 (5 mL). The aqueous phase was extracted twice with CH_2Cl_2. The collected organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude compound was purified by flash chromatography to give **8** as a white solid (120.6 mg, 51%), m.p. 108 °C. IR (KBr): $\tilde{\nu}$ = 1644, 2932, 3033 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 4.27 (s, 2 H), 5.22 (s, 2 H), 6.68 (d, J = 6.7 Hz, 2 H), 6.98 (d, J = 8.8 Hz, 2 H), 7.09–7.19 (m, 3 H), 7.31–7.44 (m, 11 H), 7.53 (d, J = 8.6 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.4, 55.3, 74.1, 113.5, 118.7, 121.9, 125.5, 127.4, 127.9, 128.0, 128.3, 128.4, 128.5, 128.8, 129.2, 132.0, 134.7, 135.2, 135.8, 136.5, 159.0, 161.8, 162.9 ppm. HRMS (ESI): calcd. for $C_{32}H_{28}NO_3$ $[M + H]^+$ 474.2063; found 474.2086.

2,4-Bis(benzyloxy)-3-iodo-5-phenylpyridine (9): A solution of iodine (1.75 g, 6.9 mmol) in dioxane (10 mL) was added dropwise over a period of 5 min to a refluxing solution of 4-hydroxy-5-phenylpyridin-2(1*H*)-one (**5**) (1.16 g, 6.2 mmol) and Na_2CO_3 (1.25 g, 11.8 mmol) in H_2O (25 mL). The solution was heated at reflux for a further 5 min, and then cooled to 5 °C. $NaHSO_3$ was added portionwise until decolouration of the solution had occurred. The mixture was then acidified with AcOH, which resulted in the precipitation of the 2,4-dihydroxy-3-iodopyridine. The product was filtered and then dried under vacuum with protection from light. The product was suspended in anhydrous benzene under argon, Ag_2CO_3 (3.42 g, 12.4 mmol) was added, and the resulting slurry was homogenised by magnetic stirring at room temperature for 5 min to give a yellowish suspension. Benzyl bromide (3.28 mL, 27.6 mmol) was added dropwise to the suspension, and the mixture was further stirred at room temperature in the dark for 3 d. After this period, the suspension was diluted with EtOAc, and filtered

through Celite, and the remaining greenish solid was washed five times with small portions of EtOAc. The solution was then concentrated, and the residual solid was recrystallised from hexane/toluene to give pure product **9** (1.86 g, 61%) as a white solid, m.p. 113–114 °C. IR (ZnSe): $\tilde{\nu}$ = 1577, 1457, 1435, 1367, 1360, 1204, 1069, 737, 696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.57 (s, 2 H), 5.52 (s, 2 H), 7.16–7.26 (m, 2 H), 7.29–7.61 (m, 13 H), 8.05 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.0, 161.7, 149.0, 136.6, 135.4, 133.7, 130.8, 129.0, 128.73, 128.70, 128.62, 128.58, 128.55, 128.53, 128.1, 127.9, 76.5, 75.1, 69.8 ppm. HRMS (ESI): calcd. for $C_{25}H_{21}INO_2$ $[M + H]^+$ 494.0617; found 494.0628.

2,4-Bis(benzyloxy)-3-iodoquinoline (11): Following the procedure described for the synthesis of **9**, compound **11** was obtained from 2,4-dihydroxyquinoline (**10**) after recrystallisation from hexane/toluene, as a white solid (898 mg, 31%), m.p. 141–142 °C. IR (ZnSe): $\tilde{\nu}$ = 3064, 3033, 2935, 1613, 1597 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.01 (d, J = 8.1 Hz, 1 H), 7.95 (d, J = 8.2 Hz, 1 H), 7.75–7.61 (m, 5 H), 7.57–7.34 (m, 7 H), 5.68 (s, 2 H), 5.22 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 160.0, 147.2, 137.1, 136.2, 130.5, 128.7, 128.6, 128.4, 127.8, 127.6, 127.4, 124.5, 122.1, 121.9, 77.5, 76.0, 69.0 ppm. HRMS (ESI): calcd. for $C_{23}H_{19}INO_2$ $[M + H]^+$ 468.0460; found 468.0477.

