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Use of Suzuki cross-coupling as a route to 2-phenoxy-6-iminopyridines and chiral 2-phenoxy-6-(methanamino)pyridines

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ABSTRACT

The anisyl boronic acids, 2-OMe-3-R^2-5-R^1-$C_6H_2B(OH)_2$ (R^1=R^2=H (**a**); R^1=H, R^2=Ph (**b**); R^1=Me, R^2=H (**c**); R^1=Cl, R^2=H (**d**); R^1=*t*-Bu, R^2=H (**e**)), have been employed in Suzuki cross-coupling reactions with either 2-bromo-6-formylpyridine (**I**) or 2-bromo-6-acetylpyridine (**II**) generating, following a facile deprotection step, the 2-phenoxy-6-carbonylpyridines, 2-(2′-OH-3′-R^2-5′-R^1-C_6H_2)-6-(CH=O)C_5H_3N (R^1=R^2=H (**1a**); R^1=Me, R^2=H (**1c**); R^1=Cl, R^2=H (**1d**); R^1=*t*-Bu, R^2=H (**1e**)) and 2-(2′-OH-3′-R^2-5′-R^1-C_6H_2)-6-(CMe=O)C_5H_3N (R^1=R^2=H (**2a**); R^1=H, R^2=Ph (**2b**)). Condensation reactions of **1** and **2** with 2,6-diisopropylaniline proceed smoothly to give the 2-phenoxy-6-iminopyridines, 2-(2′-OH-3′-R^2-5′-R^1-C_6H_2)-6-{CH=N(2,6-*i*-$Pr_2C_6H_3$)}C_5H_3N (R^1=R^2=H (**3a**); R^1=Me, R^2=H (**3c**); R^1=Cl, R^2=H (**3d**); R^1=*t*-Bu, R^2=H (**3e**)) and 2-(2′-OH-3′-R^2-5′-R^2-C_6H_2)-6-{CMe=N(2,6-*i*-$Pr_2C_6H_3$)}C_5H_3N (R^1=H, R^2=Ph (**4a**), R^1=H, R^2=Ph (**4b**)). Reduction of the imino unit (and concomitant C–C bond formation) in **3** can be achieved by treatment with trimethylaluminium or methyllithium which, following hydrolysis, furnishes the racemic chiral 2-phenoxy-6-(methanamino)pyridines, 2-(2′-OH-3′-R^2-5′-R^1-C_6H_2)-6-{CHMe-NH(2,6-*i*-$Pr_2C_6H_3$)}C_5H_3N (R^1=R^2=H (**5a**); R^1=Me, R^2=H (**5c**); R^1=Cl, R^2=H (**5d**); R^1=*t*-Bu, R^2=H (**5e**)). This work represents a straightforward and rapid synthetic route to libraries of sterically and electronically variable phenoxy-substituted imino- and methanamino-pyridines, which are expected to act as useful ligands or proligands for late and early transition metal-mediated alkene polymerisation catalysis.

1. Introduction

With the advent of high-throughput-screening (HTS) technologies for the evaluation of large numbers of catalysts for olefin polymerisation,[1] there presents a need to develop promising libraries of ligands that can support polymerisation-active metal centres (e.g., Ti, Hf, Zr, Cr, V, Ni, Fe, Co). In recent years, the discovery of highly active alkene polymerisation catalysts based on sterically bulky tridentate *N*,*N*,*N*-chelating ligands such as 2,6-bis(imino)pyridines[2–4] and 2,6-bis(methanaminato)pyridines[5] has help signpost future possibilities for ligand design. The *O*,*N*,*O*-chelating ligand family, 2,6-bis(phenolate)pyridine,[6] has proved an effective support for zirconium-based catalysts while the disclosure of thermally robust hafnium propene polymerisation catalysts based on dianionic *N*,*N*,*C*-chelating ligands (viz., 2-methanaminato-6-phenylpyridines[7]) has shown the great potential of developing a unsymmetrical ligand environment.

Herein, we introduce a simple general strategy for preparing a wide variety of unsymmetrical *N*,*N*,*O*-donor 2-phenoxy-6-iminopyridines (**3**/**4**, Fig. 1) and 2-phenoxy-6-(methanamino)pyridines (**5**, Fig. 1), each incorporating a sterically bulky *N*-2,6-diisopropylphenyl group.[4,8] Variation in the steric and electronic properties of the R^1 and R^2 positions of the phenol unit in **3**–**5** is demonstrated while a stereogenic centre can be readily incorporated in the case of **5**. The ligand synthesis proceeds via the preparation of 6-formyl- and 6-acetyl-functionalised 2-phenoxypyridines (using Suzuki coupling methodologies[9]), which can be smoothly converted to their aryl-imine counterparts and subsequently reduced to their aryl-amines.

2. Results and discussion

2.1. Synthesis of the anisyl boronic acids

The anisyl boronic acids, 2-OMe-3-R^2-5-R^1-$C_6H_2B(OH)_2$ (R^1=R^2=H (**a**); R^1=H, R^2=Ph (**b**); R^1=Me, R^2=H (**c**); R^1=Cl, R^2=H

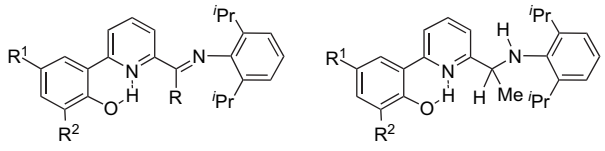

Figure 1. 2-Phenoxy-6-iminopyridine (**3**/**4**) and 2-phenoxy-6-(methanamino)pyridine (**5**); R=H, Me; R^1 or R^2=H, hydrocarbyl, halide.

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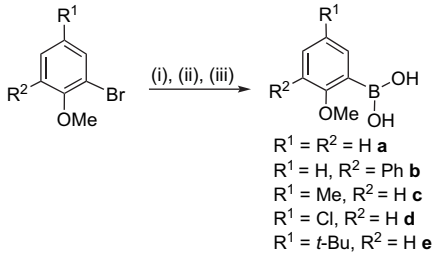
(**d**); R^1=*t*-Bu, R^2=H (**e**)), can be prepared in good overall yield from the corresponding anisyl bromide using the literature procedures (Scheme 1)[10,11] or obtained commercially (**a**, **c**, **d**). The molecular structure of **b** is depicted in Figure 2; selected bond distances and angles are collected in Table 1. The structure of **b** consists of a trigonal planar [O(1)–B(1)–O(2) 119.58(11)°] boron atom linked to two hydroxide groups and an anisyl ring with the 3-substituted phenyl ring tilted with respect to the anisyl ring [tors.: C(2)–C(3)–C(7)–C(8) 48.7°]; a hydrogen bonding interaction between one of the hydroxide hydrogen atoms and the anisyl oxygen [O(2)···O(3) 2.743 Å] is also apparent.



Scheme 1. Reagents and conditions: (i) *n*-BuLi, Et_2O, −78 °C or Mg, THF, heat; (ii) B(O-*i*-Pr)$_3$, Et_2O, −78 °C; (iii) H^+/H_2O.

2.2. Suzuki coupling of a–e with 2-bromo-6-carbonylpyridine

Suzuki cross-coupling reactions of **a**–**e** were carried out with either 2-bromo-6-formylpyridine (**I**) or 2-bromo-6-acetylpyridine (**II**) in toluene at elevated temperature in the presence of potassium carbonate and catalytic quantities of $Pd(PPh_3)_4$ (1–2 mol %) to afford, following a BBr_3 mediated deprotection, the 2-phenoxy-6-formylpyridines, 2-(2′-OH-3′-R^2-5′-R^1-C_6H_2)-6-(CH═O)C_5H_3N (R^1=R^2=H (**1a**); R^1=Me, R^2=H (**1c**); R^1=Cl, R^2=H (**1d**); R^1=*t*-Bu, R^2=H (**1e**)) and the 2-phenoxy-6-acetylpyridines, 2-(2′-OH-3′-R^2-5′-R^1-C_6H_2)-6-(CMe═O)C_5H_3N (R^1=R^2=H (**2a**); R^1=H, R^2=Ph (**2b**)) in good yield (Table 2). All the new compounds have been characterised by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and ESI mass spectrometry (see Section 4).

The IR spectra for **1** and **2** show characteristic absorption bands for their carbonyl functionalities (range: 1698–1717 cm^{-1}) while protonated molecular ion peaks were revealed in their ESI mass spectra. In the ^{13}C{^{1}H} NMR spectra, the carbonyl carbon atoms fall between δ 189.6 and 196.6 with the *CH*═O and C*Me*═O protons being seen at ca. δ 10.0 (**1**) and ca. δ 2.6 (**2**) in their ^{1}H NMR spectra, respectively.

