Stabilised 2,3-Pyridyne Reactive Intermediates of Exceptional Dienophilicity

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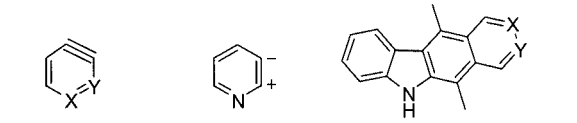
The enhanced dienophilicity of 4-methoxy, 4-aryloxy and 4-thiophenoxy analogues **6**–**9** of 2,3-pyridyne (**2**) relative to **2** itself is reported. The regioselective lithiation of 4-alkoxy- (**22**, **23** and **25**) and 4-thiophenoxy-2-chloropyridine (**24**) at low temperatures, followed by elimination of lithium chloride affords 4-alkoxy- and 4-thiophenoxypyridynes, which can be trapped in situ in a [4+2] cycloaddition reaction with furan to give endoxides **28**–**31** in moderate to good yields (25–58%). In contrast, precursors with a hydrogen (**18**) or methyl (**12**) substituent at C-4 give no evidence for pyridyne formation under these conditions. Attempts to generate 6-isopropoxy-2,3-pyridyne (**10**) from the low-temperature lithiation of 2-chloro-6-isopropoxypyridine were unsuccessful due to the instability of the 2-chloro-6-isopropoxy-5-lithiopyridine.

Introduction

Pyridynes (didehydropyridines)[1a−1c] are reactive intermediates formally derived from the removal of two adjacent hydrogen atoms from a pyridine ring. Despite the high synthetic potential of these species for carbon−carbon bond formation (particularly pyrido-fused rings) through cycloaddition reactions, over the last decade they have received only scant attention. Several methods have been reported for the generation of the more stable 3,4-pyridyne (**1**),[1c][2a−2g] and a Diels−Alder cycloaddition involving **1** has been used as a key step in the total synthesis of the antitumour alkaloid ellipticine (**3**) and the isomeric isoellipticine (**4**).[3] In contrast, the structurally similar 2,3-pyridyne (**2**) has proven to be a hetaryne problem child; previous attempts to generate and trap it in Diels−Alder reactions with dienes resulted in either failure, or low cycloadduct yields.[2b,2d,4,5] To the best of our knowledge, unsubstituted 2,3-pyridyne has not been unambiguously generated under dehydrohalogenation conditions.[1] Hence, it is unsurprising that **2** has traditionally been considered of lower synthetic value than **1**.[6]

We have recently shown that **1** is considerably stabilised by 2- or 6-alkoxy groups, with furan-trapped cycloadduct yields in the range 66−89% possible.[7] In line with this earlier work, it is logical to assume that **2** is also destabilised to a considerable extent by the partial polarisation of the strained hetaryne bond due to the electron-withdrawing effect of the pyridine ring nitrogen atom, giving 2,3-pyridyne some dipolar character[8] (i.e., a contribution from **2a** toward the overall structure of **2**), thus reducing its reactivity towards Diels−Alder cycloaddition processes by making deleterious attack by nucleophiles/anionic precursors competitive.[1]



1 X = N, Y = H
2 X = H, Y = N

2a

3 X = N, Y = H Ellipticine
4 X = H, Y = N Isoellipticine

Figure 1. Pyridynes and ellipticine

The proximity of the hetaryne bond to the ring nitrogen atom in **2** relative to **1** would therefore appear to account for its lower stability. Given our earlier success in reducing the electrophilicity of **1**, it was decided to apply this methodology to the stabilisation of the more challenging and recalcitrant 2,3-isomer **2**. Our strategy involved the generation of 2,3-pyridynes with electron-donating substituents *ortho* and *para* to the ring nitrogen atom at either C-2 or C-4. Poor cycloadduct yields have been obtained with 4-methoxy-[9,10] and 4-ethoxy-2,3-pyridynes[11] using metallation/elimination strategies. However, the role which the 4-alkoxy group plays in the stabilisation of either the hetaryne, the metallated precursor (through coordination of the metal counterion to the heteroatom), or both, remains to be established.[10] Since this question is of particular importance in the design and synthesis of superior 2,3-pyridyne precursors, we investigated the furan trapping of vari-

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ous 4- and 6-substituted 2,3-pyridynes (**5**−**10**; Figure 2), generated by dehydrohalogenation of the corresponding 2-chloropyridines with lithiating reagents.[12]

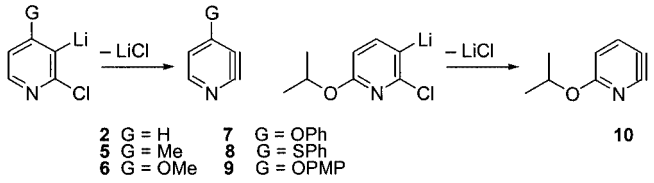
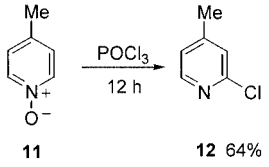


Figure 2. Substituted 2,3-pyridynes

Results and Discussion

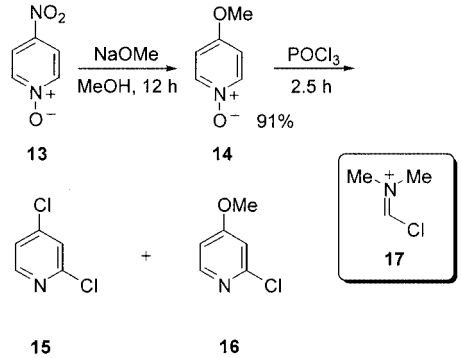
4-Substituted 2,3-Pyridynes

Our first strategy for the preparation of the required 4-substituted 2-chloropyridine precursors involved the chlorination of the corresponding *N*-oxides. For instance treatment of commercially available 4-methylpyridine *N*-oxide (**11**) with phosphoric trichloride at reflux temperature gave 2-chloro-4-methylpyridine (**12**) in 64% yield (Scheme 1).