General Procedure for the Suzuki Coupling of 2,4-Bis(benzyloxy)-3-iodo-5-phenylpyridine (9) and 2,4-Bis(benzyloxy)-3-iodoquinoline (11): A suspension of **9** or **11** (0.2 mmol), boronic acid (0.24 mmol), Na_3CO_3 (64 mg, 0.6 mmol), and Pd/C (10.6 mg, 5 mol-%) in a mixture of *i*PrOH (0.5 mL) and H_2O (0.5 mL) was stirred at 80 °C for 12 h. The mixture was then diluted with EtOAc (5 mL) and hot-filtered through a Celite pad. The pad was washed with two portions of warm EtOAc, and then the combined fractions were washed with brine and dried with Na_2SO_4. The solution was filtered and concentrated under reduced pressure to give the crude product, which was purified by recrystallisation or flash chromatography.

2,4-Bis(benzyloxy)-3,5-diphenylpyridine (12a): Purification by recrystallisation from petroleum ether gave **12a** (68.2 mg, 77%) as a white solid, m.p. 111–112 °C. IR (ZnSe): $\tilde{\nu}$ = 3031, 2920, 2850, 1633, 1583 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.61 (d, J = 6.5 Hz, 2 H), 7.56 (d, J = 6.5 Hz, 2 H), 7.53–7.29 (m, 11 H), 7.25–7.10 (m, 3 H), 6.67 (d, J = 6.7 Hz, 2 H), 5.52 (s, 2 H), 4.29 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 161.5, 146.8, 137.7, 135.9, 135.6, 132.6, 130.9, 129.5, 128.5, 128.5, 128.3, 128.1, 128.0, 128.0, 127.5, 127.5, 127.4, 127.1, 126.3, 118.2, 74.6, 67.7 ppm. HRMS (ESI): calcd. for $C_{31}H_{25}NO_2Na$ $[M + Na]^+$ 466.1783; found 466.1771.

2,4-Bis(benzyloxy)-3-phenylquinoline (13a): Purification by flash chromatography (50:50 CH_2Cl_2/petroleum ether) gave **13a** (65.9 mg, 79%) as a white solid, m.p. 74–75 °C. IR (ZnSe): $\tilde{\nu}$ = 3066, 3032, 2944, 1614, 1595, 1570 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (d, J = 8.3 Hz, 1 H), 7.98 (d, J = 8.3 Hz, 1 H), 7.76–7.63 (m, 3 H), 7.60–7.29 (m, 11 H), 7.26–7.17 (m, 2 H), 5.67 (s, 2 H), 4.70 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9, 160.6, 146.6, 147.8, 137.8, 136.5, 133.1, 131.1, 129.9, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 127.8, 127.3, 127.3, 127.1, 121.8, 116.6, 75.5, 76.7 ppm. HRMS (ESI): calcd. for $C_{29}H_{23}NO_2Na$ $[M + Na]^+$ 440.1626; found 440.1632.

2,4-Bis(benzyloxy)-5-phenyl-3-*p*-tolylpyridine (12b): Purification by flash chromatography (50:50 CH_2Cl_2/petroleum ether) gave **12b** (79.5 mg, 87%) as a white solid, m.p. 136–137 °C. IR (ZnSe): $\tilde{\nu}$ = 3031, 1582, 1498 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.21 (s, 1 H), 7.66–7.59 (m, 2 H), 7.54–7.12 (m, 15 H), 6.76–6.68 (m, 2 H), 5.55 (s, 2 H), 4.33 (s, 2 H), 2.60 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 161.6, 146.6, 137.9, 137.2, 136.1, 135.7, 130.7, 129.6, 129.5, 128.7, 128.6, 128.4, 128.3, 128.1, 128.0, 127.4, 127.4, 127.2, 126.3, 118.1, 74.6, 67.7, 21.6 ppm. HRMS (ESI): calcd. for $C_{32}H_{28}NO_2$ $[M + H]^+$ 458.2041; found 458.2120.