The overall yields obtained for the combination of both the coupling reaction and the deprotection step are generally good (>60%) but start to decrease as catalyst loadings are reduced below 1%. Attempts at using alternative bases in the Suzuki coupling (e.g., KO*t*-Bu and NBu_4OH) gave lower yields of the desired product as did the use of alternative deprotection procedures (e.g., molten pyridium chloride[12]).

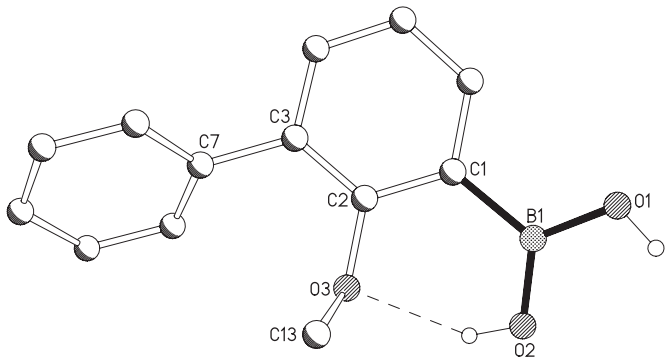


Figure 2. Molecular structure of **b** including a partial atom numbering scheme. All hydrogen atoms, apart from H1 and H2, have been omitted for clarity.

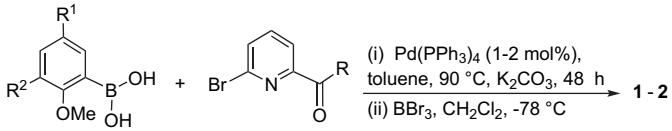
Table 1
Selected bond distances (Å) and angles (°) for **b**

B(1)–O(1)	1.3482(16)	C(3)–C(7)	1.4886(16)
B(1)–O(2)	1.3636(16)	O(3)–C(2)	1.3930(14)
B(1)–C(1)	1.5701(17)	O(3)–C(13)	1.4303(16)
O(2)–B(1)–O(1)	119.58(11)	C(2)–O(3)–C(13)	114.14(9)

2.3. Condensation reaction of carbonyl compounds with 2,6-diisopropylaniline

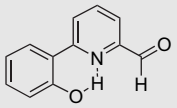
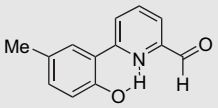
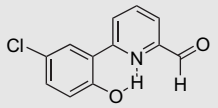
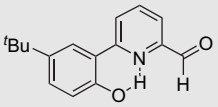
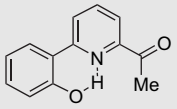
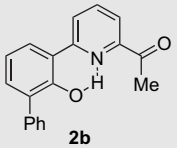
Treatment of **1** and **2** with 2,6-diisopropylaniline in ethanol at temperatures between 50 °C and 80 °C, in the presence of a catalytic

Table 2
Synthesis of 2-phenoxy-6-carbonylpyridines via Suzuki cross-coupling of **a**–**e** with 2-bromo-6-carbonylpyridines



R^1 = R^2 = H **a**
R^1 = H, R^2 = Ph **b**
R^1 = Me, R^2 = H **c**
R^1 = Cl, R^2 = H **d**
R^1 = *t*-Bu, R^2 = H **e**

R = H **I**
R = Me **II**

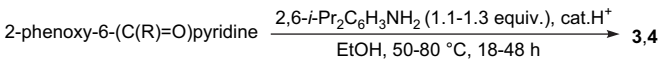
Entry	Boronic acid	2-Bromo-6-carbonylpyridine	Deprotected product	Yield[a] (%)
1	**a**	**I**	 **1a**	70
2	**c**	**I**	 **1c**	65
3	**d**	**I**	 **1d**	69
4	**e**	**I**	 **1e**	75
5	**a**	**II**	 **2a**	73
6	**b**	**II**	 **2b**	61

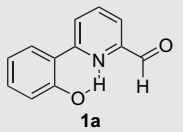
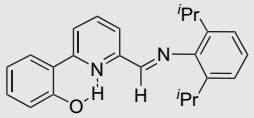
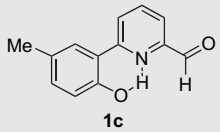
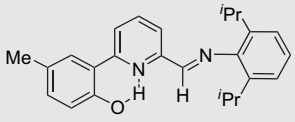
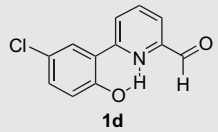
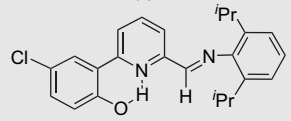
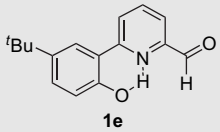
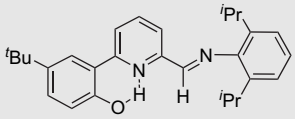
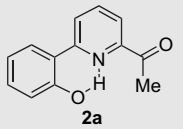
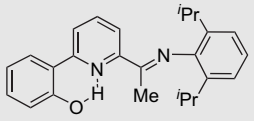
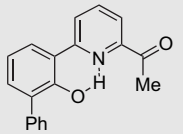
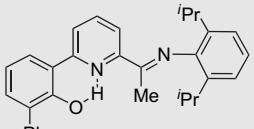
[a] Isolated yields from both steps.

amount of glacial acetic acid gave the 2-phenoxy-6-iminopyridines, 2-(2′-OH-3′-R^2-5′-R^1-C_6H_2)-6-{CH=N(2,6-*i*-$Pr_2C_6H_3$)}C_5H_3N (R^1=R^2=H (**3a**); R^1=Me, R^2=H (**3c**); R^1=Cl, R^2=H (**3d**); R^1=*t*-Bu, R^2=H (**3e**)) and 2-(2′-OH-3′-R^1-5′-R^2-C_6H_2)-6-{CMe=N(2,6-*i*-$Pr_2C_6H_3$)}C_5H_3N (R^1=R^2=H (**4a**); R^1=H, R^2=Ph (**4b**)) as pale yellow solids in moderate to good yield (see Table 3). All the new compounds have been characterised by ^{1}H NMR, ^{13}C NMR, IR spectroscopy and ESI mass spectrometry (see Section 4).

Single crystal X-ray diffraction studies have been performed on **3a**, **3d** and **4a**. A perspective view of **3d** is depicted in Figure 3; selected bond distances and angles for all three structures are listed in Table 4. Each structure consists of a central pyridine ring that is substituted at its 2-position by a phenol group and at the 6-position by an imine unit [C(12)–N(2) 1.2600(12) Å (**3a**), 1.2595(17) Å (**3d**), 1.266(4) Å (**4a**)]. The pyridine nitrogen adopts a trans configuration with respect to the neighbouring imine nitrogen [tors.: N(1)–C(11)–C(12)–N(2) 171.2° (**3a**), 178.8° (**3d**), 177.3° (**4a**)] while it is cis to the phenol oxygen; the latter configuration is the result of a hydrogen bonding interaction between the phenol hydrogen atom and the neighbouring pyridine nitrogen [O(1)···N(1) 2.562 Å (**3a**), 2.563 Å (**3d**), 2.536 Å (**4a**)]. For all three structures, the 2,6-diisopropylphenyl rings are inclined essentially orthogonal to the plane of the adjacent pyridylimine unit.

Table 3
Condensation reactions of **1** and **2** with 2,6-diisopropylaniline



Entry	2-Phenoxy-6-carbonylpyridine	2-Phenoxy-6-iminopyridine product	Yield[a] (%)
7	 **1a**	 **3a**	56
8	 **1c**	 **3c**	72
9	 **1d**	 **3d**	61
10	 **1e**	 **3e**	72
11	 **2a**	 **4a**	80
12	 **2b**	 **4b**	61

[a] Isolated yields.

The mass spectra of **3** and **4** reveal protonated molecular ion peaks while in their IR spectra absorption bands characteristic for their imino functionalities (ca. 1635 cm^{-1}) are evident. In their ^{1}H NMR spectra, the aldimine compounds (**3**) gave singlets at ca. δ 8.2 consistent with the presence of C*H*=N protons while the C*Me*=N protons are seen at ca. δ 2.2 for the ketimine compounds (**4**).

