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Pyridino-directed lithiation of anisylpyridines: new access to functional pyridylphenols

Michaël Parmentier, Philippe Gros* and Yves Fort*

Synthèse Organométallique et Réactivité, UMR CNRS 7565, Université Henri Poincaré, Bd des Aiguillettes, 54506, Vandoeuvre-lès-Nancy, France

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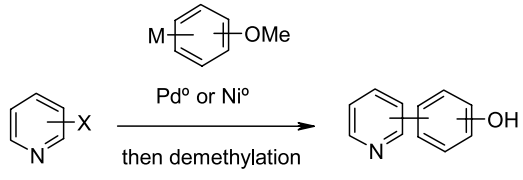
Abstract—The lithiation of nine anisylpyridines has been studied. While usual reagents did not react or gave addition products on pyridine ring, the BuLi-LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$) superbase induced exclusive pyridino directed metallation. The usefulness of this new reaction allowed the efficient preparation of a range of alpha functional pyridylphenols. A successful subsequent cyclisation of an appropriate isomer into corresponding benzofuropyridine was also performed.

1. Introduction

Pyridylphenols constitute key structures for biologically active molecules (e.g., adrenergic receptor ligands),[1] metal ligands for asymmetric synthesis[2] or building blocks for supramolecular architectures.[3] They are generally prepared from halogenated heterocycles by Pd-catalyzed Suzuki[3] or Ni-catalyzed Corriu–Kumada–Tamao[4] cross-couplings followed by a demethylation step (Scheme 1).

This methodology however suffers from limitations when functional pyridyl derivatives have to be coupled since substituents can display steric hindrance, reactivity towards the organometallic species (e.g., carbonyl moieties towards Grignards) or act as poisons or competing ligands for the catalyst (e.g., sulfides or phosphines). Thus, methodologies allowing the selective functionalization of parent methoxyphenylpyridines are a valuable alternative to couplings for the preparation of functional pyridylphenols. Our laboratory has recently reported the selective C-2 pyridine ring lithiation of phenylpyridines using the BuLi-containing aggregates BuLi-LiDMAE (LiDMAE = $Me_2N(CH_2)_2OLi$)[5] which thus could be of great interest for introduction of functionalities in the methoxy-phenylpyridine series.[6] At the beginning of this work a paper by Quéguiner and coworkers[4b] appeared dealing with lithiation of some methoxyphenylpyridines with LiTMP as basic reagent. The aim was to metallate the pyridine ring using the remote directing ability of the methoxy group. From this work it appeared that lithiation of the pyridine ring was strongly substrate dependent. Only 2-(2-methoxy-phenyl)pyridine **1** underwent lithiation with subsequent introduction of electrophiles at the C-6 position but not at the expected C-3 one! This latter selectivity could be attributed to an internal cooperating lithium complexation by both the pyridine nitrogen and methoxy group. This kind of concomitant chelation effect was already observed in our recent works on lithiation of phenylchloropyridine with *t*-BuLi[7] (Fig. 1).



Scheme 1. Usual synthetic route to pyridylphenols.

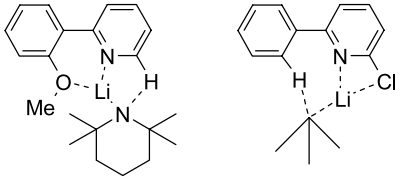


Figure 1. Proposed models for cooperative internal chelations in substituted phenylpyridines.

Keywords: Selective lithiation; Pyridino-direction; Anisylpyridines; Cyclization.
* Corresponding authors. Tel.: +33 3 83 68 47 81; fax: +33 3 83 68 47 85; e-mail addresses: philippe.gros@sor.uhp-nancy.fr; yves.fort@sor.uhp-nancy.fr

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On the other hand lithiation did not occur with isomers bearing a methoxy group more distant from nitrogen. Indeed, **4** was found unreactive and **7** led to a dimer. Consequently lithiation of these isomers could be achieved using a reagent bringing an external lithium chelating agent and the BuLi-LiDMAE superbase could be the ideal candidate for such task due to its affinity for the pyridine nitrogen[5] (Fig. 2).

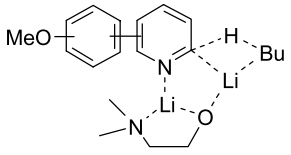


Figure 2. Expected external chelation by lithium aggregates.

Herein we report a new process for the clean pyridino-directed lithiation of methoxyphenylpyridines with high selectivity regardless of the position of the methoxyphenyl group on pyridine.

2. Results and discussion

A series of nine isomers was first prepared in acceptable to good yields by Corriu–Kumada–Tamao couplings between the appropriate anisylmagnesium bromides and bromopyridines except for derivatives **7–9** for which 4-chloropyridine was used (Scheme 2).

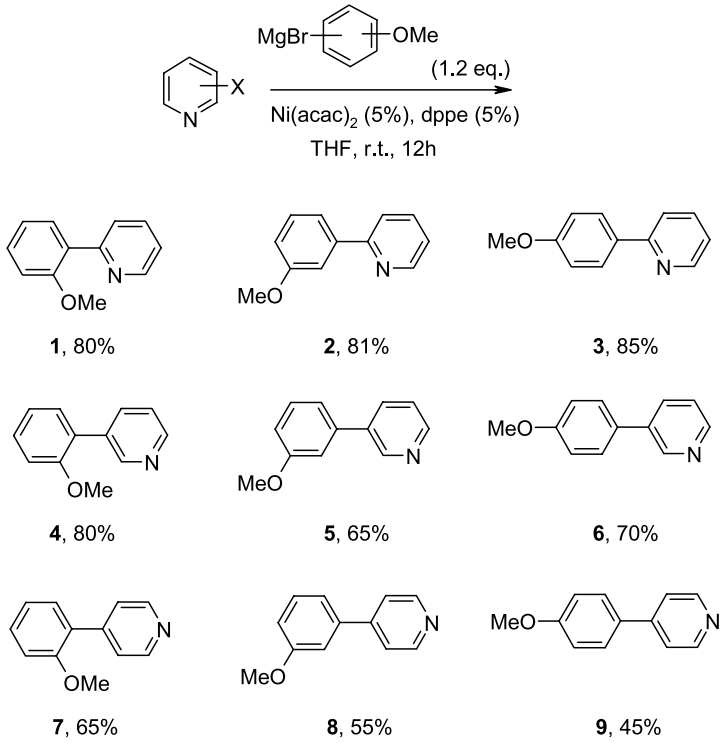
The first lithiation experiments were carried out with *n*-BuLi, *t*-BuLi, *n*-BuLi-TMEDA and BuLi-*t*-BuOK under various conditions. Sluggish reactions generally occurred with all substrates leading to nucleophilic addition products on the pyridine ring. Then we turned to lithiation with the BuLi-LiDMAE reagent, which was expected to display lower nucleophilicity.[5]