2,4-Bis(benzyloxy)-3-*p*-tolylquinoline (13b): Purification by recrystallisation from petroleum ether/EtOAc gave **13b** (75.9 mg, 88%) as a white solid, m.p. 137–138 °C. IR (ZnSe): $\tilde{\nu}$ = 3061, 3030, 2938, 2877, 1582 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.58 (d, J = 6.7 Hz, 2 H), 7.52–7.08 (m, 13 H), 6.68 (d, J = 7.0 Hz, 2 H), 5.51 (s, 2 H), 4.29 (s, 2 H), 2.47 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 161.6, 146.5, 137.8, 137.1, 136.0, 135.6, 130.7, 129.5, 129.5, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.3, 127.3, 127.2, 126.3, 118.1, 74.5, 67.6, 21.4 ppm. HRMS (ESI): calcd. for $C_{30}H_{26}NO_2$ $[M + H]^+$ 432.1964; found 432.1959.

2,4-Bis(benzyloxy)-3-(4-methoxyphenyl)-5-phenylpyridine (12c): Purification by flash chromatography (50% CH_2Cl_2/petroleum ether) gave **12c** (74.9 mg, 79%) as a white solid, m.p. 132–133 °C. IR (ZnSe): $\tilde{\nu}$ = 3035, 2375, 1582, 1513 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (s, 1 H), 7.62–7.56 (m, 2 H), 7.54–7.10 (m, 13 H), 7.02 (d, J = 8.9 Hz, 2 H), 6.74–6.68 (m, 2 H), 5.51 (s, 2 H), 4.30 (s, 2 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.2, 161.6, 159.0, 146.4, 137.8, 136.0, 135.6, 132.0, 129.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.4, 127.4, 127.1, 126.3, 124.7, 117.8, 113.4, 74.5, 67.7, 55.3 ppm. HRMS (ESI): calcd. for $C_{32}H_{28}NO_3$ $[M + H]^+$ 474.2094; found 474.2069.

2,4-Bis(benzyloxy)-3-(4-methoxyphenyl)quinoline (13c): Purification by flash column chromatography (15% EtOAc/petroleum ether) gave **13c** (76.0 mg, 85%) as a white solid, m.p. 124–125 °C. IR (ZnSe): $\tilde{\nu}$ = 3064, 3033, 2935, 1613, 1597, 1572 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.10 (d, J = 8.3 Hz, 1 H), 7.90 (d, J = 7.9 Hz, 1 H), 7.65 (t, J = 7.8 Hz, 1 H), 7.55 (d, J = 8.8 Hz, 2 H), 7.49–7.26 (m, 9 H), 7.25–7.18 (m, 2 H), 7.04 (d, J = 8.8 Hz, 2 H), 5.62 (s, 2 H), 4.66 (s, 2 H), 3.91 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 160.7, 159.1, 146.3, 137.8, 136.6, 132.2, 129.7, 128.4, 128.3, 128.2, 128.2, 127.4, 127.3, 127.0, 125.0, 123.9, 122.7, 121.8, 121.2, 113.6, 75.2, 67.6, 55.3 ppm. HRMS (ESI): calcd. for $C_{30}H_{25}NO_3Na$ $[M + Na]^+$ 470.1732; found 470.1733.

2,4-Bis(benzyloxy)-3-(3,4-dimethoxyphenyl)-5-phenylpyridine (12d): Purification by flash chromatography (CH_2Cl_2) gave **12d** (96.6 mg, 96%) as a white solid, m.p. 94–95 °C. IR (ZnSe): $\tilde{\nu}$ = 3062, 3031, 2934, 2834, 1585 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.18 (s, 1 H), 7.59 (d, J = 6.5 Hz, 2 H), 7.52–7.29 (m, 8 H), 7.26–7.11 (s, 4 H), 7.08 (d, J = 1.9 Hz, 1 H), 6.97 (d, J = 8.3 Hz, 1 H), 6.76–6.69 (m, 2 H), 5.51 (s, 2 H), 4.32 (s, 2 H), 3.99 (s, 3 H), 3.80 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 161.5, 148.3, 146.4, 137.7, 136.1, 135.6, 129.5, 128.5, 128.4, 128.3, 128.3, 128.1, 128.0, 127.5, 127.4, 127.3, 126.4, 124.9, 123.6, 117.7, 114.1, 110.7, 74.5, 67.7, 55.9, 55.8 ppm. HRMS (ESI): calcd. for $C_{33}H_{29}NO_4Na$ $[M + Na]^+$ 526.1994; found 526.2008.