2.4. Formation of the 2-phenoxy-6-(methanamino)pyridines

Reaction of **3a**, **3c**, **3d** or **3e** with trimethylaluminium in toluene at 110 °C followed by hydrolysis afforded 2-(2′-OH-3′-R^2-5′-R^1-C_6H_2)-6-{CHMe-NH(2,6-*i*-$Pr_2C_6H_3$)}C_5H_3N (R^1=R^2=H (**5a**); R^1=Me, R^2=H (**5c**); R^1=Cl, R^2=H (**5d**); R^1=*t*-Bu, R^2=H (**5e**)) in high yield (Table 5; method A), respectively. Alternatively, **5** could be prepared by treating **3** with methyllithium in diethylether at −40 °C followed by hydrolysis (Table 5; method B); the method yielding the best yield for **5** is indicated in Table 5. In the case of **5a**, reduction of the imine unit in **4a** using excess sodium borohydride in ethanol also allows access to **5a**. The ^{1}H NMR spectra of **5** confirm the formation of the saturated –CHMeNH(Ar) moiety with the C*H*MeNH(Ar) proton taking the form of a quartet that is coupled to the geminal methyl group ($^3J_{H-H}$ 6.7 Hz). In their ^{13}C NMR spectra the expected number of independent carbon signals are shown, while their ESI mass spectra display peaks corresponding to the protonated molecular ions.

To support the spectroscopic data, crystals of **5a** and **5e** have been the subject of single crystal X-ray diffraction studies. A perspective view of **5e** is depicted in Figure 4; selected bond distances and angles for both structures are listed in Table 6. Both structures consist of a central pyridine linked at its 2-position by a *cis*-oriented phenol (**5a**) or a 5-*tert*-butylphenol (**5e**) group and at its 6-position by an amine-containing CHMeNH(2,6-*i*-$Pr_2C_6H_3$) unit. The phenol moieties are almost co-planar with respect to the pyridine unit [tors.: C(1)–C(6)–C(7)–N(1) 14.9° (**5a**), 12.8° (**5e**)] and are disposed mutally cis as a result of a hydrogen bonding interaction between the phenol hydrogen atom and the neighbouring pyridine nitrogen [O(1)···N(1) 2.581 Å (**5a**), 2.578 Å (**5e**)]. The chiral –Py*C*HMeNH(Ar) carbons in **5a** display the (*S*) configuration while in **5e** the (*R*) configuration is exhibited.

3. Conclusions

In summary, we have described a straightforward and efficient synthesis for a broad range of sterically and electronically variable phenoxy-substituted pyridylimines via a palladium-mediated Suzuki cross-coupling approach. In addition, aluminium alkyls and lithium alkyls have been employed to facilitate C–C bond formation and the production of a series of racemic chiral phenoxy-substituted pyridylamines. The coordination chemistry of these new ligand types and the potential as supports for polymerisation-active metal centres will be explored elsewhere.

4. Experimental

4.1. General

All reactions, unless otherwise stated, were carried out under an atmosphere of dry, oxygen-free nitrogen using standard Schlenk techniques. Solvents were distilled under nitrogen from appropriate drying agents and degassed prior to use.[13] The infrared spectra were recorded on a Perkin–Elmer Spectrum One FT-IR spectrometer on solid samples. The electrospray ionisation (ESI) and the fast atom bombardment (FAB) mass spectra were recorded using a micromass Quattro LC mass spectrometer and a Kratos Concept spectrometer with chloroform or NBA as the matrix, respectively. High resolution FAB mass spectra were recorded on Kratos Concept

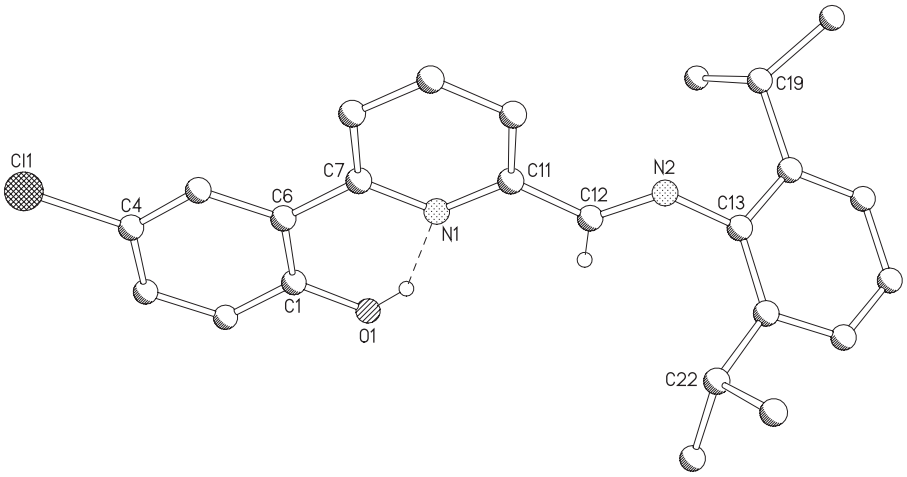


Figure 3. Molecular structure of **3d** including a partial atom numbering scheme. All hydrogen atoms, apart from H1 and H12, have been omitted for clarity.

spectrometer (xenon gas, 7 kV) with NBA as matrix. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX spectrometer (300 MHz); chemical shifts (ppm) are referred to the residual protic solvent peaks; coupling constants are in Hertz (Hz). Melting points (mp) were measured on a Gallenkamp melting point apparatus (model MFB-595) in open capillary tubes and were uncorrected. Elemental analyses were performed on a Carlo Erba CE1108 instrument at the Science Technical Support Unit, London Metropolitan University.

The reagents, 2-methoxyphenylboronic acid (**a**), 2-methoxy-5-methylphenylboronic acid (**c**), 2-methoxy-5-chlorophenylboronic acid (**d**), 2-bromo-6-formylpyridine (**I**), 2-bromo-6-acetylpyridine (**II**), triisopropylborate, 2,6-diisopropylaniline, boron tribromide (1 M solution in dichloromethane), methyllithium (1.4 M solution in diethylether) and trimethylaluminium (2 M solution in toluene) were purchased from Aldrich Chemical Co. and used without further purification. The compounds, 3-phenyl-2-methoxyphenylboronic acid (**b**),[10] 2-methoxy-*tert*-butylphenylboronic acid (**e**),[11] tetrakis(triphenylphosphine)palladium(0),[14] were prepared according to previously reported procedures. All other chemicals were obtained commercially and used without further purification.

4.2. Suzuki cross-coupling/deprotection reactions

*4.2.1. 2-(2′-Phenoxy)-6-formylpyridine (**1a**)*

An oven-dried Schlenk flask equipped with a magnetic stirrer bar was evacuated and back filled with nitrogen. The flask was charged with **I** (0.53 g, 2.79 mmol), [Pd(PPh$_3$)$_4$] (0.067 g, 0.057 mmol, 0.02 equiv), toluene (10 mL) and aqueous 2 M solution of potassium carbonate (2.80 mL, 5.55 mmol, 2 equiv). The solution was stirred for 15 min followed by the addition of the boronic acid **a** (0.753 g, 3.62 mmol, 1.3 equiv) in ethanol (5 mL). After heating the solution to 90 °C for 42 h, the flask was allowed to cool to room temperature and 30% hydrogen peroxide (0.2 mL) added and the solution left to stir at room temperature for 1 h. The product was extracted with diethylether (2×50 mL) and washed sequentially with saturated sodium chloride solution and water (3×30 mL). The organic extracts were combined, dried over magnesium sulfate and the volatiles removed under reduced pressure. The residue was adsorbed onto silica and applied to the top of a short silica column and eluted with dichloromethane/hexane (80:20) to give the protected product, after drying under reduced pressure, as a yellow oil (0.503 g). The oil (0.503 g, 2.36 mmol) was loaded into a Schlenk vessel under nitrogen, dissolved in dry dichloromethane (10 mL) and cooled to −78 °C. Boron tribromide (4.96 mL, 4.96 mmol, 2.1 equiv) was added dropwise to the cooled solution and the resulting brown solution allowed to warm to room temperature and left to stir for 6 h. Water (5 mL) was carefully added and the mixture neutralised (with 2 M potassium carbonate) and left to stir overnight. The organic phase was separated and the aqueous phase washed with chloroform (2×50 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the volatiles removed by rotary evaporation to afford **1a** as a brown solid (70%, 0.399 g). Mp: 104–106 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.51 (br s, 1H, OH), 6.90 (td, 1H, J_{H-H} 8.2, J_{H-H} 1.5, 1H, Ar–H), 7.10 (dd, 1H, J_{H-H} 8.2, J_{H-H} 1.1, 1H, Ar–H), 7.30 (m, 1H, Ar–H), 7.75 (d, 1H, J_{H-H} 1.5, 1H, Py–H/Ar–H), 7.78 (d, 1H, J_{H-H} 1.8, 1H, Py–H/Ar–H), 7.97 (t, 1H, J_{H-H} 8.2, 1H, Py–H), 8.09 (d, 1H, J_{H-H} 4.1, Py–H), 10.04 (s, 1H, CHO). ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ 117.1, 117.8, 118.3 (CH), 125.6 (C), 130.1, 131.3, 135.3, 137.8 (CH), 148.3, 157.6, 158.6 (C), 190.0 (CHO). IR (cm^{-1}): 1708 (C=O). ESIMS: *m*/*z* 200 [M+H]$^+$. HRMS (FAB): calcd for $C_{12}H_{10}NO_2$ [M+H]$^+$ 200.0712, found 200.0713.

