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Deprotonative metalation of aromatic compounds using mixed lithium–iron combinations

Elisabeth Nagaradja, Floris Chevallier, Thierry Roisnel, Viatcheslav Jouikov *, Florence Mongin *

Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS, Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes, France

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ABSTRACT

The deprotonation of 2-methoxypyridine was attempted using putative $(TMP)_3FeLi$ prepared from different iron sources. Using iodine to intercept the metalated 2-methoxypyridine, the best result was obtained from $FeBr_2$ (1 equiv) using THF at room temperature; nevertheless, in addition to the expected iodide, the corresponding 2,2′-dimer was obtained (86% total yield). The origin of the competitive formation of the 2,2′-dimer was not identified but mechanisms were suggested to explain its formation. It was observed that the nature of the electrophile employed to trap the 3-metalated 2-methoxypyridine has a strong impact on this dimer formation, the latter being favored using iodine (35% yield), but also benzophenone (28%), benzoyl chloride (22%), methyl iodide (27%), allyl bromide (15%), benzyl bromide (41%), and tetramethylthiuram disulphide (36%); for this reason, the yields of the expected derivatives were only 51, 15, 62, 0, <5, 18, and 0%, respectively. In contrast, using aldehydes readily led to the expected pyridine alcohols without dimerization (59% yield using 3,4,5-trimethoxybenzaldehyde and 66% yield using pivalaldehyde). 2,6-Dimethoxypyridine (in 68% yield), anisole (47%), 2,4-dimethoxypyrimidine (50% at C5 and 3% at C6), 2-fluoropyridine (64%), and thiophene (49%) were similarly converted into the corresponding alcohols after subsequent trapping with pivalaldehyde. Using iodine to trap the 2-metalated anisole did not lead to dimer formation, and 2-iodoanisole was isolated in 71% yield.

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1. Introduction

The deprotonative metalation using lithium bases has been widely used as a powerful method for the regioselective functionalization of aromatic compounds.[1–5] The use of bimetal combinations in order to get more efficient and/or more chemoselective bases is a fascinating field. Pioneer studies carried out in the groups of Schlosser[6] and Lochmann[7] with LIC-KOR (1:1 BuLi/^{t}BuOK), and by Caubère, Gros, and Fort[8,9] in the pyridine series with BuLi/LiDMAE (DMAE=2-dimethylaminoethoxide) and Me_3SiCH_2Li/LiDMAE merged alkyllithiums and alkali-metal alkoxides. More recently, other $(R)_n(R')_{n'}MLi$-type bases, with M being softer than an alkali-metal (M=Mg, Al, Cr, Mn, Cu, Zn, Cd…), have been described by different groups for their ability to deprotonate aromatic compounds.[10–14] From 2009, Klett, Mulvey and co-workers have showed that it is possible to design sodium–iron(II) bases, and extended the ability to deprotonate to group 8 ate compounds.[15] The same year, Knochel and co-workers showed that ferration (Fe–H exchange) can be achieved using salt-solubilized $(TMP)_2Fe\cdot 2MgCl_2\cdot 4LiCl$ (TMP=2,2,6,6-tetramethylpiperidino).[16,17]

We recently accomplished the room temperature deprotometalation of a large range of substrates including sensitive heterocycles and functionalized benzenes using newly developed lithium–zinc,[18–23] lithium–cadmium,[22,24–31] lithium–copper(I),[32–34] and lithium–cobalt[35] combinations, in situ prepared from $MCl_2\cdot TMEDA$ (M=Zn, Cd or Cu, TMEDA=*N*,*N*,*N*′,*N*′-tetramethylethylenediamine), CuCl, or $CoBr_2$ on the one hand, and lithium reagents (alkyllithiums or lithium amides) on the other hand. The studies performed using lithium–zinc and lithium–cadmium combinations have notably shown that the more efficient bases were obtained by mixing the metal salt with 3 equiv of LiTMP.[21,30] A main drawback of the methods developed being the lack of reactivity of such generated arylmetals in direct electrophilic trapping, we turned to other bimetallic combinations in order to identify candidates able to perform efficient deprotonations, but also to allow direct (and if possible new) functionalizations. We recently documented the use of lithium–cobalt combinations for this purpose,[35] and here describe our efforts to deproto-metalate aromatic compounds using similar lithium–iron combinations.