2,4-Bis(benzyloxy)-3-(3,4-dimethoxyphenyl)quinoline (13d): Purification by flash chromatography (15% EtOAc/petroleum ether) gave **13d** (84.9 mg, 89%) as a white solid, m.p. 98–100 °C. IR (ZnSe): $\tilde{\nu}$ = 3064, 3031, 2935, 1597 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.14 (d, J = 8.1 Hz, 1 H), 7.93 (d, J = 8.2 Hz, 1 H), 7.75–7.62 (m, 1 H), 7.61–7.11 (m, 13 H), 7.01 (d, J = 8.2 Hz, 1 H), 5.65 (s, 2 H), 4.71 (s, 2 H), 4.00 (s, 3 H), 3.84 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.7, 160.6, 148.6, 148.5, 146.3, 137.7, 136.6, 129.8, 128.7, 128.5, 128.3, 128.2, 127.6, 127.5, 127.1, 125.2, 124.1, 123.7, 122.7, 121.8, 116.1, 114.2, 110.8, 75.2, 67.8, 55.9, 55.8 ppm. HRMS (ESI): calcd. for $C_{31}H_{28}NO_4$ $[M + H]^+$ 478.2039; found 478.2018.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2,4-bis(benzyloxy)-5-phenylpyridine (12e): Purification by recrystallisation from petroleum ether/EtOAc gave **12e** (78.9 mg, 81%) as a white solid, m.p. 139–140 °C. IR (ZnSe): $\tilde{\nu}$ = 3063, 3031, 2941, 2884, 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.15 (s, 1 H), 7.56 (d, J = 8.1 Hz, 2 H), 7.48–7.29 (m, 8 H), 7.21–7.12 (m, 3 H), 7.02–6.97 (m, 2 H), 6.99–6.85 (m, 1 H), 6.74 (d, J = 6.6 Hz, 2 H), 6.02 (s, 2 H), 5.49 (s, 2 H), 4.32 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.3, 161.6, 147.4, 147.0, 146.7, 137.8, 136.1, 135.6, 129.5, 128.5, 128.4, 128.2, 127.5, 127.3, 126.4, 126.1, 124.6, 117.8, 111.5, 108.1, 101.1, 74.7, 67.8 ppm. HRMS (ESI): calcd. for $C_{32}H_{26}NO_4$ $[M + H]^+$ 488.1862; found 488.1801.

3-(Benzo[*d*][1,3]dioxol-5-yl)-2,4-bis(benzyloxy)quinoline (13e): Purification by recrystallisation from petroleum ether/toluene gave **13e** (76.5 mg, 83%) as a white solid, m.p. 120–121 °C. IR (ZnSe): $\tilde{\nu}$ = 3064, 3031, 2884, 1596, 1571 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.11 (d, J = 8.2 Hz, 1 H), 8.34 (d, J = 8.3 Hz, 1 H), 7.67 (t, J = 7.6 Hz, 1 H), 7.51–7.22 (m, 11 H), 7.14–7.06 (m, 2 H), 6.97 (dd, J = 8.4, J = 1.5 Hz, 1 H), 6.06 (s, 2 H), 5.64 (s, 2 H), 4.74 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9, 160.6, 147.5, 147.1, 146.3, 137.8, 136.6, 129.8, 128.5, 128.3, 128.2, 128.2, 127.5, 127.4, 127.1, 126.3, 124.7, 124.0, 122.7, 121.8, 116.1, 111.5, 108.2, 101.1, 75.3, 67.7 ppm. HRMS (ESI): calcd. for $C_{30}H_{24}NO_4$ $[M + H]^+$ 462.1697; found 462.1705.

4-[2,4-Bis(benzyloxy)-5-phenylpyridin-3-yl]benzoic Acid (12f): Purification by recrystallisation from petroleum ether/EtOAc gave **12f** (69.2 mg, 71%) as a light yellow solid, m.p. 197–198 °C. IR (ZnSe): $\tilde{\nu}$ = 3062, 3031, 2947, 2877, 2547, 1610, 1582 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 8.13 (s, 1 H), 8.04 (d, J = 8.3 Hz, 2 H), 7.56 (d, J = 6.5 Hz, 2 H), 7.56–7.37 (m, 5 H), 7.34–7.11 (m, 6 H), 7.06 (t, J = 7.3 Hz, 2 H), 6.62 (d, J = 7.0 Hz, 2 H), 5.40 (s, 2 H), 4.27 (s, 2 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 171.7, 162.1, 161.1, 147.0, 137.3, 135.7, 135.3, 130.7, 129.0, 129.0, 128.8, 128.2, 128.2, 128.0, 127.9, 127.7, 127.7, 127.3, 127.2, 127.0, 126.3, 117.6, 74.4, 67.6 ppm. HRMS (ESI): calcd. for $C_{32}H_{26}NO_4$ $[M + H]^+$ 488.1862; found 488.1873.