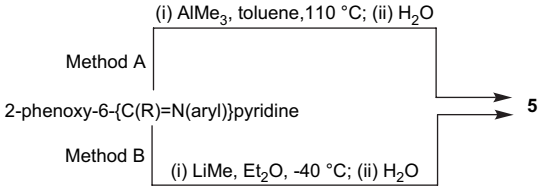
Table 4
Selected bond distances (Å) and angles (°) for **3a**, **3d** and **4a**

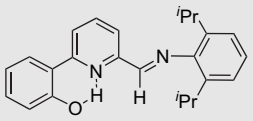
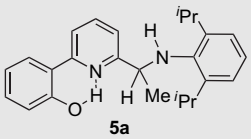
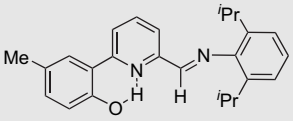
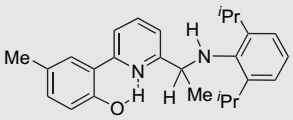
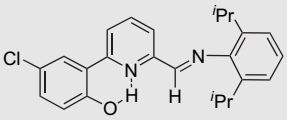
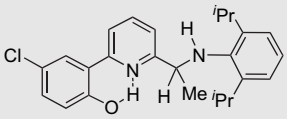
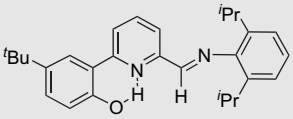
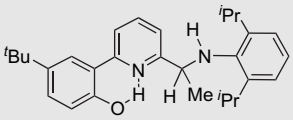
	3a	3d	4a
C(1)–O(1)	1.3539(16)	1.3520(15)	1.362(4)
C(6)–C(7)	1.4765(19)	1.4778(18)	1.487(5)
C(11)–C(12)	1.4656(18)	1.4762(17)	1.490(5)
C(12)–N(2)	1.2600(16)	1.2595(17)	1.266(4)
N(2)–C(13)	1.4283(16)	1.4241(16)	1.422(4)
C(4)–Cl(1)	—	1.7451(13)	—
C(12)–C$_{ketimine}$	—	—	1.502(5)
C(12)–N(2)–C(13)	119.12(12)	121.70(11)	121.4(3)
C(11)–C(12)–N(2)	122.48(13)	120.52(12)	116.9(3)

*4.2.2. 2-(5′-Methyl-2′-phenoxy)-6-formylpyridine (**1c**)*

A similar procedure to that described for **1a** was followed, using **I** (0.53 g, 2.79 mmol), **c** (0.57 g, 3.42 mmol, 1.2 equiv) and [Pd(PPh$_3$)$_4$] (0.066 g, 0.056 mmol, 0.02 equiv) to obtain, following deprotection with BBr$_3$, **1c** as a brown solid (0.39 g, 65%). Mp: 102–104 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ 1.51 (br s, 1H, OH), 2.29 (s, 3H, Me), 6.90 (d, 1H, J_{H-H} 8.2, Ar–H), 7.10 (dd, 1H, J_{H-H} 8.2, J_{H-H} 1.1, Ar–H), 7.52 (m, 1H, Ar–H), 7.69 (d, 1H, J_{H-H} 7.8, 1H, Py–H), 7.93 (t, 1H, J_{H-H} 8.2, 1H, Py–H), 8.09 (d, 1H, J_{H-H} 4.1, Py–H), 9.99 (s, 1H, CHO). ^{13}C{^{1}H} NMR (75 MHz, CDCl$_3$): δ 19.7 (Me), 116.7 (C), 117.5, 118.7, 122.5, 125.7 (CH), 128.5 (C), 132.1, 137.6 (CH), 148.3 (C), 156.3 (C), 157.6 (C), 190.0 (HC=O). IR (cm^{-1}): 1713 (C=O). ESIMS: *m*/*z* 214

Table 5
Reduction of **3** with trimethylaluminium and methylithium



Entry	Method	2-Phenoxy-6{C(R)=N(aryl)}pyridine	2-Phenoxy-6{C(R)MeNH(aryl)}pyridine product	Yield[a] (%)
13	A	 **3a**	 **5a**	77
14	B	 **3c**	 **5c**	55
15	A	 **3d**	 **5d**	73
16	A	 **3e**	 **5e**	65

[a] Isolated yields.

$[M+H]^+$. HRMS (FAB): calcd for $C_{13}H_{12}NO_2$ $[M+H]^+$ 214.0868, found 214.0866.

*4.2.3. 2-(5′-Chloro-2′-phenoxy)-6-formylpyridine (**1d**)*

A similar procedure to that described for **1a** was followed, using **I** (0.70 g, 3.74 mmol), **d** (0.84 g, 4.49 mmol, 1.2 equiv) and $[Pd(PPh_3)_4]$ (0.043 g, 0.038 mmol, 0.01 equiv) to obtain, following deprotection with BBr_3, **1d** as a light brown solid (0.73 g, 69%). Mp: 170–172 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 1.56 (br s, 1H, OH), 6.94 (d, 1H, J_{H-H} 8.8, Ar–H), 7.23 (dd, 1H, J_{H-H} 8.8, J_{H-H} 2.6, Ar–H), 7.70 (d, 1H, J_{H-H} 2.6, Ar–H), 7.86 (dd, 1H, J_{H-H} 8.5, J_{H-H} 2.0, Py–H), 8.03 (m, 2H, Py–H), 10.03 (s, 1H, CHO). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 118.1 (C), 119.3, 119.5 (CH), 122.7 (C), 123.1, 125.2, 131.1, 138.2 (CH), 148.4, 156.4, 157.2 (C), 189.6 (CH=O). IR (cm^{-1}): 1717 (C=O), 1590 (C=N_{Py}). ESIMS: *m*/*z* 234 $[M+H]^+$. HRMS (FAB): calcd for $C_{12}H_9NO_2Cl$ $[M+H]^+$ 234.0322, found 234.0322.

*4.2.4. 2-(5′-tert-Butyl-2′-phenoxy)-6-formylpyridine (**1e**)*

A similar procedure to that described for **1a** was followed, using **I** (0.70 g, 3.74 mmol), **e** (0.93 g, 4.49 mmol, 1.2 equiv) and $[Pd(PPh_3)_4]$ (0.043 g, 0.038 mmol, 0.01 equiv) to obtain, following

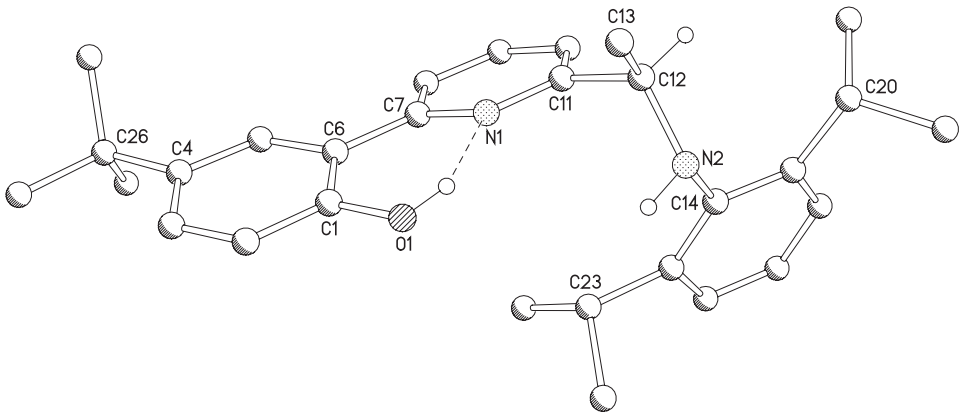


Figure 4. Molecular structure of **5e** including a partial atom numbering scheme. All hydrogen atoms, apart from H12 and the hydroxyl and amino hydrogens, have been omitted for clarity.