Scheme 1. Synthesis of 2-chloro-4-methylpyridine (**12**)

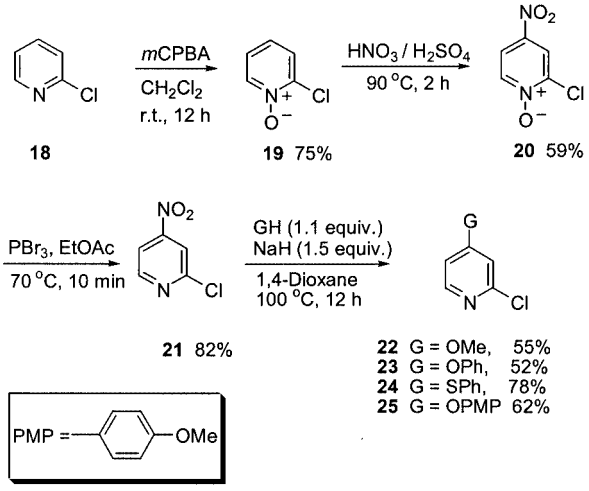
Attempts to use this methodology to prepare 4-alkoxy-2-chloropyridines were less successful. Substitution of the 4-nitro group in **13** with sodium methoxide afforded 4-methoxypyridine *N*-oxide (**14**). However, subsequent chlorination overnight gave only 2,4-dichloropyridine (**15**). A shorter reaction time of 2.5 h resulted in a poor yield (29%) of 2-chloro-4-methoxypyridine (**16**) (Scheme 2).



Scheme 2. Chlorination of **14**

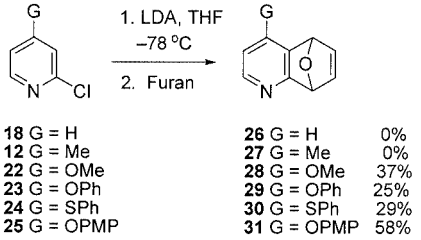
The chlorination of 2-alkoxypyridines under Vilsmeier−Haack conditions is known,[13,14] the attacking species in these cases is proposed to be cation **17** (Scheme 2). The chlorination of **14** at 106 °C was monitored by ^{1}H NMR spectroscopy, and analysis of samples taken periodically showed that the conversion of **16** to **15** occurred before complete consumption of **14**, indicating that stoichiometric control of this reaction would be difficult. The use of lower temperatures did not improve the yield of **16**, largely due to the insolubility of **14** in phosphoric trichloride below ca. 80 °C.

An alternative route to 4-alkoxy-2-chloropyridines involves the displacement of the nitro group in 2-chloro-4-nitropyridine (**21**) by sodium alkoxide.[15] Starting from **18**, oxidation with *m*CPBA gave the *N*-oxide **19**, which was then nitrated under relatively mild conditions to give 2-chloro-4-nitropyridine *N*-oxide (**20**). Smooth reduction with phosphorus tribromide afforded **21** as a yellow solid. Reaction of **21** with the appropriate alkoxides afforded **22**−**25** (Scheme 3).



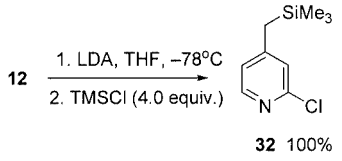
Scheme 3. Synthesis of 4-substituted 2,3-pyridyne precursors

Attempts to generate substituted 2,3-pyridynes from precursors **22**−**25** with *n*-, *sec*-, or *tert*-butyllithium failed due to competing substitution and halogen exchange reactions. This problem was avoided with the use of the sterically hindered LDA as the lithiating reagent, which does not undergo halogen/metal exchange reactions in these systems. A disadvantage associated with the use of this reagent is the nucleophilic attack of LDA (or its conjugate acid) on the putative aryne intermediate.[7] The results of lithiation of these precursors with LDA at −78 °C in THF and subsequent trapping with furan are presented in Scheme 4.



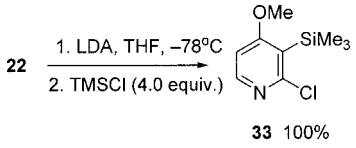
Scheme 4. [4+2] Cycloadditions of 4-substituted-2,3-pyridynes with furan

The failure of **18** to give a trapped adduct is not surprising,[1c] the main product most likely arises from nucleophilic attack on **2** by its lithiated precursor to give a resinous black tar. Bearing in mind that Gribble has reported the regioselective lithiation of **18** at C-3 with LDA,[2f] we propose that the lack of cycloadduct reflects the instability of **2** under the reaction conditions. The unsuitability of **12** as a 2,3-pyridyne precursor is due to the acidity of the methyl group protons,[16] and this was confirmed by trapping the intermediate lithio species with TMSCl to give silylation of the methyl group as the sole product detected by ^{1}H NMR spectroscopy (Scheme 5).