4-[2,4-Bis(benzyloxy)quinolin-3-yl]benzoic Acid (13f): Purification by recrystallisation from petroleum ether/EtOAc gave **13f** (61.8 mg, 67%) as a light yellow solid, m.p. 161 °C (decomp). IR (ZnSe): $\tilde{\nu}$ = 3064, 3031, 2945, 1694, 1598 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ = 8.08 (d, J = 8.0 Hz, 2 H), 8.02 (d, J = 8.2 Hz, 1 H), 7.82 (d, J = 8.4 Hz, 1 H), 7.61 (t, J = 7.6 Hz, 1 H), 7.53 (d, J = 8.0 Hz, 2 H), 7.42–7.17 (m, 9 H), 7.14–7.03 (m, 2 H), 5.49 (s, 2 H), 4.60 (s, 2 H) ppm. ^{13}C NMR (75 MHz, CD_3OD): δ = 173.3, 160.8, 160.3, 146.4, 137.3, 136.3, 135.3, 133.7, 130.3, 129.7, 128.7, 128.0, 127.9, 127.9, 127.1, 127.0, 126.6, 123.8, 122.4, 121.5, 116.3, 108.7, 75.3, 67.5 ppm. HRMS (ESI): calcd. for $C_{30}H_{24}NO_4$ $[M + H]^+$ 462.1705; found 462.1700.

Methyl 4-[2,4-Bis(benzyloxy)quinolin-3-yl]benzoate (12g): Purification by flash column chromatography (50% CH_2Cl_2/petroleum ether) gave **12g** (95.2 mg, 95%) as a white solid, m.p. 153–154 °C. IR (ZnSe): $\tilde{\nu}$ = 2949, 2374, 1720, 1579, 1528, 1498 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.24 (s, 1 H), 8.15 (d, J = 8.5 Hz, 2 H), 7.66–7.59 (m, 4 H), 7.55–7.10 (m, 11 H), 6.71–6.63 (m, 2 H), 5.51 (s, 2 H), 4.31 (s, 2 H), 4.01 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 162.1, 161.2, 147.6, 137.8, 137.4, 135.6, 135.4, 131.1, 130.2, 129.4, 129.1, 129.1, 128.6, 128.5, 128.4, 128.2, 127.6, 127.6, 127.2, 126.2, 117.3, 74.8, 67.9, 52.2 ppm. HRMS (ESI): calcd. for $C_{33}H_{28}NO_4$ $[M + H]^+$ 502.2018; found 502.2018.

Methyl 4-[2,4-Bis(benzyloxy)quinolin-3-yl]benzoate (13g): Purification by flash column chromatography (15% EtOAc/petroleum ether) gave **13g** (90.3 mg, 95%) as a white solid, m.p. 133–134 °C. IR (ZnSe): $\tilde{\nu}$ = 3064, 3032, 2949, 1723, 1610, 1572 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.28 (d, J = 8.5 Hz, 2 H), 8.21 (d, J = 8.2 Hz, 1 H), 8.05 (d, J = 8.1 Hz, 1 H), 7.79 (d, J = 8.5 Hz, 2 H), 7.74 (t, J = 8.5 Hz, 1 H), 7.53–7.32 (m, 9 H), 7.29–7.20 (m, 2 H), 5.71 (s, 2 H), 4.73 (s, 2 H), 4.05 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.1, 161.2, 160.1, 146.9, 138.2, 137.5, 136.3, 131.3, 130.3, 129.4, 128.6, 128.4, 128.4, 128.4, 128.3, 127.6, 127.6, 127.4, 124.3, 122.9, 121.6, 115.9, 75.9, 68.0, 52.2 ppm. HRMS (ESI): *m*/*z* calcd. for $C_{31}H_{26}NO_4$ $[M + H]^+$ 476.1862; found 476.1871.