Table 6
Selected bond distances (Å) and angles (°) for **5a** and **5e**

	5a	5e
C(1)–O(1)	1.3596(15)	1.3581(15)
C(6)–C(7)	1.4773(17)	1.4807(18)
C(11)–C(12)	1.5134(17)	1.5173(18)
C(12)–N(2)	1.4671(15)	1.4683(17)
N(2)–C(14)	1.4235(14)	1.4283(17)
C(12)–C(13)	1.5219(17)	1.5219(18)
C(4)–C(26)	—	1.5350(18)
C(11)–C(12)–N(2)	113.87(10)	113.66(11)
C(11)–C(12)–C(13)	112.25(10)	112.77(11)

deprotection with BBr_3, **1e** as a brown solid (0.72 g, 75%). Mp: 92–94 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.50 (br s, 1H, OH), 1.29 (s, 9H, C(CH_3)$_3$), 6.95 (d, 1H, J_{H-H} 8.5, Ar–H), 7.35 (dd, 1H, J_{H-H} 8.5, J_{H-H} 2.3, Ar–H), 7.72 (d, 1H, J_{H-H} 2.3, Ar–H), 7.80 (d, 1H, J_{H-H} 7.6, Py–H), 7.96 (t, 1H, J_{H-H} 7.6, Py–H), 8.09 (d, 1H, J_{H-H} 7.9, Py–H), 10.02 (s, 1H, CHO). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 30.5 (C(CH_3)$_3$), 33.2 (*C*(CH_3)$_3$), 116.3 (C), 117.4, 118.6, 121.9, 122.6, 125.8, 137.7 (CH), 140.9, 148.5, 156.3, 158.1 (C), 190.2 (CH=O). IR (cm^{-1}): 1717 (C=O), 1590 (C=N_{Py}). ESIMS: *m*/*z* 256 [M+H]$^+$. HRMS (FAB): calcd for $C_{16}H_{18}NO_2$ [M+H]$^+$ 256.1338, found 256.1339.

4.2.5. 2-(2′-Phenoxy)-6-acetylpyridine (**2a**)

A similar procedure to that described for **1a** was followed, using **II** (0.500 g, 2.50 mmol), **a** (0.455 g, 3.00 mmol, 1.2 equiv) and [Pd(PPh_3)$_4$] (0.058 g, 0.050 mmol, 0.02 equiv) to obtain, following deprotection with BBr_3, **2a** as a brown solid (0.39 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.66 (s, 3H, C*Me*=O), 6.84–6.98 (m, 1H, Ar–H), 6.96 (dd, 1H, J_{H-H} 8.1, J_{H-H} 1.2, Ar–H), 7.24–7.29 (m, 1H, Ar–H), 7.73 (dd, 1H, J_{H-H} 8.1, J_{H-H} 1.1, Ar–H), 7.88–7.90 (m, 2H, Py–H), 8.00 (dd, 1H, J_{H-H} 6.4, J_{H-H} 2.6, Py–H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 25.1 (C*Me*=O), 117.2 (C), 117.5, 118.3, 118.8, 121.8, 125.5, 131.1, 137.7 (CH), 148.9, 156.2, 158.5 (C), 196.5 (*C*Me=O). IR (cm^{-1}): 3330 (O–H), 1698 (C=O), 1586 (C=N_{Py}). ESIMS: *m*/*z* 214 [M+H]$^+$. HRMS (FAB): calcd for $C_{13}H_{12}NO_2$ [M+H]$^+$ 214.0868, found 214.0869.

4.2.6. 2-(3′-Phenyl-2′-phenoxy)-6-acetylpyridine (**2b**)

A similar procedure to that described for **1a** was followed, using **II** (0.500 g, 2.50 mmol), **b** (0.68 g, 3.00 mmol, 1.2 equiv) and [Pd(PPh_3)$_4$] (0.058 g, 0.050 mmol, 0.02 equiv) to obtain, following deprotection with BBr_3, **2b** as an orange/brown solid (0.44 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65 (s, 3H, C*Me*=O), 6.93 (m, 1H, Ar–H), 7.25–7.40 (m, 5H, Ar–H), 7.58 (d, 2H, J_{H-H} 7.3, Ar–H), 7.72–7.75 (m, 2H, Py–H), 8.03–8.07 (m, 1H, Py–H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 25.3 (C*Me*=O), 117.6 (C), 118.1, 127.1, 128.5 (CH), 130.3 (C), 132.3 (CH), 137.2 (C), 137.8 (CH), 148.9, 155.8, 156.5 (C), 196.6 (*C*Me=O). IR (cm^{-1}): 1700 (C=O). ESIMS: *m*/*z* 290 [M+H]$^+$. HRMS (FAB): calcd for $C_{19}H_{16}NO_2$ [M+H]$^+$ 290.1181, found 290.1182.

4.3. Synthesis of the 2-phenoxy-6-iminopyridines (3 and 4)

4.3.1. 2-(2′-Phenoxy)-6-(iminoformyl)pyridine (2,6-diisopropylanil) (**3a**)

To a solution of **1a** (0.397 g, 1.99 mmol) in absolute ethanol (4 mL) was added 2,6-diisopropylaniline (0.457 g, 2.58 mmol, 1.3 equiv). The solution was stirred at 50 °C for 5 min before the addition of one drop of glacial acetic acid. After stirring at 50 °C overnight, the reaction mixture was cooled to room temperature and the suspension filtered, washed with cold ethanol and dried to give **3a** as a yellow solid (0.398 g, 56%). Mp: 168–170 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, 12H, $^3J_{H-H}$ 6.7, CH(*Me*)$_2$), 2.89 (sept, 2H, C*H*(Me)$_2$), 6.88 (td, 1H, J_{H-H} 8.2, J_{H-H} 1.5, Ar–H), 6.97 (dd, 1H, J_{H-H} 8.2, J_{H-H} 1.5, Ar–H), 7.07 (m, 3H, Ar–H), 7.27 (td, 1H, J_{H-H} 8.2, J_{H-H} 1.5, Ar–H), 7.77 (dd, 1H, J_{H-H} 7.9, J_{H-H} 1.8, Ar–H), 7.96 (m, 2H, Py–H), 8.08 (dd, $^3J_{H-H}$ 7.0, J_{H-H} 1.8, 1H, Py–H), 8.26 (s, 1H, CH=N). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 23.5 (CH_3), 28.1 (CH), 118.6 (CH), 118.7 (C), 119.1, 119.4, 121.9, 123.2, 124.8, 126.5, 131.9, 137.2, 138.6 (CH), 148.2, 151.0, 158.1, 159.8 (C), 161.1 (CH=N). IR (cm^{-1}): 1647 (C=N_{imine}), 1592 (C=N_{Py}). ESIMS: *m*/*z* 359 [M+H]$^+$. Anal. Calcd for $C_{24}H_{26}N_2O$: C, 80.39; H, 7.32; N, 7.82. Found: C, 80.29; H, 7.44; N, 7.84.

4.3.2. 2-(5′-Methyl-2′-phenoxy)-6-(iminoformyl)pyridine (2,6-diisopropylanil) (**3c**)

Using a similar procedure to that described for **3a**, with **1c** (0.227 g, 1.07 mmol), 2,6-diisopropylaniline (0.264 g, 1.49 mmol, 1.4 equiv) and absolute ethanol (4 mL), gave **3c** as a yellow solid (0.286 g, 72%). Mp: 149–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (d, 12H, J_{H-H} 7, CH(*Me*)$_2$), 2.25 (s, 3H, Ar–Me), 2.88 (sept, 2H, C*H*(Me)$_2$), 6.8–7.2 (m, 5H, Ar–H), 7.51 (s, 1H, Ar–H), 7.81–7.95 (m, 2H, Py–H), 8.05 (d, 1H, J_{H-H} 7.6, Py–H), 8.22 (s, 1H, HC=N). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 23.5, 28.1 (CH_3), 28.0 (CH), 118.2 (CH), 118.5 (C), 119.2, 120.9 123.2, 124.8, 126.7, 128.1, 132.8, 137.2, 138.5 (CH), 148.3, 151.1, 157.5, 158.2 (C), 161.2 (C=N). IR (cm^{-1}): 2959, 1636 (C=N), 1565, 1425, 1263, 1181, 1077, 991, 772. ESIMS: *m*/*z* 373 [M+H]$^+$. Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.65; H, 7.53; N, 7.53. Found: C, 80.88; H, 7.61; N, 7.33.