Scheme 5. Lithiation of **12** followed by trapping with TMSCl

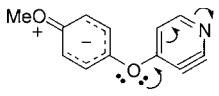
In contrast, ^{1}H NMR spectroscopic analysis of the crude reaction mixture obtained from the lithiation of **22** with LDA followed by quenching with trimethylsilyl chloride (TMSCl) indicated quantitative lithiation at C-3 (Scheme 6), as would be expected given the known directing effects of both the methoxy and chloro substituents towards *ortho*-lithiation.[7,17]



Scheme 6. Lithiation of **22** followed by trapping with TMSCl

Reasonable to good yields of cycloadduct were obtained with 2-chloro-4-alkoxy- and 4-thiophenoxypyridines. The decrease in adduct yield as the C-4 substituent is changed from methoxy to the relatively weaker electron-donating phenoxy and thiophenoxy groups indicates that electron donation into the pyridine ring system is the dominant factor in 2,3-pyridyne stabilisation by these substituents; the consequential reduction in hetaryne electrophilicity (compared with unsubstituted **2**, which gives no cycloadduct under identical conditions) allows [4+2] cycloaddition with furan to become more competitive with attack by nucleophiles,[18] resulting in a dienophilicity more usually associated with the less electrophilic **1**. This theory is also supported by the fact that significantly improved adduct yields were obtained from **25** over **23**. While it is conceivable that stabilisation of the initially formed 3-lithio species (by coordination to the heteroatom at C-4) may contribute to the relatively high yields of Diels–Alder adduct obtained using 4-alkoxy-2,3-pyridynes under metallation/elimination conditions, it is perhaps useful to point out at this juncture that it has been shown[7] that 2- and 6-isopropoxy-3,4-pyridyne (generated under dehydrohalogenation conditions from 2-alkoxy- and 6-isopropoxy-3-chloro-4-lithiopyridines, respectively) give considerably higher yields of Diels–Alder adducts with furan than **1**, despite the alkoxy groups being incapable of coordinative stabilisation of the (4-)lithiated intermediate. We conclude that while the 4-alkoxy substituent is required for selective anion formation, it is the reduced propensity of **6**–**9** to react with LDA/diisopropylamine and/or lithiated hetaryne precursors present in solution which results in the relatively high dienophilicity observed.

These reactions were relatively clean in that the only other products detected were 4-alkoxy-2-(diisopropylamino)pyridines (derived from nucleophilic attack by diisopropylamine on hetarynes **6**–**9**) and starting material. The strong stabilisation exhibited by the *p*-methoxyphenoxy group resulting in a 58% isolated yield of **31** represents a significant improvement over present literature methods and is unexpected when compared with the results obtained when the methoxy group is directly attached to the 4-position (as is the case with **28**). This could be rationalised in terms of the electron-rich 4-methoxy-substituted benzoid ring which encourages preferential electron donation towards the ring nitrogen atom by the pyridyl ether oxygen atom (Figure 3; **9a**). Of particular synthetic potential is the novel use of a sulfur-based stabilising group (i.e., precursor **24**) which may conceivably be cleaved after cycloaddition by hydrogenolysis[19] to afford access to adducts formally derived from "unstabilised" **2**, which itself is not a useful dienophile under dehydrohalogenation (vide supra) conditions.

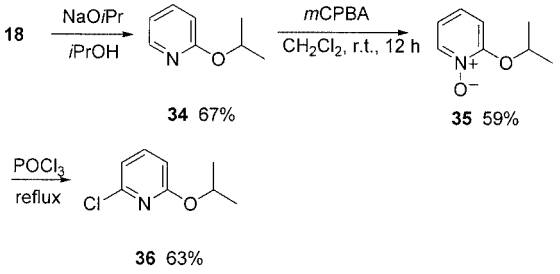


9a

Figure 3. Rationale for the improved dienophilicity exhibited by **9**

Attempted Trapping of 6-Substituted 2,3-Pyridynes

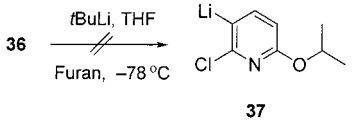
With the trapping of 4-substituted 2,3-pyridynes **6**–**9** with furan accomplished, attention then turned to the isomeric 6-alkoxy-2,3-pyridynes, in which the alkoxy electron-donating group is positioned *ortho* to the ring nitrogen atom. By analogy with the successful generation of 6-isopropoxy-3,4-pyridyne from 5-chloro-2-isopropoxypyridine and *t*BuLi,[7] it was envisaged that the lithiation of 6-chloro-2-isopropoxypyridine (**36**) would afford **10** after the elimination of LiCl. The synthesis of precursor **36** is outlined in Scheme 7.



Scheme 7. Synthesis of 6-chloro-2-isopropoxypyridine

Starting from **18**, substitution with sodium isopropoxide gave the desired ether **34**, which was oxidised with *m*CPBA at room temperature to give the *N*-oxide **35**. Subsequent chlorination with excess phosphoric trichloride afforded **36** in reasonable yield after chromatography. Surprisingly, significant amounts of 4-chloro and 2,6-dichloro products in a 55:45 ratio (by ^{1}H NMR spectroscopy) were also present in the crude mixture.

Treatment of **36** with *t*BuLi at −78 °C in THF gave a light yellow colour usually associated with lithiation; however, addition of furan and warming to room temperature gave only starting material on workup. Attempted trapping of the intermediate anion with TMSCl also failed to confirm the formation of the lithiopyridine **37** (Scheme 8). We conclude that this is due to a difficulty in accommodating a negative charge at a carbon atom of augmented electron density situated *para* to the electron-donating isopropoxy group.