2,4-Bis(benzyloxy)-3-(4-nitrophenyl)-5-phenylpyridine (12h): Purification by flash chromatography (50% CH_2Cl_2-petroleum ether) gave **12h** (69.3 mg, 71%) as a yellow solid, m.p. 159–160 °C. IR (ZnSe): $\tilde{\nu}$ = 3063, 3031, 2939, 1600, 1580, 1519 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.25 (s, 1 H), 8.23 (d, J = 9.9 Hz, 2 H), 7.63–7.58 (m, 4 H), 7.52–7.43 (m, 3 H), 7.35–7.30 (m, 5 H), 7.23–7.18 (m, 1 H), 7.14–7.08 (m, 2 H), 6.64 (d, J = 7.2 Hz, 2 H), 5.47 (s, 2 H), 4.29 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.1, 160.9, 148.4, 147.0, 140.0, 137.1, 135.3, 135.2, 132.1, 129.3, 128.8, 128.5, 128.4, 128.3, 127.9, 127.8, 127.4, 126.1, 122.9, 116.3, 75.2, 68.1 ppm. HRMS (ESI): calcd. for $C_{31}H_{25}N_2O_4$ $[M + H]^+$ 489.1814; found 489.1904.

2,4-Bis(benzyloxy)-3-(4-nitrophenyl)quinoline (13h): Purification by flash chromatography (50% CH_2Cl_2-petroleum ether) gave **13h** (67.5 mg, 73%) as a yellow solid, m.p. 136–137 °C. IR (ZnSe): $\tilde{\nu}$ = 3065, 3033, 2945, 1602, 1571 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.42–8.25 (m, 2 H), 8.14 (d, J = 8.2 Hz, 1 H), 7.99 (d, J = 8.2 Hz, 1 H), 7.82–7.70 (m, 3 H), 7.62–7.24 (m, 9 H), 7.22–7.10 (m, 2 H), 5.64 (s, 2 H), 4.75 (s, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.4, 159.5, 147.1, 147.1, 144.9, 140.2, 137.2, 135.8, 132.1, 130.7, 128.6, 128.5, 128.3, 128.2, 127.8, 127.7, 127.4, 123.1, 122.4, 121.3, 115.1, 76.4, 68.1 ppm. HRMS (ESI): calcd. for $C_{29}H_{23}N_2O_4$ $[M + H]^+$ 463.1658; found 463.2123.

4-[2,4-Bis(benzyloxy)-5-phenylpyridin-3-yl]phenyl 4-Methylbenzenesulfonate (12i): Purification by flash column chromatography (20% EtOAc/petroleum ether) gave **12i** (69.9 mg, 57%) as a white solid, m.p. 161–162 °C. IR (ZnSe): $\tilde{\nu}$ = 2921, 2851, 1652, 1635, 1577, 1558 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (s, 1 H), 7.75 (d, J = 8.3 Hz, 2 H), 7.59 (d, J = 6.5 Hz, 2 H), 7.52–7.12 (m, 15 H), 7.07 (d, J = 8.8 Hz, 2 H), 6.67 (d, J = 7.8 Hz, 2 H), 5.46 (s, 2 H), 4.24 (s, 2 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 161.2, 148.9, 147.3, 145.3, 137.4, 135.6, 135.3, 132.5, 132.2, 131.7, 129.8, 129.7, 129.3, 128.6, 128.4, 128.3, 128.2, 128.2, 127.6, 127.5, 127.1, 126.1, 121.9, 117.0, 74.7, 67.8, 21.7 ppm. HRMS (ESI): calcd. for $C_{38}H_{32}NO_5S$ $[M + H]^+$ 614.2001; found 614.1989.