2.1. Lithiation of 2-anisylpyridines

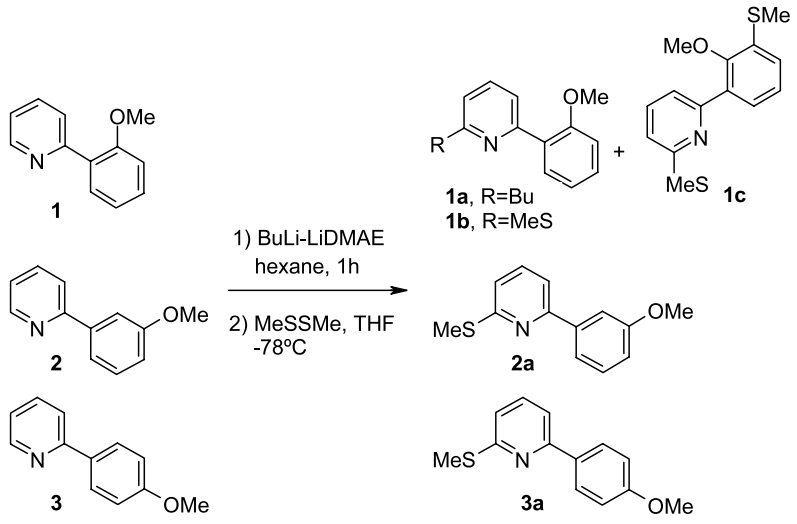
2-Anisylpyridines **1–3** were first reacted with BuLi-LiDMAE under usual conditions in hexane at various temperatures (Scheme 3, Table 1). All substrates led to efficient lithiation α to nitrogen. With **1**, the selectivity was in agreement with those observed by Quéguiner and co-workers.[4b] However the lithiation of this isomer was found highly temperature-sensitive since lithiation conducted at 0 °C led, besides nucleophilic addition product **1a**, to the derivative **1c** resulting from a bis-sulfuration of both the pyridine and phenyl ring (*ortho* to methoxy) (run 1). The temperature had to be decreased to −40 °C to ensure selective monolithiation and good conversion (runs 3–5). An increase of base amount and substitution of toluene to hexane in the metallation step to improve the solubility of **1** in the reaction medium were also beneficial. This was not necessary with **2–3** which were soluble in hexane. Moreover, no temperature effect was observed and **2a–3a** were obtained in good yields after metallation at 0 °C with 3 equiv of the reagent (runs 6–7).

These different behaviours are in good agreement with the relative heat of formation of potential carbanions in substrates as depicted in Figure 3.[8]

As shown, the carbanion *ortho* to methoxy in **1** is thermodynamically more stable than those α to nitrogen. Deprotonation on pyridine ring is obtained as a single reaction at low temperature (−40 °C) and is thus assumed



Scheme 2. Preparation of methoxyphenylpyridine **1–9**.



Scheme 3. Lithiation of **1–3** with BuLi-LiDMAE.

Table 1. Study of pyridino lithiation in **1–3**[a]

Entry	Substrate	Base (equiv)	*T* (°C)	Products (yield,%)[b]	Isolated yield (%)
1	**1**	3	0	**1a** (18) +**1b** (36) +**1c** (20)	—
2	**1**	3	−78	**1b** (15)	—
3	**1**	3	−40	**1b** (73)	—
4	**1**	4	−40	**1b** (80)	70
5	**1**	4	−40	**1b** (91)	85[c]
6	**2**	3	0	**2a** (92)	85
7	**3**	3	0	**3a** (85)	76

[a] All reactions performed on 2 mmol of substrate.
[b] GC yield.
[c] Metallation performed in toluene.

to be under kinetic control. On the other hand dilithiation at both α to nitrogen and *ortho* to methoxy was observed only at higher temperature (0 °C) rather under thermodynamic conditions. With the two other isomers **2–3**, the carbanion α to nitrogen is always the most stable explaining exclusive lithiation at this position even at 0 °C. The inertness of these latter substrates towards LTMP could be explained by the insufficient basicity of such reagent to abstract both the phenyl and pyridine protons. With BuLi-LiDMAE, chelation by the pyridine nitrogen and higher basicity allowed the deprotonation of the pyridinic site.

These selective lithiations were subsequently exploited for introduction of functionalities on the pyridine ring. Substrates **1–3** were then lithiated under the best conditions reported in Table 1 and reacted with various electrophiles (Table 2).

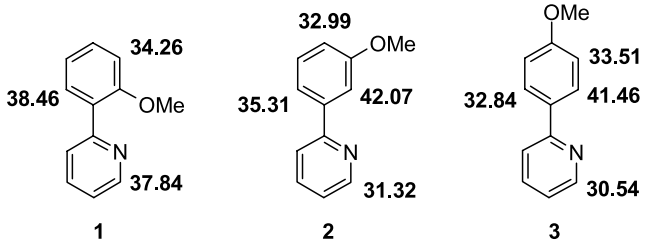


Figure 3. Calculated relative heats of formation (kcal/mol) of potential carbanions in **1–3**.

Several functional derivatives were prepared efficiently, especially alcohol **3d** and ketone **2d** not easy to obtain via classical couplings and the new P,N,O ligand **1f**. Note that **1** again behaved differently from **2** and **3** since it was not fully deuterated indicating that incomplete lithiation may be due to competitive chelation of lithium aggregates by the methoxy group thus partially impeding lithiation α to nitrogen.

2.2. Lithiation of 3- and 4-anisylpyridines

Then, we turned to the lithiation of isomers **4–9** displaying two available protons α to the pyridine nitrogen thus offering possibility for new selectivities (Fig. 4).

We first studied substrates **4** and **7** with a methoxy group at the *ortho* position on the phenyl ring which was expected to induce directing effects on pyridine (Scheme 4). As already observed with derivative **1**, **4** was poorly soluble in hexane and best results were obtained when metallation was performed in toluene at −20 °C. The lithiation occurred exclusively at C-6 and not at C-2 as could be expected from the directing power of the methoxy and a potential cooperative effect. This selectivity could be attributed to steric hindrance generated by the methoxyphenyl group at the C-2 position preventing the formation of aggregates. Note that such a compound was found inert towards LTMP supporting the need for external chelation to ensure pyridine lithiation and the role of steric hindrance. The reaction

Table 2. Preparation of functional methoxyphenylpyridines from **1–3**

Substrate	Electrophile	Product	Yield (%)[a]
1	D_2O	E=D, **1d**	80 (d%=75)[b]
1	C_2Cl_6	E=Cl, **1e**	82
1	$ClPPh_2$	E=PPh_2, **1f**	50
2	D_2O	E=D, **2b**	75 (d%>95)[b]
2	CBr_4	E=Br, **2c**	74
2	$PhCONMe_2$	E=COPh, **2d**	78
3	D_2O	E=D, **3b**	80 (d%>98)[b]
3	C_2Cl_6	E=Cl, **3c**	90
3	PhCHO	E=CH(OH)Ph, **3d**	75

[a] Isolated yield after column chromatography.
[b] Determined by ^1H NMR.