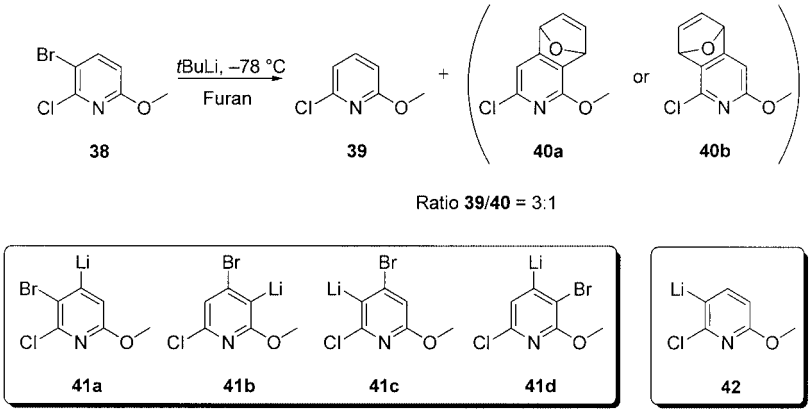


Scheme 8. Attempted regioselective lithiation of **36**

Since lithiation at C-3 is not possible due to the steric bulk of the isopropoxy group,[7] an alternative would be the formation of small amounts of a C-4 anion; however, no 4-silylated material was detected. This was surprising, as this trapping methodology has previously proven to be reliable even for the detection of only transiently stable lithiopyridines.[7] Although the failure to generate anion **37** was disappointing, low thermodynamic (5-H) acidity in 2-alkoxy-6-chloropyridines is not unprecedented,[1c] and it is known that trapping lithiopyridines that are not stabilised by adjacent substituents (lithiopyridine, for example) with conventional electrophiles at low temperatures can be problematic.[2f]

The possibility of forming anions such as **37** using a halogen/metal exchange strategy as opposed to a direct deprotonation reaction was also investigated. Unfortunately, the inherent instability of 2-alkoxy-6-chloro-5-lithiopyridines was further underlined by the failure of methoxybromochloropyridine **38** to furnish a cycloadduct derived from a 2,3-pyridyne on treatment with *t*BuLi and furan in THF at −78 °C. Only the 3,4-pyridyne-derived compound **40** (clearly identifiable by the presence of an aromatic singlet at δ = 6.61 ppm and vinylic double doublets at δ = 6.93 and 7.06 ppm) and debrominated starting material **39** were detected in the crude reaction mixture by ^{1}H NMR spectroscopy (Scheme 9).

The presence of **39** and absence of **38** in the crude mixture indicates that halogen/metal exchange does occur; however, the resultant (transiently stable) anion does not eliminate LiCl to form the expected 2,3-pyridyne derivative. The instability of **42** under the reaction conditions is illustrated by the formation of a single 3,4-pyridyne-derived Diels−Alder adduct **40**, requiring the intermediacy of either **19a** (formed after deprotonation at C-4 followed by elimination of LiBr and trapping by furan), or more plausibly anions **41b**−**d**, which could arise after an initial base-catalysed halogen dance (BCHD) reaction,[20,21] driven by the formation of a more stable lithiopyridine.[17] A repeat of the above reaction where the lithiated pyridine intermediate was trapped with TMSCl at −78 °C gave a 5:1 mixture of a C-3/C-5-silylated methoxy analogue of **36**[17] and a monosilylated material with a single aromatic proton resonance (δ = 6.72 ppm), further implicating one of the anions **41a**−**d** as intermediates. In any case, it is clear that



Scheme 9. Attempted generation of **5** from **16** and *t*BuLi

6-alkoxy-2-chloro-3-lithiopyridine anions such as **37** or **42** are unsuitable for use as precursors for 6-alkoxy-2,3-pyridynes.

Conclusions

In summary, the isopropoxypyridine **36** did not serve as a precursor to the hetaryne **10** under low-temperature dehydrohaolgenation conditions due to a general lack of acidity at C-5. An alternative strategy involving the deprotonation of isomeric 4-alkoxy- and 4-thiophenoxy-2-chloropyridines **22**−**25** was successful, giving reasonable to good yields of Diels−Alder adducts with furan where unsubstituted and 4-methyl-substituted analogues fail. Lithiopyridine trapping experiments have demonstrated that a 4-(thio)alkoxy substituent is required to effect the regioselective formation of the 2-chloro-3-lithiopyridine precursor, while a comparison of the observed dienophilicities of hetarynes **6**−**9** derived from these precursors strongly indicates that these species are stabilised by mesomeric electron donation toward the pyridine ring nitrogen atom by the heteroatomic C-4 substituents. These results demonstrate that under judiciously chosen conditions 4-alkoxy-2-chloropyridines can serve as precursors for 2,3-pyridyne derivatives of synthetically useful stability and dienophilicity.

Experimental Section

General: General experimental details have been described in a previous publication.[7] Endoxides **28**−**31** aromatise over time; storage of these compounds below 0 °C under N_2 and immediate analysis is advised. Nitropyridines **20** and **21** were prepared according to a literature procedure.[15] Note: Unless otherwise specified "workup" refers to concentration of the reaction mixture in vacuo, taking up the residue in $CHCl_3$, washing with 10% $NaHCO_3$ solution, H_2O, and brine, followed by drying (Na_2SO_4) of the organic layer and removal of the solvent in vacuo.