4-[2,4-Bis(benzyloxy)quinolin-3-yl]phenyl 4-Methylbenzenesulfonate (13i): Purification by flash column chromatography (20% EtOAc/petroleum ether) gave **13i** (50.5 mg, 43%) as a white solid, m.p. 132–134 °C. IR (ZnSe): $\tilde{\nu}$ = 3063, 3358, 3062, 2921, 2850, 1657, 1596 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.08 (d, J = 8.2 Hz, 1 H), 7.91 (d, J = 8.0 Hz, 1 H), 7.73 (d, J = 8.2 Hz, 2 H), 7.66 (d, J = 6.9 Hz, 1 H), 7.51 (d, J = 8.7 Hz, 2 H), 7.46–6.98 (m, 15 H), 5.58 (s, 2 H), 4.61 (s, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9, 160.1, 149.1, 146.7, 145.3, 137.4, 136.1, 132.4, 132.3, 132.0, 130.2, 129.7, 128.5, 128.5, 128.4, 128.3, 128.2, 127.5, 127.3, 127.2, 124.2, 122.7, 122.1, 121.5, 115.5, 75.6, 67.7, 21.7 ppm. HRMS (ESI): calcd. for $C_{36}H_{29}NO_5S$ $[M + Na]^+$ 610.1664; found 610.1678.

3-Biphenyl-4-hydroxypyridin-2(1*H*)-one (14): $Pd(OH)_2/C$ (20 mol-%) was added to a solution of pyridone **4a** (184 mg, 0.5 mmol) in AcOH (5 mL), and the mixture was stirred at 60 °C under an atmosphere of H_2 for 12 h. The mixture was filtered and concen-

trated under reduced pressure, and the residue was precipitated from Et_2O. The resulting grey solid was filtered and used in the next step without further purification, due to its insolubility in most organic solvents.

Nucleoside 15: *N*,*O*-Bis(trimethylsilyl)acetamide (245 μL, 1 mmol) was added to a solution of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (207 mg, 0.65 mmol) and compound **14** (0.5 mmol) in CH_3CN (3 mL) at room temperature. The resulting mixture was stirred for 2 h, and then TMSOTf (181 μL, 1 mmol) was added dropwise. After being stirred for 18 h at room temperature, the solution was diluted with CH_2Cl_2 (10 mL) and washed with water (1×) and saturated aqueous $NaHCO_3$ solution (2×). The aqueous phase was extracted with CH_2Cl_2 (3×). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (80% EtOAc/petroleum ether) gave **15** (161.5 mg, 62% over two steps) as a white foam. $[\alpha]_D^{25}$ = +92.2 (*c* 1.09, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 1652, 1750, 2939, 3031, 3082, 3401 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 2.03 (s, 3 H), 2.05 (s, 3 H), 2.13 (s, 3 H), 4.30–4.39 (m, 3 H), 5.29 (t, *J* = 6.2 Hz, 1 H), 5.45 (dd, *J* = 3.4, 5.6 Hz, 1 H), 6.08 (d, *J* = 7.7 Hz, 1 H), 6.18 (d, *J* = 3.4 Hz, 1 H), 7.24 (br. s, 1 H), 7.32–7.37 (m, 1 H), 7.41–7.46 (m, 5 H), 7.56–7.64 (m, 4 H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 20.4, 20.7, 62.6, 69.3, 74.1, 78.9, 89.1, 100.9, 112.1, 127.1, 127.4, 127.7, 128.8, 130.0, 130.9, 131.9, 140.7, 140.9, 162.0, 162.2, 169.5, 170.3 ppm. HRMS (ESI): calcd. for $C_{28}H_{27}NO_9Na$ $[M + Na]^+$ 544.1578; found 544.1571.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra.

Acknowledgments

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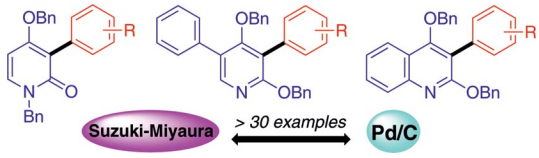

A heterogeneous Pd/C-catalysed Suzuki–Miyaura cross-coupling reaction for the preparation of 3-aryl-4-oxypyridin-2(1*H*)-ones, 3-aryl-2,4-oxypyridines, and 3-aryl-2,4-oxyquinolines represents a useful and efficient alternative to homogeneous conditions. These interesting heterocycles can be used as platforms for the synthesis of biologically active compounds.

Heterogeneous Catalysis

Keywords: Heterogeneous catalysis / Palladium / Cross-coupling / Nitrogen heterocycles / Nucleosides / Medicinal chemistry / Antiviral agents