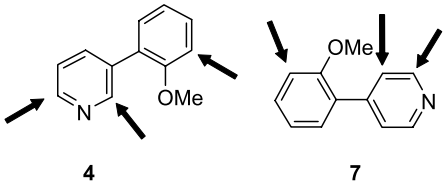
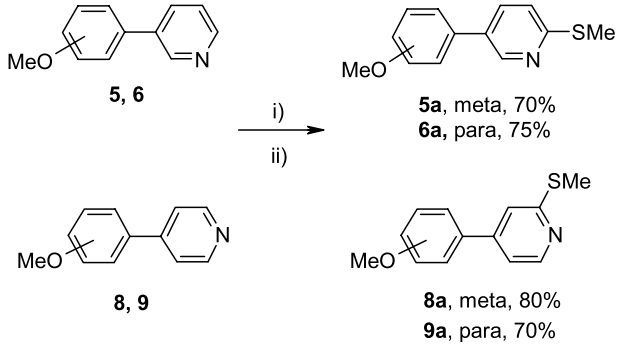


Figure 4. Potential deprotonation sites in **4** and **7**.

conditions were then applied to isomer **7**. As shown, lithiation also occurred selectively α to nitrogen. Interestingly, **7** did not lead to the radical induced dimerisation product[9] as was observed with LTMP indicating actual formation of the lithio intermediate (supported by a deuteration experiment) and subsequent stabilisation by lithium aggregates. A number of functionalities were further introduced efficiently leading to a range of new derivatives.

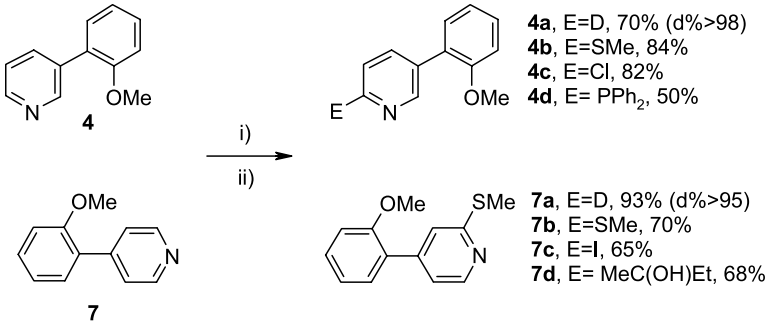
We then studied the remaining isomers **5**, **6**, **8** and **9** (Scheme 5). These compounds were lithiated under the above determined conditions. The reaction was also selectively pyridino directed at the α position. Note that



Scheme 5. Lithiation of **5**, **6**, **8**, **9**. For conditions see Scheme 4.

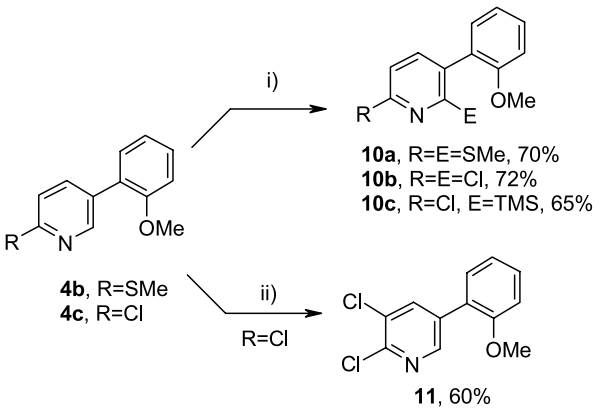
substrates **5**, **6** and **9** were soluble in hexane and the reaction proceeded as well in this solvent.

We next focused on the use of this new reaction for preparation of bifunctional derivatives via iterative lithiations. Then, compounds **4b** and **4c** bearing synthetically useful and base compatible substituents were first subjected



Scheme 4. Lithiation of **4** and **7**. Conditions: (i) BuLi-LiDMAE (3 equiv), toluene, −20 °C, 1 h. (ii) MeOD or MeSSMe or C_2Cl_6 or $ClPPh_2$ (3.2 equiv), THF, −78 °C to rt, 1 h.

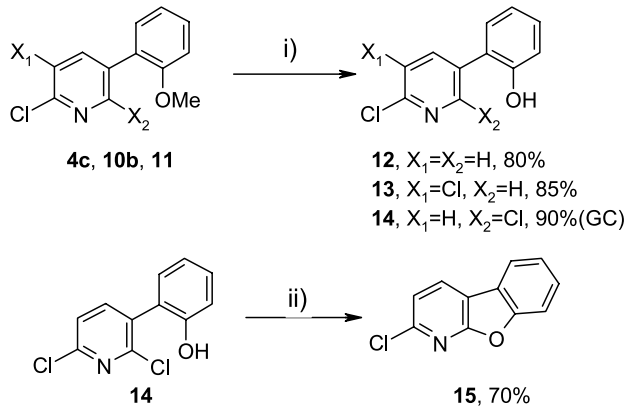
to reaction with BuLi-LiDMAE in order to check the ability of the available α proton to be abstracted (Scheme 6).



Scheme 6. Sequential lithiations. Conditions: (i) (1) BuLi-LiDMAE (3 equiv), toluene, −20 °C, 1 h. (2) MeSSMe or C_2Cl_6 or $ClSiMe_3$ (3.2 equiv), THF, −78 °C to −20 °C, 1 h. (ii) (1) LTMP (3.2 equiv), THF, −20 °C, 1 h. (2) C_2Cl_6 (3.5 equiv), THF, −20 °C 1 h.

As shown, the C-2 position was lithiated in slightly lower yield than was the C-6 one in **4**, presumably due to the previously proposed steric effects. However bifunctional derivatives **10a–c** were obtained in good overall yields (typically 60% from **4**). Reaction of **4c** with LTMP yielded exclusively the 2,3-dichloro derivative in 60% yield indicating the poor remote directing power of the methoxy group compared to those of chlorine on pyridine.

In order to demonstrate the usefulness of our methodology for the synthesis of functional pyridylphenols we examined the demethylation of some of the prepared derivatives (Scheme 7). We chose chlorinated compounds, which are useful precursors for further introduction of diversity. A clean demethylation was obtained by reaction of **4c**, **10b** and **11** with BBr_3 solutions in CH_2Cl_2 at room temperature furnishing the expected phenols in high yields. Finally, crude phenol **14** was not purified and involved as such in cyclisation under basic conditions leading to chlorinated benzofuropyridine **15** in good yield (70%).



Scheme 7. (i) BBr_3 (5 equiv),CH_2Cl_2, −78 °C then rt overnight. (ii) K_2CO_3 (3 equiv), CH_3CN, reflux, 5 h.

3. Conclusion

We have developed an efficient methodology for the functionalisation of nine methoxyphenylpyridines. The BuLi-LiDMAE superbase effected a selective pyridino directed lithiation α to nitrogen. The obtained functional derivatives were smoothly deprotected under mild conditions and converted into the corresponding phenols. Work is now in progress to extend such reactions to the preparation of various functional benzofuropyridines such as **15** and fused polyheterocyclic compounds.