2-Chloro-4-methylpyridine (12): In a 50-mL round-bottomed flask, phosphoric trichloride (20 mL) was added to 4-methylpyridine *N*-oxide (1.50 g, 10.45 mmol), and the resulting suspension was heated under reflux for 3 h. ***Caution:*** An extremely exothermic reaction occurs on dissolution of the substrate at about 80 °C! After cooling to room temperature, excess phosphoric trichloride was removed in vacuo, the residue basified with 10% NaOH and extracted with $CHCl_3$ (3 × 40 mL). The organic extracts were combined, dried ($MgSO_4$), and the solvent removed in vacuo to give a black oil, which was distilled under reduced pressure to afford **12** (0.851 g, 64%) as a colourless liquid. B.p. 62−64 °C/3 Torr (ref.[22] 68−69 °C/4 Torr). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 7.02 [dd, *J*(H,H) = 5 Hz, 1 Hz, 1 H], 7.14 [d, *J*(H,H) = 1 Hz, 1 H], 8.22 [d, *J*(H,H) = 5 Hz, 1 H] ppm.

4-Methoxypyridine *N*-Oxide (14). Procedure A: In a 250-mL round-bottomed flask fitted with a stirring bar, sodium metal (about 1.5 g) was added to dry methanol (100 mL) at 0 °C. When hydrogen liberation ceased, 4-nitropyridine *N*-oxide (5.01 g, 35.76 mmol) was added and the resulting mixture heated under reflux overnight. The reaction mixture was cooled to room temperature, quenched with saturated aqueous NH_4Cl (30 mL) and extracted with $CHCl_3$ (4 × 100 mL). The organic extracts were combined, dried (Na_2SO_4), and the solvent was removed in vacuo to give **14** (4.08 g, 91%) as an off-white solid, which was used directly without further purification. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 6.83 [d, *J*(H,H) = 8 Hz, 2 H], 8.14 [d, *J*(H,H) = 8 Hz, 2 H] ppm.

2-Chloropyridine *N*-Oxide (19): In a 500-mL round-bottomed flask, *m*CPBA (57−86%, 50.0 g) was added to a solution of 2-chloropyridine (10.02 g, 88.28 mmol) in CH_2Cl_2 (200 mL). The flask was fitted with a magnetic stirring bar and a stopper, and stirred at room temperature overnight with precipitation of *m*-chlorobenzoic acid. The resulting suspension was washed with cold 10% NaOH solution (3 × 100 mL). The layers were separated, and the aqueous portion extracted with $CHCl_3$ (5 × 100 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent removed in vacuo to give a viscous oil, which was confirmed to be pure by ^{1}H NMR spectroscopy. A solid product could be precipitated by the addition of either dry ether or hexane. Filtration gave **19** (8.61 g, 75%) as yellow plates. M.p. 66−68 °C (ref.[15] 69−69.5 °C). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.30 (m, 2 H), 7.57 (m, 1 H), 8.39 (m, 1 H) ppm.

2-Chloro-4-methoxypyridine (22). Procedure B: In a 25-mL round-bottomed flask, dry methanol (0.28 mL, 6.91 mmol) was added in small portions to a suspension of sodium hydride (0.227 g, 9.46 mmol) in dry 1,4-dioxane (10 mL) at 0 °C. When the liberation of hydrogen gas had ceased, 2-chloro-4-nitropyridine (1.00 g, 6.31 mmol) was added, and the resulting brown solution was heated under reflux overnight. After cooling to room temperature, the mixture was quenched with saturated aqueous NH_4Cl (10 mL) and extracted with $CHCl_3$ (4 × 25 mL). The organic extracts were combined, dried (Na_2SO_4), and the solvent was removed in vacuo to give a brown liquid. Flash chromatography ($CHCl_3$) gave a colourless oil, which was further purified by kugelrohr distillation to give **22** (0.497 g, 55%). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 3.86 (s, 3 H), 6.75 [dd, *J*(H,H) = 6 Hz, 2 Hz, 1 H], 6.83 [d, *J*(H,H) = 2 Hz, 1 H], 8.18 [d, *J*(H,H) = 6 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 55.6, 109.5, 109.8, 150.3, 152.6, 167.3 ppm. EI MS (70 eV): *m*/*z* (%) = 143 (2) [M^+], 129, 113, 107, 101, 78. C_6H_6ClNO (143.6): calcd. C 50.19, H 4.21, Cl 24.69, N 9.76; found C 49.72, H 4.57, Cl 24.52, N 9.65.

2-Chloro-4-phenoxypyridine (23): Procedure B was applied using phenol (1.21 g, 12.86 mmol), dry 1,4-dioxane (18 mL), sodium hydride (0.422 g, 17.58 mmol) and 2-chloro-4-nitropyridine (1.86 g, 11.73 mmol). Workup (as per procedure B) and flash chromatography ($CHCl_3$/EtOAc, 90:10; R_f = 0.65) gave a colourless oil, which was further purified by kugelrohr distillation to give **23** (1.25 g, 52%) as a colourless viscous oil: IR (neat): $\tilde{\nu}$ = 3060, 1608, 1595, 1509, 1376, 1248, 1198, 1060, 738, 697 cm^{-1}. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 6.81 [dd, *J*(H,H) = 6 Hz, 2 Hz, 1 H], 6.97 [d, *J*(H,H) = 2 Hz, 1 H], 7.08 (m, 2 H), 7.28 (m, 1 H), 7.44 (m, 2 H), 8.20 [d, *J*(H,H) = 6 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 111.8, 115.7, 120.9, 126.0 130.4, 143.0, 151.1, 153.5, 166.0 ppm. EI MS (70 eV): *m*/*z* (%) = 205 (11) [M^+], 170, 140, 129, 112, 94, 77. $C_{11}H_8ClNO$ (205.6): calcd. C 64.25, H 3.92, Cl 17.24, N 6.81; found C 63.97, H 3.70, Cl 17.52, N 6.82.