* Corresponding authors. Fax: +33 2 2323 6955; e-mail addresses: viatcheslav.jouikov@univ-rennes1.fr (V. Jouikov), florence.mongin@univ-rennes1.fr (F. Mongin).

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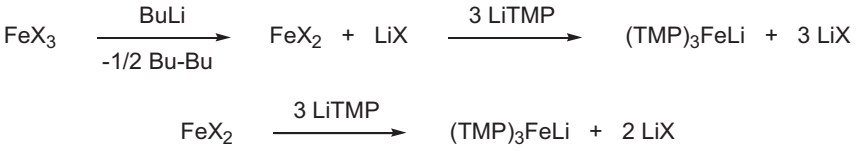
2. Results and discussion

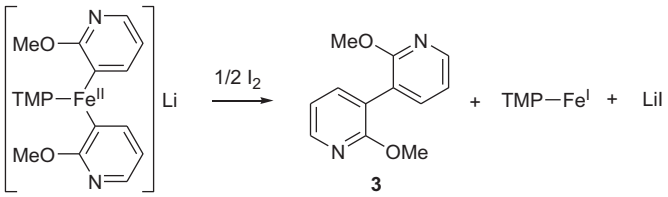
The synthesis of organoiron(II) ate compounds is well-documented in the literature. They can be obtained from $FeCl_2$,[36–40] but alternative ways employ iron(III) halides in the presence of an excess of an organolithium.[36,37] The access to mixed lithium–iron(II) amides is far less documented, but seems possible similarly.[41,42] The in situ generation of putative[43,44] $(TMP)_3FeLi$ in tetrahydrofuran (THF) was considered using different iron halides (Scheme 1). Iron(III) halides were successively treated with BuLi (1 equiv), in order to achieve their reduction and LiTMP (3 equiv) whereas iron(II) halides were only combined with 3 equiv of LiTMP.



Scheme 1. Generation of putative $(TMP)_3FeLi$ using different iron halides.

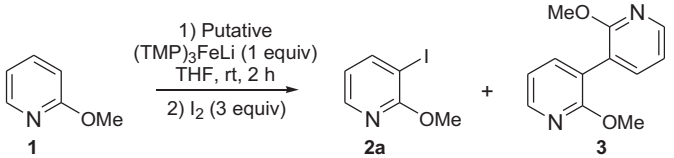
We chose 2-methoxypyridine (**1**) as substrate and iodine as electrophile to evaluate the ability to deprotonate of putative $(TMP)_3FeLi$, prepared using the different iron sources (Table 1). This substrate had previously been metalated either at its 3-position using *t*-BuLi,[45–47] PhLi in the presence of a catalytic amount of diisopropylamine,[45–47] LiDA (DA=diisopropylamino),[45–47] LiTMP,[45–47] a mixed lithium–aluminum base,[13] and a mixed lithium–cobalt base,[35] or at its 6-position using BuLi/LiDMAE.[8] When 2-methoxypyridine (**1**) was treated by the lithium–iron base (prepared by using the methods above) for 2 h at room temperature and the reaction mixtures then quenched by iodine, mixtures of 3-iodo-2-methoxypyridine (**2a**) and 2,2′-dimethoxy-3,3′-bipyridine (**3**) were obtained in all cases but in different yields. Except when FeF_2 was employed as iron source to prepare the base (entry 6), the conversions observed were good, even when 1 equiv of base was used; these results show that changing the lithium salt formed at the same time as the base (LiCl, LiBr, or even LiI) has a low effect on the deprotonation efficiency. The use of 0.5 and 2 equiv of base led to lower conversion and some degradation, respectively, and the yields were found lower. There is no direct link between the **2a**:**3** ratio and the iron source, and it was moreover observed for a given iron source that this ratio can be modified (±10–20%) by varying the iodine addition time.

In order to identify how the dimer **3** is formed, different experiments were carried out. First, using water instead of iodine to trap the metalated 2-methoxypyridine (iron source: $FeCl_3$) resulted in a very low 4% yield of **3**, showing that the electrophile employed has an impact on the dimer **3** formation. Iodine could competitively behave as an oxidative agent in the reaction (Scheme 2); indeed, when nitrobenzene and chloranil were tested instead of iodine (iron source: $FeBr_2$), the dimer **3** was isolated in 14 and 17% yield, respectively.