4. Experimental

4.1. General

Et_2O, THF, and hexane were distilled and stored over sodium wire before use. 2-Dimethylaminoethanol was distilled under nitrogen and stored on molecular sieves. *n*-BuLi was used as a 1.6 M solution in hexanes. All other reagents were commercially available and used as such. ^1H and ^{13}C and ^{31}P NMR were obtained in $CDCl_3$ (unless otherwise stated) on a Bruker AC400 instrument at 400, 100 and 162 MHz respectively. GC experiments were performed on a Shimadzu chromatograph fitted with a 15 m capillary column. GC/MS (EI) were obtained on HP5971 spectrometer.

4.2. Preparation of starting anisylpyridines

To a mixture of appropriate bromo or chloropyridine (9 mmol), $Ni(acac)_2$ (120 mg, 0.45 mmol) and dppe (180 mg, 0.45 mmol) in THF (30 mL) was added dropwise the appropriate anisylmagnesium bromide (10 mmol) (prepared by dropwise addition of the anisyl bromide (10 mmol) to a refluxing suspension of Mg turnings (240 mg, 10 mmol) in THF). The mixture was then stirred for 18 h at room temperature before hydrolysis with water (20 mL). The aqueous layer was then extracted twice with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. The crude products were then purified by column chromatography on silica gel.

4.2.1. 2-(2-Methoxyphenyl)pyridine 1. Column chromatography (80% hexanes/AcOEt) afforded **1** (1.33 g, 80%) as a pale yellow oil. Spectrocopic data consistent with that reported in the literature.[10]

4.2.2. 2-(3-Methoxyphenyl)pyridine 2.[11] Column chromatography (80% hexanes/AcOEt) afforded **2** (1.35 g, 81%) as a pale yellow oil. δ_H 3.89 (s, 3H), 6.96 (d, J=9.0 Hz, 1H), 7.22–7.24 (m, 1H), 7.38 (t, J=8.0 Hz, 1H), 7.52 (t, J=1.4 Hz, 1H), 7.52–7.60 (m, 1H), 7.71–7.75 (m, 2H), 8.68 (d, J=4.8 Hz, 1H). δ_C 55.6, 112.3, 115.4, 119.6, 120.9, 122.5, 130.0, 137, 141.2, 149.9, 157.5, 160.4. *m/z* (EI) 185 (M, 100), 154 (M−31, 100), 140 (M−45, 22), 126 (M−59, 8), 114 (M−71, 9), 89 (M−96, 4), 63 (M−122, 4%).

4.2.3. 2-(4-Methoxyphenyl)pyridine 3.[12] Column chromatography (80% hexanes/AcOEt) afforded **3** (1.41 g, 85%) as a white solid. Mp 54–55 °C [Lit[10a] 53–55 °C]. δ_H 3.89 (s, 3H), 7.02 (d, J=8.9 Hz, 2H), 7.18 (dd, J=3.4, 1.4 Hz, 1H),

7.68–7.75 (m, 2H), 7.97 (d, J=9.0 Hz, 2H), 8.67 (d, J=5.3 Hz, 1H). δ_C 55.7, 114.5, 120.2, 121.8, 128.5, 137, 149.9. m/z (EI) 185 (M, 100), 170 (M−15, 42), 142 (M−43, 74), 141 (M−44, 56), 115 (M−70, 21), 89 (M−96, 17),78 (M−107, 9), 63 (M−122, 21), 51 (M−134, 14%).

4.2.4. 3-(2-Methoxyphenyl)pyridine 4. Column chromatography (80% hexanes/AcOEt) afforded **4** (1.33 g, 80%) as a colourless oil. Spectrocopic data consistent with that reported in the literature.[10a,13]

4.2.5. 3-(3-Methoxyphenyl)pyridine 5. Column chromatography (80% hexanes/AcOEt) afforded **5** (1.08 g, 65%) as a pale yellow oil. Spectrocopic data consistent with that reported in the literature.[14]

4.2.6. 3-(4-Methoxyphenyl)pyridine 6. Column chromatography (70% hexanes/AcOEt) afforded **6** (1.16 g, 70%) as a white solid. Mp 59–60 °C [Lit[10a] 60–61 °C]. δ_H 3.85 (s, 3H), 6.99 (d, J=8.4 Hz, 2H), 7.32 (dd, J=7.8, 4.8 Hz, 1H), 7.51 (d, J=8.5 Hz, 2H), 7.82 (d, J=7.9 Hz, 1H), 8.55 (s, 1H), 8.82 (s, 1H). δ_C 55.5, 114.7, 123.7, 128.4, 130.4, 134.0, 148.0, 148.4, 159.9. m/z (EI) 185 (M, 100), 170 (M−15, 40), 142 (M−43, 32), 115 (M−70, 16), 89 (M−96, 10), 63 (M−122, 10%).

4.2.7. 4-(2-Methoxyphenyl)pyridine 7. 4-Chloropyridine was used as halopyridine. Column chromatography (70% hexanes/AcOEt) afforded **7** (1.08 g, 65%) as a white solid. Mp 63–64 °C [Lit[10a] 63–65 °C]. Spectrocopic data consistent with that reported in the literature.[15]

4.2.8. 4-(3-Methoxyphenyl)pyridine 8.[15] 4-Chloropyridine was used as halopyridine. Column chromatography (50% hexanes/AcOEt) afforded **8** (0.92 g, 55%) as a pale yellow oil. Spectrocopic data consistent with that reported in the literature.[15]

4.2.9. 4-(4-Methoxyphenyl)pyridine 9. 4-Chloropyridine was used as halopyridine. Column chromatography (50% hexanes/AcOEt) afforded **9** (0.75 g, 45%) as a white solid. Mp 94–96 °C [Lit[10a] 95–96 °C]. δ_H 3.88 (s, 3H), 7.03 (d, J=8.7 Hz, 2H), 7.48 (d, J=5.9 Hz, 2H), 7.62 (d, J=8.6 Hz, 2H), 8.64 (d, J=5.5 Hz, 2H). δ_C 55.8, 114.9, 121.5, 128.5, 150.6. MS (EI) m/z: 185 (M, 100), 170 (M−15, 26), 142 (M−43, 34), 115 (M−70, 24), 89 (M−96, 10), 63 (M−122, 10%).

4.3. Procedure for lithiation of anisylpyridines

A solution of 2-dimethylaminoethanol (0.8 mL, 8 mmol) in hexane or toluene (10 mL) was cooled at 0 °C and treated dropwise with n-BuLi (10 mL, 16 mmol). After 30 min at 0 °C, a solution of the anisylpyridine (2 mmol for 4 equiv of n-BuLi LiDMAE or 2.66 mmol for 3 equiv) in hexane or toluene (5 mL) was added dropwise. After 1 h at appropriate temperature, the red brown reaction mixture was cooled to −78 °C and treated with a solution of appropriate electrophile in THF (20 mL). After 30 min at −78 °C, the temperature was allowed to raise the room temperature. The hydrolysis was then performed at 0 °C with H_2O. The aqueous layer was then extracted twice with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. The crude products were then purified by column chromatography with hexane/AcOEt mixture as eluent.