4.3.3. 2-(5′-Chloro-2′-phenoxy)-6-(iminoformyl)pyridine (2,6-diisopropylanil) (**3d**)

Using a similar procedure to that described for **3a**, with **1d** (0.227 g, 0.97 mmol), 2,6-diisopropylaniline (0.241 g, 1.36 mmol, 1.4 equiv) and absolute ethanol (4 mL), gave **3d** as a yellow solid (0.233 g, 61%). Mp: 145–147 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, J_{H-H} 6.7, 12H, CH(*Me*)$_2$), 1.49 (br s, 1H, OH), 2.89 (sept, 2H, C*H*(Me)$_2$), 6.91 (d, 1H, J_{H-H} 8.8, Ar–H), 7.10 (m, 3H, Ar–H), 7.21 (dd, 1H, J_{H-H} 8.8, J_{H-H} 2.3, Ar–H), 7.74 (d, 1H, J_{H-H} 2.3, Ar–H), 7.96 (m, 2H, Py–H), 8.12 (dd, 1H, J_{H-H} 7.3, J_{H-H} 1.5, Py–H), 8.26 (s, 1H, CH=N). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 23.5 (CH_3), 28.1 (CH), 119.6 (C), 112.0, 120.2, 121.0, 123.2, 123.8, 124.9, 126.0, 131.6 (CH), 137.1 (C), 138.8 (CH), 148.2, 151.1, 156.8, 158.4 (C), 160.6 (CH=N). IR (cm^{-1}): 1643 (C=N_{imine}), 1588 (C=N_{Py}). ESIMS: *m*/*z* 393 [M+H]$^+$. Anal. Calcd for $C_{24}H_{25}N_2OCl$: C, 73.38; H, 6.37; N, 7.13. Found: C, 73.46; H, 6.66; N, 6.76.

4.3.4. 2-(5′-tert-Butyl-2′-phenoxy)-6-(iminoformyl)pyridine (2,6-diisopropylanil) (**3e**)

Using a similar procedure to that described for **3a**, with **1e** (0.227 g, 0.889 mmol), 2,6-diisopropylaniline (0.220 g, 1.25 mmol, 1.4 equiv) and absolute ethanol (4 mL), gave **3e** as a yellow solid (0.267 g, 72%). Mp: 149–151 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.12 (d, J_{H-H} 6.7, 12H, CH(*Me*)$_2$), 1.30 (s, 9H, C(CH_3)$_3$), 1.48 (br s, 1H, OH), 2.89 (sept, 2H, C*H*(Me)$_2$, 6.92 (d, 1H, J_{H-H} 8.8, Ar–H), 7.10 (m, 3H, Ar–H), 7.32 (dd, 1H, J_{H-H} 8.8, J_{H-H} 2.3, Ar–H), 7.75 (d, 1H, J_{H-H} 2.3, Ar–H), 7.97 (m, 2H, Py–H), 8.08 (d, 1H, J_{H-H} 7.3, Py–H), 8.26 (s, 1H, HC=N). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 22.4 (CH_3), 27.0 (CH), 30.5 (C(*C*H_3)$_3$), 33.2 (*C*(CH$_3$)$_3$), 116.8 (C), 117.2, 118.1, 119.9, 121.1, 123.7, 128.8 (CH), 136.1, 137.4 (C), 140.6 (CH), 147.2, 150.0, 156.3, 157.5 (C), 160.6 (CH=N). IR (cm^{-1}): 1648 (C=N_{imine}), 1592 (C=N_{Py}). ESIMS: *m*/*z* 415 [M+H]$^+$. Anal. Calcd for $C_{28}H_{34}N_2O$) C, 81.10; H, 8.28; N, 6.76. Found: C, 80.92; H, 8.27; N, 6.65.

4.3.5. 2-(2′-Phenoxy)-6-(iminoacetyl)pyridine (2,6-diisopropylanil) (**4a**)

To a solution of **2a** (0.397 g, 1.99 mmol) in absolute ethanol (4 mL) was added 2,6-diisopropylaniline (0.459 g, 2.59 mmol, 1.3 equiv). The solution was stirred at 80 °C for 5 min before the addition of one drop of glacial acetic acid. After stirring at 80 °C for

2 days, the reaction mixture was cooled to room temperature and the suspension filtered, washed with cold ethanol and dried to give **4a** as a yellow solid (0.594 g, 80%). Mp: 190–192 °C. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.08 (d, 12H, J_{H-H} 6.9, CH(*Me*)$_2$), 1.54 (br s, 1H, OH), 2.18 (s, 3H, CMe=N), 2.65 (sept, 2H, C*H*(Me)$_2$), 6.88 (dt, 1H, $^3J_{H-H}$ 8.8, J_{H-H} 0.7, Ar–H), 6.97 (dd, 1H, J_{H-H} 6.5, J_{H-H} 0.8, Ar–H), 7.11–7.15 (m, 3H, Ar–H), 7.28 (dt, 1H, $^3J_{H-H}$ 6.6, J_{H-H} 1.0, Ar–H), 7.79 (dd, 1H, $^3J_{H-H}$ 6.9, J_{H-H} 1.4, Ar–H), 7.85–8.00 (m, 2H, Py–H), 8.23 (dd, 1H, J_{H-H} 7.1, J_{H-H} 1.2, Py–H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 16.2 (C*Me*=N), 21.7, 22.0 (CH_3), 27.2 (CH), 117.3 (CH), 117.6 (C), 118.0, 118.2, 119.2, 121.9, 122.8, 125.3, 130.6 (CH), 134.5 (C), 137.3 (CH), 144.8, 151.9, 155.6, 158.4 (C), 163.6 (*C*Me=N). IR (cm^{-1}): 3381 (O–H), 1644 (C=N_{imine}), 1588 (C=N_{Py}). ESIMS: *m*/*z* 373 [M+H]$^+$. Anal. Calcd for $C_{25}H_{28}N_2O$: C, 80.65; H, 7.53; N, 7.53. Found: C, 80.82; H, 7.61; N, 7.40.

4.3.6. 2-(5′-Phenyl-2′-phenoxy)-6-(iminoacetyl)pyridine (2,6-diisopropylanil) (*4b*)

Using a similar procedure to that described for **4a**, with **1b** (0.358 g, 1.24 mmol), 2,6-diisopropylaniline (0.33 g, 1.86 mmol, 1.5 equiv) and absolute ethanol (4 mL), gave **4b** as a yellow solid (0.339 g, 61%). Mp: 197–199 °C. ^{1}H NMR (300MHz, $CDCl_3$): δ 1.06 (d, 12H, J_{H-H} 6.9, CH(*Me*)$_2$), 2.16 (s, 3H, CMe=N), 2.63 (sept, 2H, C*H*(Me)$_2$), 6.94 (t, 1H, J_{H-H} 7.9, Ar–H), 6.97–7.11 (m, 3H, Ar–H), 7.23–7.38 (m, 4H, Ar–H), 7.59 (d, 2H, J_{H-H} 7.1, Ar–H), 7.79 (dd, 1H, J_{H-H} 8.2, J_{H-H} 1.1, Ar–H), 7.90 (t, 1H, J_{H-H} 7.9, Py–H), 8.00 (d, 1H, J_{H-H} 7.6, Py–H), 8.28 (dd, 1H, J_{H-H} 7.3, J_{H-H} 1.1, Py–H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 17.6 (C*Me*=N), 22.9, 23.2 (CH_3), 28.4 (CH), 118.9 (CH), 119.1 (C), 119.5, 120.9, 123.1, 123.9, 126.1, 127.1, 128.1, 129.6 (CH), 131.2 (C), 132.9 (CH), 135.7 (C), 138.5 (CH), 146.0, 153.1, 156.9, 157.1 (C), 164.9 (*C*Me=N). IR (cm^{-1}): 3387 (O–H), 1632 (C=N_{imine}), 1588 (C=N_{Py}). ESIMS: *m*/*z* 449 [M+H]$^+$. Anal. Calcd for $C_{31}H_{32}N_2O$: C, 83.04; H, 7.14; N, 6.25. Found: C, 83.22; H, 7.23; N, 6.19.

4.4. Synthesis of the 2-phenoxy-6-(methanamino)-pyridines (5)

Method A. An oven-dried Schlenk flask equipped with a magnetic stir bar was evacuated and back filled with nitrogen. 2-Phenoxy-6-iminopyridine **3** (0.591 mmol) was introduced into the flask and dissolved in dry toluene (15 mL). Trimethylaluminium (0.59 mL, 1.18 mmol, 2 equiv) was added and the reaction mixture stirred at 110 °C overnight. On cooling to room temperature all volatiles were removed under reduced pressure. Pentane (20 mL) was added followed by water (20 mL) and the reaction mixture stirred vigorously for 1 h. The product was extracted into chloroform (50 mL) and the aqueous phase washed (3×50 ml) with more chloroform. The organic extracts were combined and dried over anhydrous magnesium sulfate and filtered. The residue was dried under reduced pressure to give the 2-phenoxy-6-(methanamino)pyridine.