2-Chloro-4-thiophenoxypyridine (24): Procedure B was applied using thiophenol (0.684 g, 6.21 mmol), dry 1,4-dioxane (10 mL), sodium hydride (0.203 g, 8.46 mmol) and 2-chloro-4-nitropyridine (0.894 g, 5.64 mmol). Workup (as per procedure B) and flash chromatography ($CHCl_3$) gave a colourless oil, which was further purified by kugelrohr distillation to give **24** (0.973 g, 78%) as a foul-smelling, colourless viscous oil: IR (neat): $\tilde{\nu}$ = 3057, 1562, 1516,

1449, 1363, 1223, 1135, 1071, 745, 685 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 6.87 [dd, *J*(H,H) = 5 Hz, 2 Hz, 1 H], 7.05 [d, *J*(H,H) = 2 Hz, 1 H], 7.45−7.6 (m, 5 H), 8.08 [d, *J*(H,H) = 5 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 119.6, 123.8, 128.2, 130.1, 130.2, 135.4, 142.4, 149.3, 153.8 ppm. MS EI (70 eV): *m*/*z* (%) = 221 (7) [M^+], 186, 144, 112, 109, 77. $C_{11}H_8ClNS$ (221.7): calcd. C 59.59, H 3.64, Cl 15.99, N 6.32; found C 59.34, H 3.91, Cl 15.85, N 6.39.

2-Chloro-4-(4-methoxyphenoxy)pyridine (25): Procedure B was applied using 4-methoxyphenol (1.07 g, 8.62 mmol), dry 1,4-dioxane (12 mL), sodium hydride (0.281 g, 11.71 mmol) and 2-chloro-4-nitropyridine (1.24 g, 7.82 mmol). Workup (as per procedure B) and flash chromatography ($CHCl_3$/EtOAc, 90:10) gave a colourless oil, which was further purified by kugelrohr distillation to give **25** (1.14 g, 62%) as a colourless viscous oil. IR (neat): $\tilde{\nu}$ = 3061, 2836, 1608, 1594, 1557, 1503, 1292, 1234 1034, 907, 866 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 3.85 (s, 3 H), 6.79 [dd, *J*(H,H) = 6 Hz, 2 Hz, 1 H], 6.95 [d, *J*(H,H) = 9.5 Hz, 2 H], 7.02 [d, *J*(H,H) = 9.5 Hz, 2 H], 7.05 [d, *J*(H,H) = 2 Hz, 1 H], 8.18 [d, *J*(H,H) = 6 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 55.7, 111.4, 115.2, 115.3, 121.9, 143.0, 146.6, 151.0, 157.4, 166.7 ppm. MS EI (70 eV): *m*/*z* (%) = 235 (11) [M^+], 220, 200, 156, 129, 112, 77. $C_{12}H_{10}ClNO_2$ (235.7): calcd. C 61.16, H 4.28, Cl 15.04, N 5.94; found C 60.89, H 4.17, Cl 15.11, N 5.73.

5,8-Dihydro-5,8-epoxy-4-methoxyquinoline (28). Procedure C: A 25-mL round-bottomed flask under N_2 (balloon) was charged with dry diisopropylamine (0.40 mL, 2.86 mmol), dry THF (3 mL) and cooled to −78 °C. After 15 min at this temperature, *n*-butyllithium (1.8 mL of a 1.6 M solution in hexane, 2.88 mmol) was added by syringe. The solution was stirred at −78 °C for 20 min, and 2-chloro-4-methoxypyridine (0.363 g, 2.53 mmol) in THF (2 mL) was added by syringe. After stirring for a further 20 min, furan (3.7 mL, 50.87 mmol) was added and the reaction mixture warmed to room temperature overnight. After workup, flash chromatography (EtOAc/$CHCl_3$, 80:20) gave **28**[10] (0.165 g, 37%) as a dark amber oil. ***Note:*** The chromatography is greatly simplified by the product being visible as an amber band. ^1H NMR (270 MHz, $CDCl_3$): δ = 3.87 (s, 3 H), 5.59 (s, 1 H), 5.98 (s, 1 H), 6.48 [d, *J*(H,H) = 6 Hz, 1 H], 7.11 (m, 2 H), 7.96 [d, *J*(H,H) = 6 Hz, 1 H] ppm. MS EI (70 eV): m/z (%) = 175 (3) [M^+], 159, 145, 117, 104, 77. $C_{10}H_9NO_2$ (175.2): calcd. C 68.56, H 5.18, N 8.00; found C 68.40, H 5.09, N 7.88.