4.3.1. Compound 1b. (522 mg, 85%) was obtained as a yellow viscous oil after column chromatography (90% hexanes/AcOEt) as eluents. δ_H 2.59 (s, 3H), 3.80 (s, 3H), 6.9 (d, J=8.2 Hz, 1H), 7.0 (d, J=3.0 Hz, 1H), 7.1 (d, J=3.0 Hz, 1H), 7.33 (d, J=7.2 Hz, 1H), 7.44 (d, J=7.9 Hz, 1H), 7.6 (d, J=7.9 Hz, 1H), 7.94 (m, 1H). δ_C 13.4, 55.8, 111.7, 119.7, 120.7, 121.2, 128.9, 130.2, 131.4, 135.9, 155.4, 157.4, 158.9. m/z (EI) 231 (M, 100), 230 (M−1, 42), 200 (M−31, 48), 198 (M−33, 92), 180 (M−51, 28), 170 (M−61, 40), 154 (M−77, 42), 140 (M−91, 28), 115 (M−116, 31%). Anal. Calcd for $C_{13}H_{13}NOS$: C%, 67.50; H%, 5.66; N%, 6.06. Found C%, 67.35; H%, 5.53; N%, 5.84.

4.3.2. Compound 1d.[4b] (396 mg, 80%, d%>75) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.83 (s, 3H), 6.99 (d, J=8.3 Hz, 1H), 7.07 (dt, J=7.3, 0.7 Hz, 1H), 7.17 (d, J=7.5 Hz, 2H), 7.36 (dt, J=7.8, 2.1 Hz, 1H), 7.68 (d, J=7.8 Hz, 1H), 7.81 (dd, J=7.8, 1.0 Hz, 1H). δ_C 55.9, 111.7, 125.5, 125.7, 128.6, 128.9, [129.2, 129.4, 129.6], 131.05, 135.9, 149.8, 156.3, 157.3. m/z (EI) 186 (M, 73), 185 (M−1, 100), 156 (M−30, 66), 155 (M−31, 100), 142 (M−44, 12), 128 (M−58, 17), 116 (M−70, 13), 81 (M−105, 58),63 (M−123, 21%).

4.3.3. Compound 1e. (478 mg, 82%) was obtained as a pale yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.88 (s, 3H), 7.01 (d, J=8.4 Hz, 1H), 7.10 (dt, J=7.3, 1.0 Hz, 1H), 7.24 (d, J=7.8 Hz, 1H), 7.40 (dt, J=8.0, 2.1 Hz, 1H), 7.66 (d, J=7.8 Hz, 1H), 7.84 (dd, J=7.6, 0.8 Hz, 1H), 7.88 (dd, J=7.8, 1.8 Hz, 1H). δ_C 55.9, 111.7, 121.5, 122.4, 123.9, 127.7, 130.9, 131.7, 138.7, 151.1, 156.8, 157.4. MS (EI) m/z: 219 (M, 72), 218 (M−1, 100), 189 (M−30, 28), 154 (M−65, 36), 140 (M−79, 13), 127 (M−92, 15), 114 (M−105, 32%).

4.3.4. Compound 1f. (491 mg, 50%) was obtained as a white solid after recrystallisation in MeOH. Mp 166–168 °C. δ_H 3.83 (s, 3H), 6.99 (m, 3H), 7.3–7.5 (m, 11H), 7.55 (dd, J=7.8, 2.0 Hz, 1H), 7.77 (dd, J=5.2, 1.8 Hz, 2H). δ_C 55.7, 111.5, 121.2, 123.8, 125.9, 128.8, 128.6, 129.0, 130.1, 131.8, 134.2, 136.6. δ_P −3.30. Anal. Calcd for $C_{24}H_{20}NOP$: C%, 78.04; H%, 5.46; N%, 3.79. Found C%, 78.15; H%, 5.43; N%, 3.80.

4.3.5. Compound 2a. (522 mg, 85%) was obtained as a yellow oil after column chromatography using (90% hexanes/AcOEt). δ_H 2.66 (s, 3H), 3.88 (s, 3H), 6.9 (dd, J=6.5, 2.4 Hz, 1H), 7.1 (d, J=7.5 Hz, 1H), 7.37 (d, J=7.9 Hz, 1H), 7.42 (d, J=4.0 Hz, 1H), 7.54 (d, J=7.9 Hz, 1H), 7.62–7.67 (m, 2H). δ_C 13.5, 55.6, 112.7, 114.9, 115.9, 119.5, 130.0, 136.7, 140.9, 159.6, 160.7. m/z (EI) 231 (M, 100), 230 (M−1, 62), 185 (M−46, 13), 170 (M−61, 8), 154 (M−77, 9), 142 (M−89, 20), 140 (M−91, 9), 115 (M−116, 10%).

4.3.6. Compound 2b. (371 mg, 75%, d%>98) was obtained as a yellow viscous oil after column chromatography (90% hexanes/AcOEt). δ_H 3.89 (s, 3H), 6.96 (d, J=9.0 Hz, 1H), 7.27 (d, J=8.8 Hz, 1H), 7.38 (d, J=8.0 Hz,

1H), 7.52 (d, J=1.4 Hz, 1H), 7.50–7.68 (m, 3H). δ_C 55.6, 117.3, 120.9, [122.5, 122.8, 123.1], 126.7, 130.7, 133.3, 134.9, 150.1, 158.4, 162.8. *m/z* (EI) 186 (M, 100), 171 (M−15, 35), 143 (M−43, 57), 116 (M−70, 15), 90 (M−96, 11), 63 (M−123, 17%).

4.3.7. Compound 2c. (519 mg, 74%) was obtained as a light brown oil after column chromatography using (90% hexanes/AcOEt). δ_H 3.89 (s, 3H), 6.96 (d, J=9.0 Hz, 1H), 7.39 (dd, J=7.6, 3.1 Hz, 2H), 7.52 (s, 1H), 7.52–7.57 (m, 2H), 7.65 (d, J=7.2 Hz, 1H). δ_C 55.7, 112.6, 115.8, 119.4, 119.6, 126.7, 130.0, 139.1, 142.3, 160.4. *m/z* (EI) 264 (M, 100), 233 (M−31, 32), 184 (M−80, 7), 169 (M−95, 24), 154 (M−110, 73), 140 (M−124, 67), 127 (M−137, 34), 114 (M−150, 40), 92 (M−172, 32), 77 (M−187, 32), 63 (M−201, 57%), 51 (M−213, 30%). Anal. Calcd for $C_{12}H_{10}BrNO$: C%, 54.57; H%, 3.82; N%, 5.30. Found C%, 54.85; H%, 3.76; N%, 5.06.