Method B. An oven-dried Schlenk flask equipped with a magnetic stir bar was evacuated and back filled with nitrogen. The 2-phenoxy-6-iminopyridine (0.805 mmol) was dissolved in diethylether (20 mL), cooled to −40 °C and MeLi (as a 1.4 M solution in diethylether or as a solid, 2–4 equiv) introduced. After stirring for 30 min, the reaction was quenched by the addition of water (1 mL) and the solution dried over magnesium sulfate, filtered and the filtrate dried under reduced pressure to give the 2-phenoxy-6-(methanamino)pyridine.

4.4.1. 2-(2′-Phenoxy)-6-{1″-(2,6-diisopropylanilino)ethyl}-pyridine (*5a*)

The procedure outlined in method A was followed, using **3a** (0.212 g, 0.591 mmol), trimethylaluminium (0.59 mL, 1.18 mmol, 2 equiv), to obtain **5a** as pale pink solid (0.171 g, 77%). Mp: 86–88 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, 6H, J_{H-H} 6.7, CH(*Me*)$_2$), 1.13 (d, 6H, J_{H-H} 7.0, CH(*Me*)$_2$), 1.51 (br s, 1H, OH), 1.58 (d, 3H, J_{H-H} 6.7, CH(C*H*$_3$)NH), 3.02 (sept, 2H, C*H*(Me)$_2$), 3.49 (br s, 1H, NH), 4.16 (q, 1H, J_{H-H} 6.7, C*H*(CH$_3$)NH), 6.91 (m, 6H, Ar–H), 7.26 (td, 1H, J_{H-H} 7.6, J_{H-H} 1.7, Ar–H), 7.61 (t, 1H, J_{H-H} 8.2, Py–H), 7.72 (t, 2H, J_{H-H} 7.6, Py–H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.6, 21.8 (CH_3), 23.0, 23.2 (CH), 26.7 (CH(C*H*$_3$)NH), 59.7 (*C*H(CH$_3$)NH), 116.6, 117.4, 117.9 (CH), 118.0 (C), 118.8, 122.5, 122.6, 125.3, 130.5, 137.0 (CH), 139.9, 141.3, 156.8, 158.9, 159.1 (C). ESIMS: *m*/*z* 375 [M+H]$^+$. Anal. Calcd for $C_{25}H_{30}N_2O$: C, 80.26; H, 8.09; N, 7.48. Found: C, 80.08; H, 7.87; N, 7.30.

4.4.2. 2-(5′-Methyl-2′-phenoxy)-6-{1″-(2,6-diisopropylanilino)ethyl}pyridine (*5c*)

The procedure outlined in method B was followed, using **3c** (0.300 g, 0.805 mmol), methyllithium (1.30 mL, 1.82 mmol, 2.3 equiv), to obtain **5c** as a pale yellow solid (0.170 g, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, 6H, J_{H-H} 6.7, CH(*Me*)$_2$), 1.13 (d, 6H, J_{H-H} 7.0, CH(*Me*)$_2$), 1.50 (br s, 1H, OH), 1.56 (d, 3H, J_{H-H} 6.7, CH(C*H*$_3$)NH), 2.24 (s, 3H, Ar–Me), 2.98 (sept, 2H, C*H*(Me)$_2$), 3.42 (br s, 1H, NH), 4.16 (q, 1H, $^3J_{H-H}$ 6.7, C*H*(CH$_3$)NH), 6.94 (m, 5H, Ar–H), 7.31 (dd, 1H, J_{H-H} 8.8, J_{H-H} 2.3, Ar–H), 7.62 (t, 1H, J_{H-H} 8.2, Py–H), 7.71 (m, 2H, Py–H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 20.7, 21.5 (CH_3), 24.2, 25.1 (CH), 27.1 (CH(C*H*$_3$)NH), 28.1 (CH_3), 60.7 (*C*H(CH$_3$)NH), 117.6, 118.0, 118.2, 119.6, 122.7, 123.5 (CH), 123.6 (C), 128.9, 138.0 (CH), 141.1, 141.4, 142.3, 157.6, 158.2, 160.2 (C). ESIMS: *m*/*z* 389 [M+H]$^+$. Anal. Calcd for $C_{26}H_{32}N_2O$: C, 80.41; H, 8.25; N, 7.22. Found: C, 80.69; H, 8.31; N, 7.18.

4.4.3. 2-(5′-Chloro-2′-phenoxy)-6-{1″-(2,6-diisopropylanilino)ethyl}pyridine (*5d*)

The procedure outlined in method A was followed, using **3d** (0.232 g, 0.591 mmol), trimethylaluminium (0.59 mL, 1.18 mmol, 2 equiv), to obtain **5d** as a pale pink solid (0.176 g, 73%). Mp: 157–159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (d, 6H, J_{H-H} 6.7, CH(*Me*)$_2$), 1.13 (d, 6H, J_{H-H} 7.0, CH(*Me*)$_2$), 1.30 (br s, 1H, OH), 1.59 (d, 3H, J_{H-H} 6.7, CH(C*H*$_3$)NH), 3.01 (sept, 2H, C*H*(Me)$_2$), 3.48 (br s, 1H, NH), 4.17 (q, 1H, J_{H-H} 6.7, C*H*(CH$_3$)NH), 6.93 (m, 5H, Ar–H), 7.19 (dd, 1H, J_{H-H} 8.7, J_{H-H} 2.6, Ar–H), 7.67 (m, 3H, Py–H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 19.6, 23.0 (CH_3), 23.2, 26.7 (CH), 27.0 (CH(C*H*$_3$)NH), 59.5 (*C*H(CH$_3$)NH), 116.7 (CH), 119.1 (C), 119.4, 122.5, 122.7 (CH), 130.2 (C), 130.6, 136.1, 137.8 (CH), 139.8 (C), 141.3 (CH), 155.5, 157.4, 157.5, 159.4 (C). ESIMS: *m*/*z* 409 [M+H]$^+$. Anal. Calcd for $C_{25}H_{29}N_2OCl$: C, 73.41; H, 7.16; N, 6.85. Found: C, 73.37; H, 6.94; N, 6.76.

4.4.4. 2-(5′-tert-Butyl-2′-phenoxy)-6-{1″-(2,6-diisopropylanilino)ethyl}pyridine (*5e*)

The procedure outlined in method A was followed, using **3e** (0.245 g, 0.591 mmol), trimethylaluminium (0.59 mL, 1.18 mmol, 2 equiv), to obtain **5d** as a pale pink solid (0.165 g, 65%). Mp: 158–160 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.95 (d, 6H, J_{H-H} 6.7, CH(*Me*)$_2$), 1.13 (d, 6H, J_{H-H} 7.0, CH(*Me*)$_2$), 1.29 (s, 9H, C(CH$_3$)$_3$), 1.50 (br s, 1H, OH), 1.57 (d, 3H, J_{H-H} 6.7, CH(C*H*$_3$)NH), 2.98 (sept, 2H, C*H*(Me)$_2$), 3.42 (br s, 1H, NH), 4.15 (q, 1H, $^3J_{H-H}$ 6.7, C*H*(CH$_3$)NH), 6.94 (m, 5H, Ar–H), 7.31 (dd, 1H, J_{H-H} 8.8, J_{H-H} 2.3, Ar–H), 7.62 (t, 1H, J_{H-H} 8.2, Py–H), 7.73 (m, 2H, Py–H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 20.7, 24.1 (CH_3), 24.2, 27.8 (CH), 31.6 (C(CH$_3$)$_3$), 34.2 (CH(C*H*$_3$)NH), 60.6 (*C*H(CH$_3$)NH), 117.6, 118.0, 118.2, 119.6, 122.7, 123.5 (CH), 123.6 (C), 128.9, 138.0 (CH), 141.1, 141.4, 142.3, 157.6, 158.2, 160.2 (C). ESIMS: *m*/*z* 431 [M+H]$^+$. Anal. Calcd for $C_{29}H_{38}N_2O$: C, 80.93; H, 8.84; N, 6.51. Found: C, 81.12; H, 8.83; N, 6.66.