5,8-Dihydro-5,8-epoxy-4-phenoxyquinoline (29): Procedure C was applied using dry diisopropylamine (0.25 mL, 1.79 mmol), dry THF (3 + 2 mL), *n*-butyllithium (1.1 mL of a 1.6 M solution in hexane; 1.76 mmol), 2-chloro-4-phenoxypyridine (0.330 g, 1.60 mmol) and furan (2.3 mL, 31.62 mmol). After workup, flash chromatography (EtOAc/$CHCl_3$ 80:20) gave **29** (0.094 g, 25%) as an amber oil. IR (neat): $\tilde{\nu}$ = 3025, 1605, 1580, 1509, 1490, 1263, 726, 996 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 5.21 [d, *J*(H,H) = 2 Hz, 1 H], 5.55 [d, *J*(H,H) = 2 Hz, 1 H], 6.51 [d, *J*(H,H) = 6 Hz, 1 H], 6.90 [dd, *J*(H,H) = 6 Hz, 2 Hz, 1 H], 7.07 (m, 3 H), 7.28 (m, 1 H), 7.44 (m, 2 H), 7.95 [d, *J*(H,H) = 6 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 79.9, 82.7, 110.7, 120.3, 125.5, 128.5, 130.3, 142.2, 143.3, 146.1, 155.2, 156.4, 175.6 ppm. MS EI (70 eV): *m*/*z* (%) = 237 (4) [M^+], 221, 209, 180, 160, 131, 116, 104. $C_{15}H_{11}NO_2$ (237.3): calcd. C 75.94 H 4.67 N 5.90; found C 75.68, H 4.84, N 5.65.

5,8-Dihydro-5,8-epoxy-4-thiophenoxyquinoline (30): Procedure C was applied using dry diisopropylamine (0.35 mL, 2.50 mmol), dry THF (5 + 2 mL), *n*-butyllithium (1.55 mL of a 1.6 M solution in hexane, 2.48 mmol), 2-chloro-4-thiophenoxypyridine (0.504 g, 2.27 mmol) and furan (3.4 mL, 46.74 mmol). After workup, flash chromatography (EtOAc/$CHCl_3$, 80:20) gave **30** (0.166 g, 29%) as an amber oil. ^1H NMR (270 MHz, $CDCl_3$): δ = 5.55 (m, 2 H), 6.52 [d, *J*(H,H) = 6 Hz, 1 H], 6.83 [dd, *J*(H,H) = 6 Hz, 2 Hz, 1 H], 7.08 [dd, *J*(H,H) = 6 Hz, 2 Hz, 1 H], 7.4−7.5 (m, 5 H), 7.83 [d, *J*(H,H) = 6 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 80.5, 82.7, 118.6, 129.2, 129.8, 130.8, 134.0, 139.4, 140.6, 142.3, 143.0, 143.9, 172.4 ppm. MS EI (70 eV): *m*/*z* (%) = 253 (6) [M^+], 237, 225, 176, 147, 109, 77. $C_{15}H_{11}NOS$ (253.3): calcd. C 71.12, H 4.38, N 5.53; found C 70.90, N 4.26, N 5.38.

5,8-Dihydro-5,8-epoxy-4-(4-methoxyphenoxy)quinoline (31): Procedure C was applied using dry diisopropylamine (0.30 mL, 2.14 mmol), dry THF (3 + 2 mL), *n*-butyllithium (1.35 mL of a 1.6 M solution in hexane, 2.16 mmol), 2-chloro-4-(4-methoxyphenoxy)pyridine (0.450 g, 1.91 mmol) and furan (2.8 mL, 38.50 mmol). After workup, flash chromatography (EtOAc/$CHCl_3$, 80:20) gave **31** (0.295 g, 58%) as a viscous amber oil. IR (neat): $\tilde{\nu}$ = 3021, 2852, 1608, 1594, 1557, 1503, 1462, 1292, 1234, 1194, 1034, 907 cm^{-1}. ^1H NMR (270 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 5.17 [d, *J*(H,H) = 2 Hz, 1 H], 5.53 [d, *J*(H,H) = 2 Hz, 1 H], 6.46 [d, *J*(H,H) = 6 Hz, 1 H], 6.88 [dd, *J*(H,H) = 5.5 Hz, 2 Hz, 1 H], 6.94 [d, *J*(H,H) = 7 Hz, 2 H], 6.99 [d, *J*(H,H) = 7 Hz, 2 H], 7.05 [dd, *J*(H,H) = 5.5 Hz, 2 Hz, 1 H], 7.91 [d, *J*(H,H) = 6 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 55.7, 80.0, 82.7, 110.2, 115.2, 121.7, 127.7, 142.1, 143.4, 146.0, 148.4, 157.2, 157.3, 175.5 ppm. MS EI (70 eV): *m*/*z* (%) = 267 (7) [M^+], 252, 251, 237, 221, 160, 109, 77. $C_{16}H_{13}NO_3$ (267.3): calcd. C 71.90, H 4.90, N 5.24; found C 71.78, H 5.12, N 5.46.