4.3.8. Compound 2d. (600 mg, 78%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.84 (s, 3H), 6.97 (dd, J=5.6, 2.7 Hz, 1H), 7.38 (d, J=7.9 Hz, 1H), 7.51 (d, J=7.6 Hz, 2H), 7.57–7.66 (m, 3H), 7.96 (d, J=5.5 Hz, 2H), 8.02 (d, J=4.1 Hz, 1H), 8.22 (dd, J=7.0, 1.7 Hz, 2H). δ_C 55.5, 112.4, 115.7, 122.8, 123.2, 128.2, 130.1, 131.6, 133.0, 136.7, 138.1, 154.8, 160.4. *m/z* (EI) 288 (M−1, 100), 260 (M−29, 80), 230 (M−59, 14), 105 (M−184, 25), 77 (M−112, 28%). Anal. Calcd for $C_{19}H_{15}NO_2$: C%, 78.87; H%, 5.23; N%, 4.84. Found C%, 78.75; H%, 5.35; N%, 4.96.

4.3.9. Compound 3a. (467 mg, 76%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.66 (s, 3H), 3.87 (s, 3H), 6.99 (d, J=8.6 Hz, 2H), 7.07 (d, J=7.9 Hz, 1H), 7.36 (d, J=8.6 Hz, 1H), 7.51 (d, J=7.5 Hz, 1H), 8.01 (d, J=9 Hz, 2H). δ_C 13.3, 55.5, 114.2, 114.9, 119.4, 128.2, 131.8, 136.6, 156.4, 159.2, 160.7. *m/z* (EI) 231 (M, 100), 230 (M−1, 62), 185 (M−46, 17), 170 (M−61, 34), 140 (M−91, 11), 115 (M−116, 12%).

4.3.10. Compound 3b. (396 mg, 80%, d%>98) was obtained as a yellow oil after column chromatography (80% hexanes/AcOEt). δ_H 3.85 (s, 3H), 7.01 (d, J=9.0 Hz, 2H), 7.16 (d, J=6.8 Hz, 1H), 7.65–7.70 (m, 2H), 7.97 (d, J=9.0 Hz, 2H). δ_C 55.7, 114.5, 120.2, [121.8, 122.2, 122.6], 128.5, 137, 149.9. *m/z* (EI) 187 (M+1, 36), 186 (M, 100), 171 (M−15, 35), 143 (M−43, 57), 116 (M−70, 15), 90 (M−96, 11), 63 (M−123, 17%).

4.3.11. Compound 3c. (553 mg, 90%) was obtained as a white solid after column chromatography (90% hexanes/AcOEt). Mp 77–79 °C. δ_H 3.83 (s, 3H), 6.95 (d, J=8.9 Hz, 2H), 7.14 (dd, J=7.1, 1.0 Hz, 1H), 7.53 (dd, J=8.9, 1.0 Hz, 1H), 7.59 (d, J=7.5 Hz), 7.93 (d, J=9.0 Hz, 2H). δ_C 55.5, 114.4, 117.9, 121.8, 128.6, 139.3, 142.9, 151.4, 157.9, 161.1. *m/z* (EI) 221 (M+2, 33), 219 (M, 100), 204 (M−15, 17), 176 (M−43, 25), 141 (M−78, 18%). Anal. Calcd for $C_{12}H_{10}ClNO$: C%, 65.61; H%, 4.59; N%, 6.38. Found C%, 65.50; H%, 4.60; N%, 6.26.

4.3.12. Compound 3d. (580 mg, 75%) was obtained as a yellow viscous oil after column chromatography (90% hexanes/AcOEt). δ_H 3.89 (s, 3H), 4.69 (d, J=5.0 Hz, 1H), 5.82 (d, J=3.5 Hz, 1H), 6.96 (d, J=7.5 Hz, 1H), 7.02 (d, J=8.9 Hz, 2H), 7.28–7.37 (m, 3H), 7.41 (d, J=7 Hz, 2H), 7.57 (d, J=7.6 Hz, 1H), 7.63 (d, J=7.8 Hz, 1H), 8.02 (d, J=7.0 Hz, 2H). δ_C 55.5, 74.9, 114.3, 118.4, 119.2, 127.1, 127.4, 128.0, 128.4, 128.7, 137.8, 143.5, 155.2, 160.4, 160.9. *m/z* (EI) 291 (M, 100), 214 (M−77, 72), 185 (M−106, 37), 170 (M−121, 24%).

4.3.13. Compound 4a. (346 mg, 70%, d%>98) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.84 (s, 3H), 7.03 (d, J=8.3 Hz, 1H), 7.08 (dt, J=7.6, 0.8 Hz, 1H), 7.34 (dd, J=7.8, 1.5 Hz, 2H), 7.39 (dt, J=7.8, 1.8 Hz, 1H), 7.88 (dd, J=8.0, 2.3 Hz, 1H), 8.79 (d, J=1.7 Hz, 1H). δ_C 55.9, 111.6, 121.4, 123.1, [127.4, 127.7, 128.0], 129.9, 131.0, 134.6, 137.2, 150.6, 157.0. *m/z* (EI) 186 (M, 100), 171 (M−15, 51), 116 (M−70, 30%).

4.3.14. Compound 4b. (516 mg, 84%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.60 (s, 3H), 3.81 (s, 3H), 6.98 (dd, J=8.0, 0.7 Hz, 1H), 7.0 (td, J=8.0, 1.1 Hz, 1H), 7.21 (dd, J=8.0, 1.1 Hz, 1H), 7.30 (dd, J=7.0, 1.9 Hz, 1H), 7.34 (dt, J=7.0, 1.9 Hz, 1H), 7.69 (dd, J=6.1, 2.3 Hz, 1H), 8.61 (d, J=2.3 Hz, 1H). δ_C 13.8, 55.9, 111.7, 121.0, 121.5, 127.2, 129.6, 130.7, 137.3, 150.1, 158.5. *m/z* (EI) 230 (M−1, 100), 198 (M−33, 16), 185 (M−46, 13), 169 (M−62, 8), 115 (M−116, 9%).

4.3.15. Compound 4c. (478 mg, 82%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 3.80 (s, 3H), 7.01–7.07 (m, 2H), 7.25–7.41 (m, 3H), 7.82 (dd, J=8.3, 2.4 Hz, 1H), 8.51 (d, J=2.4 Hz, 1H). δ_C 55.6, 111.5, 121.3, 123.6, 125.7, 130.1, 130.5, 133.3, 139.8, 149.7, 150.1, 156.6. *m/z* (EI) 221 (M+2, 33), 219 (M, 100), 204 (M−15, 25), 169 (M−50, 20), 168 (M−51, 29), 140 (M−79, 27%).

4.3.16. Compound 4d. (535 mg, 50%) was obtained as a white solid after column chromatography using 80:20 hexanes–AcOEt as eluents. Mp 150–151 °C. δ_H 3.81 (s, 3H), 6.97–7.07 (m, 2H), 7.12 (d, J=8.3 Hz, 1H), 7.30–7.50 (m, 12H), 7.74 (dd, J=6.3, 1.7 Hz, 1H), 8.9 (d, J=2.1 Hz, 1H). δ_C 55.5, 111.5, 121.3, 126.9, 127.5, 128.7, 128.9, 129.3, 129.9, 130.9, 134.7, 136.59, 136,65, 151.12, 161.7, 161.9. δ_P −3.69. Anal. Calcd for $C_{24}H_{20}NOP$: C%, 78.04; H%, 5.46; N%, 3.79. Found C%, 78.16; H%, 5.44; N%, 3.83.