4.5. Crystallography

Data for **b**, **3a**, **3d**, **4a**, **5a** and **5e** were collected on a Bruker APEX 2000 CCD diffractometer. Details of data collection, refinement and

Table 7
Crystallographic and data processing parameters for compounds **b**, **3a**, **3d**, **4a**, **5a** and **5e**

Complex	**b**	**3a**	**3d**	**4a**	**5a**	**5e**
Formula	$C_{13}H_{13}BO_3$	$C_{24}H_{26}N_2O$	$C_{24}H_{25}ClN_2O$	$C_{25}H_{28}N_2O\cdot 1.5CHCl_3$	$C_{25}H_{30}N_2O$	$C_{29}H_{38}N_2O$
M	228.04	358.47	392.91	551.55	374.51	430.61
Crystal size (mm^3)	0.50×0.16×0.11	0.19×0.16×0.12	0.31×0.24×0.20	0.22×0.19×0.13	0.39×0.24×0.21	0.20×0.14×0.13
Temperature (K)	150(2)	150(2)	150(2)	160(2)	150(2)	150(2)
Crystal system	Triclinic	Monoclinic	Triclinic	Monoclinic	Triclinic	Triclinic
Space group	*P*-1	*C*2/*c*	*P*-1	*C*2/*c*	*P*-1	*P*-1
a (Å)	7.7140	24.894(3)	8.2630(6)	16.8176(15)	8.733(2)	9.5600(11)
b (Å)	8.2865	9.1993(13)	9.4948(6)	20.9588(19)	10.747(2)	10.7099(12)
c (Å)	9.7850	20.583(3)	14.0487(10)	16.5257(15)	12.813(3)	13.0727(14)
α (°)	67.467	90	96.9700(10)	90	77.957(4)	98.540(2)
β (°)	85.428	121.653(2)	105.2980(10)	110.683(2)	73.112(4)	98.250(2)
γ (°)	88.708	90	100.5800(10)	90	72.509(4)	106.149(2)
U ($Å^3$)	575.87	4012.5(10)	1028.05(12)	5449.5(9)	1087.7(4)	1247.1(2)
Z	2	8	2	8	2	2
D_c ($Mg\ m^{-3}$)	1.315	1.187	1.269	1.345	1.144	1.147
F(000)	240	1536	416	2296	404	468
μ(Mo Kα)(mm^{-1})	0.091	0.073	0.203	0.506	0.069	0.069
Reflections collected	4825	14,195	8107	22,616	8582	9173
Independent reflections	2458	3535	3981	5928	4241	4389
R_{int}	0.0288	0.0359	0.0166	0.0469	0.0341	0.0297
Restraints/parameters	0/157	0/249	0/258	0/318	0/259	0/298
Final R indices ($I>2\sigma(I)$)	$R1$=0.0421	$R1$=0.0402	$R1$=0.0366	$R1$=0.0812	$R1$=0.0443	$R1$=0.0400
	$wR2$=0.1171	$wR2$=0.0811	$wR2$=0.0994	$wR2$=0.2412	$wR2$=0.1163	$wR2$=0.0950
All data	$R1$=0.0479	$R1$=0.0593	$R1$=0.0415	$R1$=0.1360	$R1$=0.0546	$R1$=0.0517
	$wR2$=0.1205	$wR2$=0.0955	$wR2$=0.1021	$wR2$=0.2614	$wR2$=0.1221	$wR2$=0.1014
Goodness of fit on F^2 (all data)	1.061	0.930	1.081	0.947	1.051	0.952

Data in common: graphite-monochromated Mo Kα radiation, λ=0.71073 Å; $R_1=\Sigma||F_o|-|F_c||/\Sigma|F_o|$, $wR_2=[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$, $w^{-1}=[\sigma^2(F_o)^2+(aP)^2]$, $P=[\max(F_o^2,0)+2(F_c^2)]/3$, where a is a constant adjusted by the program; goodness of fit$=[\Sigma(F_o^2-F_c^2)2/(n-p)]^{1/2}$ where n is the number of reflections and p the number of parameters.

crystal data are listed in Table 7. The data were corrected for Lorentz and polarisation effects and empirical absorption corrections applied. Structure solution by Patterson methods and structure refinement on F^2 employed SHELXTL version 6.10.[15] Hydrogen atoms were included in calculated positions (C–H=0.96 Å) riding on the bonded atom with isotropic displacement parameters set to 1.5 U_{eq}(C) for methyl H atoms and 1.2 U_{eq}(C) for all other H atoms. All non-H atoms were refined with anisotropic displacement parameters.

CCDC reference numbers 689030–689035 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ; fax: (Internet) +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.019.

References and notes

1. See for example: (a) Broussie, T. R.; Diamond, G. M.; Goh, C.; Hall, K. A.; LaPointe, A. M.; Leclerc, M. K.; Lund, C.; Murphy, V.; Shoemaker, J. A. W.; Tracht, U.; Turner, H.; Zhang, J.; Uno, T.; Rosen, R. K.; Stevens, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 4306; (b) Murphy, V. In *High-Throughput Screening in Heterogeneous Catalysis*; Hagemeyer, A., Strasser, P., Volpe, A. F., Jr., Eds.; Wiley-VCH GmbH KGaA: Weinheim, Germany, 2004; pp 299–312; (c) Jones, D. J.; Gibson, V. C.; Green, S. M.; Maddox, P. J.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **2005**, *127*, 11037; (d) Schofer, S. J.; Hahn, H.; Murphy, V.; Hajduk, D. A.; Diamond, G. M.; Ying, D.; Doolen, R. D.; Smith, M. *Polym. Prepr.* **2007**, *48*, 172.
2. (a) Britovsek, G. J. P.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; McTavish, S. J.; Solan, G. A.; White, A. J. P.; Williams, D. J. *Chem. Commun.* **1998**, 849; (b) Britovsek, G. J. P.; Bruce, M.; Gibson, V. C.; Kimberley, B. S.; Maddox, P. J.; Mastroianni, S.; McTavish, S. J.; Redshaw, C.; Solan, G. A.; Strömberg, S.; White, A. J. P.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *121*, 8728.
3. (a) Small, B. L.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 7143; (b) Small, B. L.; Brookhart, M.; Bennett, A. M. A. *J. Am. Chem. Soc.* **1998**, *120*, 4049.
4. For reviews, see: (a) Gibson, V. C.; Redshaw, C.; Solan, G. A. *Chem. Rev.* **2007**, *107*, 1747; (b) Bianchini, C.; Giambastiana, G.; Rios, I. G.; Mantovani, G.; Meli, A.; Segarra, A. M. *Coord. Chem. Rev.* **2006**, *250*, 1391.
5. (a) Guérin, F.; McConville, D. H.; Vittal, J. J. *Organometallics* **1996**, *15*, 5586; (b) Guérin, F.; McConville, D. H.; Payne, N. C. *Organometallics* **1996**, *15*, 5085.
6. (a) Chan, M. C. W.; Tam, K.-H.; Zhu, N.; Chiu, P.; Matsui, S. *Organometallics* **2006**, *25*, 785; (b) Chan, M. C. W.; Tam, K. H.; Pui, Y. L.; Zhu, N. *J. Chem. Soc., Dalton Trans.* **2002**, 3085.
7. Boussie, T. R.; Diamond, G. M.; Goh, C.; Hall, K. A.; LaPointe, A. M.; Leclerc, M. K.; Murphy, V.; Shoemaker, J. A. W.; Turner, H.; Rosen, R. K.; Stevens, J. C.; Alfano, F.; Busico, V.; Cipullo, R.; Talarico, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 3278.
8. For importance of the *N*-2,6-diisopropylphenyl group, see: (a) Gibson, V. C.; Spitzmesser, S. K. *Chem. Rev.* **2003**, *103*, 283; (b) Britovsek, G. J. P.; Gibson, V. C.; Wass, D. F. *Angew. Chem., Int. Ed* **1999**, *38*, 428; (c) Ittel, S. D.; Johnson, L. K.; Brookhart, M. *Chem. Rev.* **2000**, *100*, 1169; (d) Mecking, S. *Angew. Chem., Int. Ed* **2001**, *40*, 534.
9. Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
10. Yuang, H.; Hay, A. S. *J. Polym. Sci., Part A: Polym. Chem.* **1993**, *31*, 1261.
11. Bryant, J. A.; Helgeson, R. C.; Knobler, C. B.; DeGrandpre, M. P.; Cram, D. J. *J. Org. Chem.* **1990**, *55*, 4622.
12. See, for example: (a) Dietrich-Buhecker, C. O.; Sauvage, J.-P.; Kintzinger, J. P.; Maltese, P.; Pascard, C.; Guilheim, J. *New J. Chem.* **1992**, *16*, 931; (b) Constable, E. C.; Kariuki, B.; Mahmood, A. *Polyhedron* **2003**, *33*, 687.
13. Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.
14. Tellier, F.; Sauvetre, R.; Normant, J.-F. *J. Organomet. Chem.* **1985**, *292*, 2.
15. Sheldrick, G. M. *SHELXTL Version 6.10*; Bruker AXS: Madison, WI, USA, 2000.