2-Chloro-4-(trimethylsilylmethyl)pyridine (32). Procedure D: A 10-mL round-bottomed flask under N_2 (balloon) was charged with dry diisopropylamine (0.18 mL, 1.29 mol), dry THF (3 mL) and cooled to −78 °C. After 15 min, *n*-butyllithium (0.8 mL of a 1.6 M solution in hexane, 1.28 mmol) was added by syringe. The solution was stirred at −78 °C for 20 min, and a solution of 2-chloro-4-methylpyridine (0.152 g, 1.19 mmol) in THF (2 mL) was added by syringe to give a yellow solution, which was stirred for 20 min, quenched with TMSCl (0.6 mL, 4.73 mmol) by a syringe and warmed to room temperature overnight. The resulting suspension was poured slowly into 30 mL of saturated $NaHCO_3$ solution and extracted with $CHCl_3$ (3 × 40 mL). The organic extracts were combined, dried ($MgSO_4$), and the solvent was removed in vacuo to give a yellow oil (1.87 g). Compound **32** was identified as the sole silylated product from ^1H NMR spectroscopic analysis of the crude material. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.03 (s, 9 H), 2.11 (s, 2 H), 6.84 [dd, *J*(H,H) = 5 Hz, 1 Hz, 1 H], 6.96 [d, *J*(H,H) = 1 Hz, 1 H], 8.17 [d, *J*(H,H) = 5 Hz, 1 H] ppm. MS EI (70 eV): *m*/*z* (%) = 199 (19) [M^+], 184, 169, 127, 91, 73.

2-Chloro-4-methoxy-3-trimethylsilylpyridine (33): Procedure D was applied using dry diisopropylamine (0.20 mL, 1.43 mol), dry THF (3 + 2 mL), *n*-butyllithium (0.9 mL of a 1.6 M solution in hexane, 1.44 mmol) and 2-chloro-4-methoxypyridine (0.188 g, 1.31 mmol). Workup (as per procedure D) gave a light yellow oil (2.76 g). Compound **33** was identified as the sole product from ^1H and ^{13}C NMR spectroscopic analyses of the crude material. ^1H NMR (270 MHz, $CDCl_3$): δ = 0.39 (s, 9 H), 3.83 (s, 3 H), 6.68 [d, *J*(H,H) = 6 Hz, 1 H], 8.22 [d, *J*(H,H) = 6 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 1.5, 55.5, 105.2, 121.6, 151.2, 157.5, 172.3.

2-Isopropoxypyridine (34): Procedure A was applied using a 100-mL round-bottomed flask fitted with a stirring bar, sodium metal (about 1.5 g), dry propan-2-ol (70 mL) and 2-chloropyridine

(2.78 g, 24.48 mmol). ***Note:*** After addition of the metal to the alcohol, the resulting suspension was heated at 50 °C until the sodium had disappeared and hydrogen liberation ceased. Workup as per procedure A gave a yellow liquid (0.92 g). Purification by flash chromatography (light petroleum/EtOAc, 90:10) gave **34** (2.25 g, 67%) as a colourless liquid. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.34 [d, *J*(H,H) = 6 Hz, 6 H], 5.30 [sept, *J*(H,H) = 6 Hz, 1 H], 6.67 (m, 1 H), 6.78 (m, 1 H), 7.51 (m, 1 H), 8.13 (m, 1 H) ppm.

2-Isopropoxypyridine *N*-Oxide (35): In a 100-mL round-bottomed flask, *m*CPBA (57−86%, 7.5 g) was added to a solution of 2-isopropoxypyridine (1.84 g, 13.4 mmol) in CH_2Cl_2 (80 mL). The flask was fitted with a magnetic stirring bar and a stopper, and stirred at room temperature overnight with precipitation of *m*-chlorobenzoic acid. The resulting suspension was washed with cold 10% NaOH solution (3 × 50 mL). The layers were separated, and the aqueous portion extracted with $CHCl_3$ (3 × 100 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo to give a viscous yellow oil, which was usually sufficiently pure to use directly without purification. The pure product could be obtained by dissolving the crude mixture in a minimum amount of $CHCl_3$ at 0 °C followed by precipitation by slow addition of hexane. After filtration, the white solid was dried under vacuum to give hygroscopic **35** (1.22 g, 59%). M.p. 85−88 °C (ref.[23] 88 °C). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.48 [d, *J*(H,H) = 6 Hz, 6 H], 4.91 [sept, *J*(H,H) = 6 Hz, 1 H], 6.92 (m, 2 H), 7.25 (m, 1 H), 8.27 (m, 1 H) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 22.1, 74.0, 111.8, 117.7, 127.8, 140.5, 157.3 ppm.

2-Chloro-6-isopropoxypyridine (36): In a 50-mL round-bottomed flask phosphoric trichloride (20 mL) was added to 2-isopropoxypyridine *N*-oxide (1.09 g, 7.12 mmol), and the resulting solution was heated under reflux for 3 h. After cooling to room temperature, excess phosphoric trichloride was removed in vacuo, the residue was basified with 10% NaOH and extracted with $CHCl_3$ (3 × 40 mL). The organic extracts were combined, dried ($MgSO_4$), and the solvent was removed in vacuo to give a dark oil. Flash chromatography (light petroleum/$CHCl_3$, 1:1) gave **36** as a colourless liquid (0.769 g, 63%). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.33 [d, *J*(H,H) = 6 Hz, 6 H], 5.29 [sept, *J*(H,H) = 6 Hz, 1 H], 6.57 [d, *J*(H,H) = 8 Hz, 1 H], 6.83 [d, *J*(H,H) = 7.5 Hz, 1 H], 7.47 [dd, *J*(H,H) = 8 Hz, 7.5 Hz, 1 H] ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 21.9, 68.9, 109.6, 115.7, 140.5, 148.2, 163.1 ppm. $C_8H_{10}ClNO$ (171.6): calcd. C 55.99, H 5.87, Cl 20.66, N 8.16; found C 55.68, H 5.88, Cl 20.54, N 8.01.

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