4.3.17. Compound 5a. (430 mg, 70%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.60 (s, 3H), 3.85 (s, 3H), 6.91 (dd, J=8.2, 2.4 Hz, 1H), 7.06 (s, 1H), 7.12 (d, J=7.6 Hz, 1H), 7.23 (d, J=8.2 Hz, 1H), 7.37 (d, J=7.8 Hz, 1H), 7.68 (dd, J=8.3, 2.4 Hz, 1H), 8.58 (d, J=4.8 Hz, 1H), 8.67 (s, 1H). δ_C 13.5, 55.4, 112.7, 113.2, 119.3, 121.4, 130.3, 132.2, 134.5, 139.2, 147.8, 159.1, 160.2. *m/z* (EI) 231 (M, 100), 198 (M−33, 27), 185 (M−46, 19), 115 (M−116, 21), 63 (M−168, 12%). Anal. Calcd for $C_{13}H_{13}NOS$: C%, 67.50; H%, 5.66; N%, 6.06. Found C%, 67.34; H%, 5.68; N%, 6.09.

4.3.18. Compound 6a. (460 mg, 75%) was obtained as a

yellow oil after column chromatography (90% hexanes/AcOEt). Spectrocopic data consistent with that reported in the literature.[8a,16]

4.3.19. Compound 7a. (346 mg, 93%, d%>95) was obtained as a yellow oil after column chromatography (80% hexanes/AcOEt). δ_H 3.83 (s, 3H), 7.04 (dd, J=8.3, 5.5 Hz, 2H), 7.26–7.43 (m, 3H), 7.47 (s, 1H), 8.62 (d, J=3 Hz, 1H). δ_C 55.7, 111.6, 121.2, 124.4, 127.8, [129.7, 130.2, 130.7], 146.5, 149.7, 156.7. *m/z* (EI) 186 (M, 100), 171 (M−15, 30), 157 (M−29, 15), 116 (M−70, 38), 63 (M−123, 17%).

4.3.20. Compound 7b. (323 mg, 70%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.57 (s, 3H), 3.79 (s, 3H), 6.94–7.05 (m, 2H), 7.14 (dd, J=5.5, 1.7 Hz, 1H), 7.26–7.39 (m, 3H), 8.43 (dd, J=5.5, 0.7 Hz, 1H). δ_C 12.8, 55.7, 111.6, 113.1, 121.5, 124.5, 127.8, 130.3, 130.6, 146.4, 149.7, 156.7, 170.2. *m/z* (EI) 231 (M, 100), 198 (M−33, 25), 185 (M−46, 31), 115 (M−116, 33).

4.3.21. Compound 7c. (404 mg, 65%) was obtained as an orange oil after column chromatography (80% hexanes/AcOEt). δ_H 3.84 (s, 3H), 6.98–7.09 (m, 2H), 7.01 (dd, J=7.5, 1.7 Hz, 2H), 7.44 (dd, J=3.8, 1.4 Hz, 1H), 7.89 (s, 1H), 8.34 (d, J=5.2 Hz, 1H). δ_C 55.8, 111.7, 114.3, 121.3, 123.7, 130.5, 130.9, 135.3, 150.3. *m/z* (EI) 311 (M, 75), 184 (M−127, 74), 169 (M−142, 100), 140 (M−171, 16). Anal. Calcd for $C_{12}H_{10}INO$: C%, 46.33; H%, 3.24; N%, 4.50. Found C%, 46.52; H%, 3.29; N%, 4.40.

4.3.22. Compound 7d. (349 mg, 68%) was obtained as an orange oil after column chromatography (80% hexanes/AcOEt). δ_H 0.82 (t, 3H, J=7.3 Hz, 1H), 1.56 (s, 3H), 1.81–1.92 (m, 2H), 5.03 (s, 1H), 3.85 (s, 3H), 7.03 (d, J=8.3 Hz, 1H), 7.09 (d, J=7.6 Hz, 1H), 7.36–7.44 (m, 3H), 7.49 (s, 1H), 8.54 (d, J=5 Hz, 1H). δ_C 8.53, 29.30, 36.49, 55.95, 74.36, 111.85, 120.27, 121.47, 122.97, 130.59, 130.92, 147.17, 147.70, 156.9, 160.87, 164.89. *m/z* (EI) 257 (M, 2), 242 (M−15, 15), 228 (M−29, 100), 212 (M−45, 15), 185 (M−72, 10), 170 (M−87, 10), 115 (M−142, 9).

4.3.23. Compound 8a. (370 mg, 80%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.60 (s, 3H), 3.84 (s, 3H), 6.95 (dd, J=8.2, 2.5 Hz, 1H), 7.10 (d, J=1.7 Hz, 1H), 7.16 (dd, J=5.3, 1.8 Hz, 2H), 7.32–7.35 (m, 2H), 8.46 (d, J=5.3 Hz, 1H). δ_C 13.7, 55.7, 113.2, 114.8, 118.0, 119.6, 119.8, 130.5, 139.9, 148.6, 150.1, 160.5, 160.9. *m/z* (EI) 231 (M, 100), 185 (M−46, 37), 115 (M−116, 18%). Anal. Calcd for $C_{13}H_{13}NOS$: C%, 67.50; H%, 5.66; N%, 6.06. Found C%, 67.39; H%, 5.59; N%, 6.07.

4.3.24. Compound 9a.[15] (324 mg, 70%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.60 (s, 3H), 3.84 (s, 3H), 6.97 (d, J=8.0 Hz, 2H), 7.15 (d, J=5.3 Hz, 1H), 7.35 (s, 1H), 7.55 (d, J=7.7 Hz, 2H), 8.43 (d, J=5.3 Hz, 1H). δ_C 13.8, 55.8, 114.9, 117.5, 118.9, 128.6, 130.6, 148.2, 150.0, 160.7, 161.0. *m/z* (EI) 231 (M, 100), 230 (M−1, 63), 185 (M−46, 42), 170 (M−61, 14), 115 (M−116, 22%).

4.3.25. Compound 10a. (516 mg, 70%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 2.51 (s, 3H), 2.62 (s, 3H), 3.75 (s, 3H), 6.93 (d, J=7.9 Hz, 1H), 6.97 (d, J=8.6 Hz, 1H), 7.01 (d, J=7.4 Hz, 1H), 7.19 (d, J=7.8 Hz, 2H), 7.37 (dt, J=8.2, 1.6 Hz, 1H). δ_C 13.7, 13.9, 56.0, 89.3, 111.7, 116.5, 120.9, 126.9, 128.3, 130.2, 131.7, 137.5, 154.4, 157.7, 158.4. *m/z* (EI) 277 (M, 80), 246 (M−31, 100), 230 (M−47, 75), 212 (M−65, 32).