Scheme 2. I_2-mediated pathway to explain the formation of **3**.

Table 1
Metalation of 2-methoxypyridine using putative $(TMP)_3FeLi$



Entry	Iron halide	Yield of **2a**[a] (%)	Yield of **3**[a] (%)	Total yield[b] (%)
1	$FeCl_3$	35 (53)[c]	42 (32)[c]	77 (85)[c]
2	$FeBr_3$	28	58	86
3	$FeCl_2$	28	52	80
4	$FeBr_2$	51 (51)[d]	35 (40)[d]	86 (91)[d]
5	FeI_2	21	41	62
6	FeF_2	12	15	27[e]

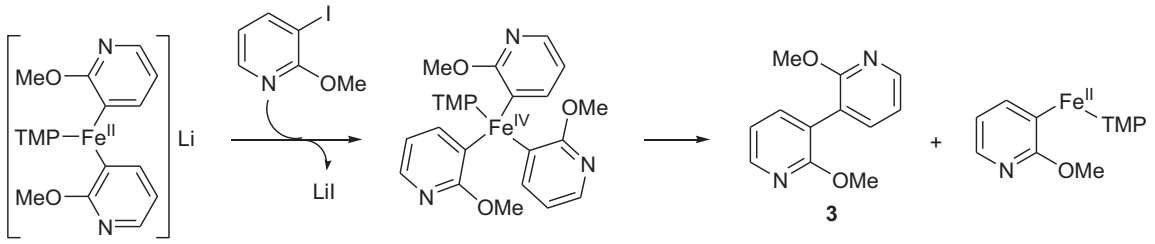
[a] After purification by column chromatography.
[b] The rest is either degradation or starting material.
[c] Using 2 equiv of base.
[d] By performing the reaction in the presence of TMEDA (4 equiv).
[e] Degradation was observed.

3-Iodo-2-methoxypyridine (**2a**), which is formed in the course of iodine addition, can also have an impact on the dimer **3** formation. Indeed, when used instead of iodine (iron source: $FeBr_2$), a 72% yield was obtained for the dimer **3**. To rationalize this result, different mechanisms can be advanced, notably one[48] based on a Fe(II)/Fe(IV) couple with two-electron transfer from iron followed by reductive elimination (Scheme 3). Nevertheless, for steric reasons, the mechanisms[48] depicted in Scheme 4 involving a Fe(II)/Fe(III) couple with one-electron transfer from iron, followed by dimerization from the Fe(III) species, appears as a more likely alternative to explain the formation of **3**.

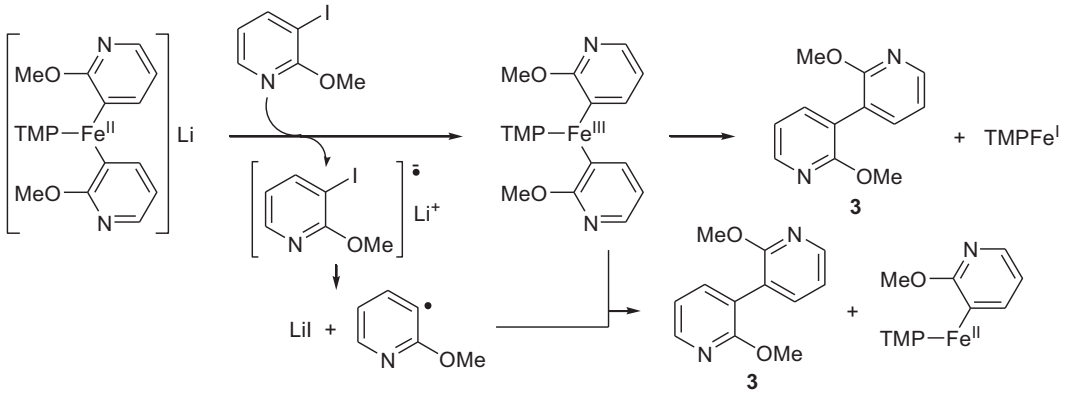
Finally, an alternative explanation could be the presence of a metal impurity in the iron source for which the corresponding diaryl metal ate compounds is prone to dimerization.