4.3.26. Compound 10b. (484 mg, 72%) was obtained as a yellow viscous oil after column chromatography using 90:10 hexanes–AcOEt as eluents. δ_H 3.79 (s, 3H), 6.99 (d, J=8.4 Hz, 1H), 7.03 (t, J=7.5 Hz, 1H), 7.18 (dd, J=7.5, 1.7 Hz, 1H), 7.31 (d, J=7.8 Hz, 1H), 7.42 (dd, J=8.4, 1.8 Hz, 3H), 7.59 (d, J=7.9 Hz, 1H). δ_C 55.9, 111.5, 120.9, 123.0, 125.7, 130.8, 131.0, 133.3, 142.8, 149.2, 150.1, 156.9. *m/z* (EI) 255 (M+2, 40), 253 (M, 63), 218 (M−35, 100), 203 (M−50, 72), 140 (M−113, 19%).

4.3.27. Compound 10c. (503 mg, 65%) was obtained as a yellow oil after column chromatography (90% hexanes/AcOEt). δ_H 0.30 (s, 9H), 3.73 (s, 3H), 6.91–6.99 (m, 2H), 7.06 (dt, J=7.5, 2.0 Hz, 1H), 7.21 (d, J=8.2 Hz, 1H), 7.35–7.42 (m, 2H). δ_C −0.69, 55.3, 110.6, 120.2, 129.8, 131.5, 139.2, 150.2, 157.1. *m/z* (EI) 291 (M, 20), 276 (M−15, 61), 261 (M−30, 55), 256 (M−35, 90), 246 (M−45,100), 73 (M−218, 71%).

4.3.28. Preparation of 11 by lithiation of 4c with LTMP. To a solution of TMP (0.58 mL, 3.4 mmol) in THF (5 mL) cooled at −30 °C was added dropwise *n*-BuLi (2 mL, 3.2 mmol). The medium was then allowed to warm at 0 °C for 30 min and cooled at −20 °C. A solution of **4c** (219 mg, 1 mmol) in THF (2 mL) was then added drowpise. The red solution was stirred for 1 h at the same temperature and cooled at −78 °C. A solution of C_2Cl_6 (830 mg, 3.5 mmol) in THF (10 mL) was then added dropwise. The reaction medium was then allowed to warm to 0 °C and hydrolysed with H_2O (5 mL). The aqueous layer was then extracted twice with diethyl ether, dried over $MgSO_4$, and evaporated under vacuum. Column chromatography (90% hexanes/AcOEt) yielded **11** (538 mg, 80%) as a white solid. Mp 81 °C. δ_H 3.84 (s, 3H), 7.00 (d, J=8.3 Hz, 1H), 7.06 (t, J=7.4 Hz, 1H), 7.29 (dd, J=7.6, 1.6 Hz, 1H), 7.40 (dt, J=8.1, 1.6 Hz, 1H), 7.97 (d, J=2.1 Hz, 1H), 8.43 (d, J=2.1 Hz, 1H). δ_C 55.9, 111.7, 121.6, 124.5, 130.7, 130.8, 134.9, 139.8, 140.2, 147.9, 156.8, 160.1. *m/z* (EI) 255 (M+2, 66), 253 (M, 100), 238 (M−15, 13), 203 (M−50, 53), 174 (M−79, 20), 140 (M−113, 16), 63 (M−190, 15%). Anal. Calcd for $C_{12}H_9Cl_2NO$: C%, 56.72; H%, 3.57; N%, 5.51. Found C%, 56.83; H%, 3.47; N%, 5.43.

4.4. Procedure for demethylation anisylpyridines

To a solution of appropriate anisylpyridine (1 mmol) in dry dichloromethane at −78 °C was added dropwise a solution of boron tribromide (5 mmol, 5 mL of a 1 M solution in dichloromethane). After addition the mixture was stirred overnight at room temperature, then treated with water and extracted with ethyl acetate. The organic layer was then dried over anhydrous $MgSO_4$, and evaporated under vacuum.

4.4.1. Compound 12. (165 mg, 80%) was obtained as a white solid after recrystallisation in dichloromethane. Mp 171–173 °C. δ_H 7.01–7.09 (m, 2H), 7.34 (t, $J=7.4$ Hz, 1H), 7.43 (d, $J=7.4$ Hz, 1H), 7.64 (d, $J=8.3$ Hz, 1H), 8.12 (d, $J=8.3$ Hz, 1H), 8.67 (s, 1H), 9.99 (s, 1H). δ_C 114.6, 118.2, 121.3, 122.3, 128.2, 128.6, 131.9, 138.4, 146.6, 148.0, 152.9. *m/z* (EI) 207 (M+2, 32), 205 (M, 100), 170 (M−35, 34), 115 (M−90, 22%). Anal. Calcd for $C_{11}H_8ClNO$: C%, 64.25; H%, 3.92; N%, 6.81. Found C%, 64.43; H%, 3.83; N%, 6.77.

4.4.2. Compound 13. (200 mg, 84%) was obtained as a white solid after recrystallisation in dichloromethane. Mp 162–164 °C. δ_H 7.02–7.11 (m, 2H), 7.37 (t, $J=7.6$ Hz, 1H), 7.50 (d, $J=7.5$ Hz, 1H), 8.39 (s, 1H), 8.68 (s, 1H), 10.14 (s, 1H). δ_C 114.7, 118.3, 119.9, 126.9, 128.8, 133.5, 137.8, 143.7, 146.2, 149.5, 153.1. *m/z* (EI) 241 (M+2, 58), 239 (M, 100), 204 (M−35, 19), 140 (M−99, 14). Anal. Calcd for $C_{11}H_8Cl_2NO$: C%, 55.03; H%, 2.94; N%, 5.83. Found C%, 55.21; H%, 2.83; N%, 5.87.

4.4.3. Compound 15. The title compound was prepared as above described in 90% yield (GC) and dissolved as such in acetonitrile (10 mL), potassium carbonate was then added (410 mg, 3 mmol) and the mixture was refluxed for 5 h. After removal of solvent, the residue was treated with water and extracted with chloroform. The organic layer was dried over anhydrous $MgSO_4$, and evaporated under vacuum. Column chromatography (90% hexanes–AcOEt) yielded **15** (142 mg, 70%) as a white solid. Mp 155–156 °C [Lit.[17] 150–157 °C]. δ_H 7.40–7.45 (m, 2H), 7.54 (dt, $J=7.2$, 1.4 Hz, 1H), 7.64 (d, $J=7.2$ Hz, 1H), 7.92 (dd, $J=8.6$, 2.5 Hz, 1H), 8.20 (d, $J=7.9$ Hz, 1H). δ_C 111.48, 112.7, 119.8, 120.7, 122.2, 124.2, 128.2, 128.9, 131.9. *m/z* (EI) 205 (M+2, 34), 203 (M, 100), 168 (M−35, 21%), 140 (M−63, 24%). Anal. Calcd for $C_{11}H_6ClNO$: C%, 64.88; H%, 2.97; N%, 6.88. Found C%, 64.69; H%, 3.01; N%, 6.77.

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