In order to check if the reduction of $FeCl_3$ to $FeCl_2$ is quantitative using 1 equiv of an organolithium (BuLi or MeLi), the reaction was monitored using electron paramagnetic resonance (EPR). To this purpose, the EPR spectra of THF solutions prepared from $FeCl_3$ and MeLi or BuLi were collected, and were compared with spectra recorded from THF solutions of $FeCl_2$ and $FeCl_3$. The spectrum of $FeCl_2$ treated by LiTMP (3 equiv) was also recorded, and only showed the signal characteristic of 2,2,6,6-tetramethylpiperidinooxy (TEMPO) already observed in the course of the preparation of LiTMP[32] (Fig. 1).

The standard redox potential of methyl radicals, determined electrochemically in DMF and converted to the aqueous scale, is $E^o(Me^{\bullet}/Me^-)=-1.19$ V vs saturated calomel electrode (SCE). Those for parent *n*-Pr$^{\bullet}$ and *s*-Bu$^{\bullet}$ radicals are −1.63 and −1.72 V vs SCE, respectively.[49] Values for *t*-Bu$^{\bullet}$ (−1.48), *s*-Bu$^{\bullet}$ (−1.38), and *n*-Bu$^{\bullet}$ ($\leq$−1.30 versus SCE) have also been estimated.[50] For the oxidant,



Scheme 3. **2a**-Mediated pathway based on a Fe(II)/Fe(IV) couple to explain the formation of **3**.



Scheme 4. **2a**-Mediated pathway based on a Fe(II)/Fe(III) couple to explain the formation of **3**.

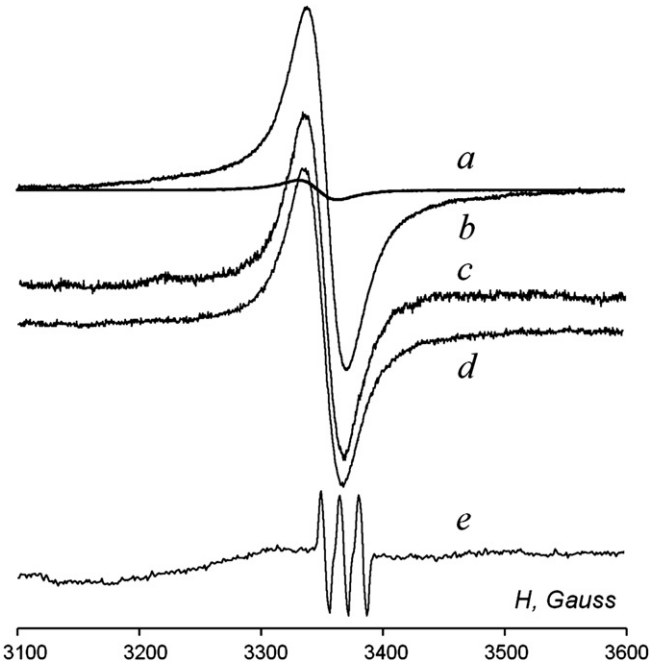


Fig. 1. EPR spectra of THF solutions (all at 10^{-4} M): (a) $FeCl_2$, (b) $FeCl_3$, (c) $FeCl_3$+MeLi (1 equiv), (d) $FeCl_3$+BuLi (1 equiv), (e) signal of TEMPO radical resulting from the reaction of $FeCl_2$ with LiTMP (3 equiv): g=2.0067, a_N=15.55 G. The signal in (a) is due to the partial oxidation of Fe^{2+} to Fe^{3+} by residual oxygen.

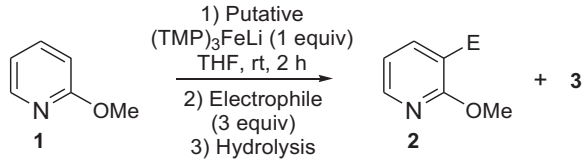
$E^o(Fe^{3+}/Fe^{2+})$=−0.771 V vs NHE[51] (−1.018 V versus SCE). In THF, these values should be corrected for the corresponding solvent transfer energies (with the loss in ΔG_{solv} for triply-charged Fe^{3+} being supposedly the largest among the concerned species), however they can be considered as a fair first approach. The fact that the EPR signal of Fe^{3+} species does not disappear after mixing $FeCl_3$ with MeLi or BuLi (Fig. 1) suggests that $E^o(Fe^{3+}/Fe^{2+})$ in THF is still not positive enough to allow efficient reduction of Fe^{3+} by these bases. Me^- is a weaker reducing agent than Bu^- for the virtue of its less negative standard potential. In fact, the intensity of the EPR signal of Fe^{3+} after reacting $FeCl_3$ with BuLi is about 1/10th weaker than after the reaction with MeLi; this is seemingly in line with the above, though this difference is comparable with the experimental error and is too small to draw further conclusions. Even though thermodynamic conditions for the reaction of Fe^{3+} with BuLi seem favorable, this reaction must be subject to kinetic limitations making it inefficient compared to the direct use of $FeCl_2$ salt (Scheme 1).

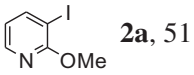
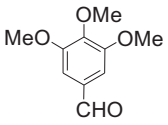
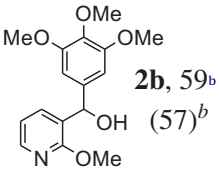
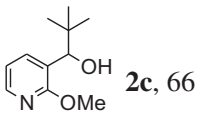
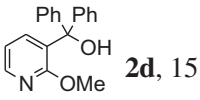
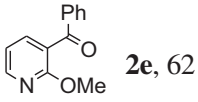
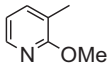
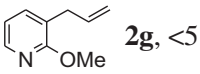
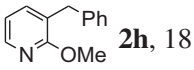
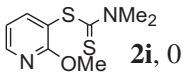
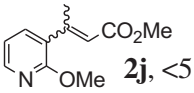
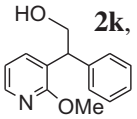
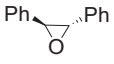
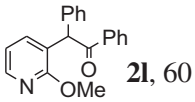
Thus, if the synthesis of organoiron(II) ate compounds using MeLi in excess is documented in the literature,[36,37] it failed in working quantitatively using 1 equiv of MeLi or BuLi in our case, compromising this approach. This result contrasts with the previously reported in situ access to $(TMP)_2CuLi$ from $CuCl_2$·TMEDA by BuLi-promoted reduction followed by addition of LiTMP (2 equiv).[32] With $E^o(Cu^{2+}/Cu^+)$=0.094 V vs SCE, the driving force of the reduction of Cu^{2+} by BuLi is about 1 eV (23 kcal/mol) greater that in the case of $FeCl_3$, explaining the difference observed.

The study was pursued using an iron(II) salt, more soluble and less hygroscopic $FeBr_2$, to generate the lithium–iron base. Since iodine did not proved to be a good choice, giving a mixture of the iodide **2a** and the dimer **3**, we turned to the use of other electrophiles to intercept the metalated 2-methoxypyridine (Table 2).

3,4,5-Trimethoxybenzaldehyde and pivalaldehyde led to the corresponding alcohols **2b**,**c** in 59–66% yield (entries 2 and 3). If the deproto-metalation step probably proceeds through amino-ligand transfer from the ferrate base without iron oxidation/reduction,

Table 2
Electrophilic trapping of metalated 2-methoxypyridine

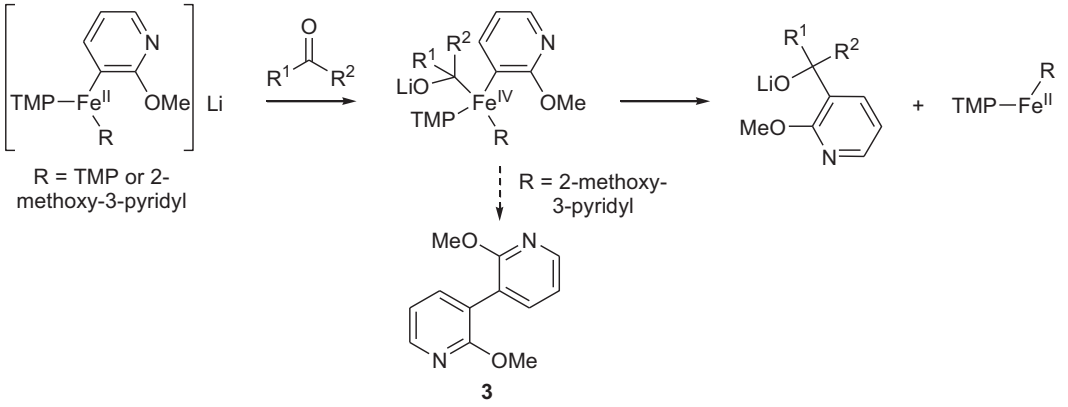


Entry	Electrophile	Yield of **2** (%)	Yield of **3** (%)
1[a]	I_2	 **2a**, 51	35
2[a]		 **2b**, 59[b] (57)[b]	<5 (<5)[b]
3[a]	^{t}BuCHO	 **2c**, 66	0
4[a]	$Ph_2C(O)$	 **2d**, 15	28
5[a]	PhC(O)Cl	 **2e**, 62	22
6[a]	ICH_3	 **2f**, 0	27
7[a]	$BrCH_2CH{=}CH_2$	 **2g**, <5	15
8[a]	$BrCH_2Ph$	 **2h**, 18	41
9[a]	$[Me_2NC(S)S]_2$	 **2i**, 0	36
10[a]	$MeC{\equiv}CCO_2Me$	 **2j**, <5	[c]
11[a]	$PhCH(CH_2O)$	 **2k**, 15[d] [d]	0
12[a]		 **2l**, 60	[c]

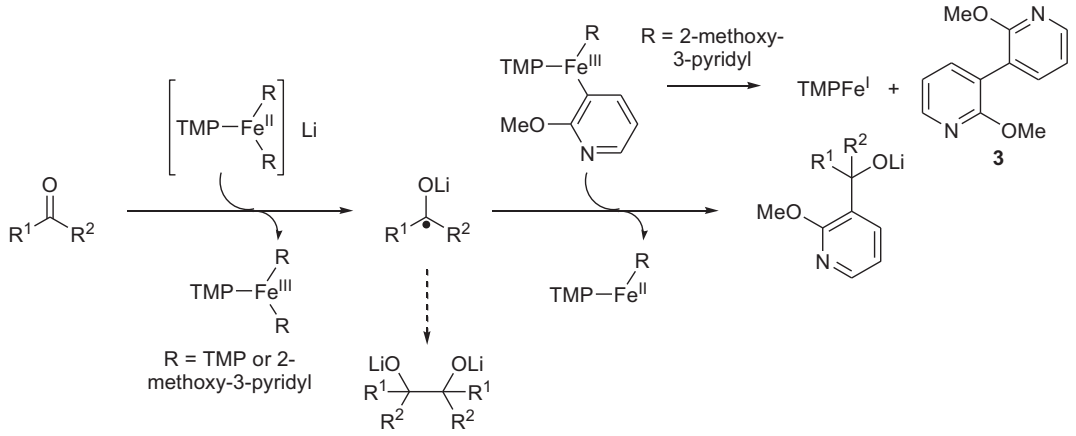
[a] Iron source: $FeBr_2$.
[b] In the presence of TMEDA (4 equiv).
[c] Dimer present in the crude but quantity not determined.
[d] The acetate was isolated.

mechanistic possibilities are less obvious concerning the trapping of the metalated 2-methoxypyridine using aldehydes. Indeed, it is not clear whether carbonyl compounds react with iron ate compounds by the addition mechanism normally found for carbanions because of possible alternative pathways[48] (Schemes 5 and 6). To explain the high equatorial selectivity of the methylation of 4-*tert*-butylcyclohexanone by Me_3FeLi,[52] an oxidative addition in which the Me_3Fe residue is forced to attack from the equatorial side was proposed.[48] In addition, one-electron transfers were suspected in the 1970s to explain peculiar results observed in the course of reactions of Grignard reagents with ketones performed in the presence of $FeCl_3$.[53,54] In our case, it is difficult to come to a decision, in particular since a dihydrodimer[48,55] corresponding to an aldehyde employed was not detected. Nevertheless, the dimer **3** being only observed as traces using aldehydes, and also for steric reasons, the mechanism depicted in Scheme 6 seems more likely.

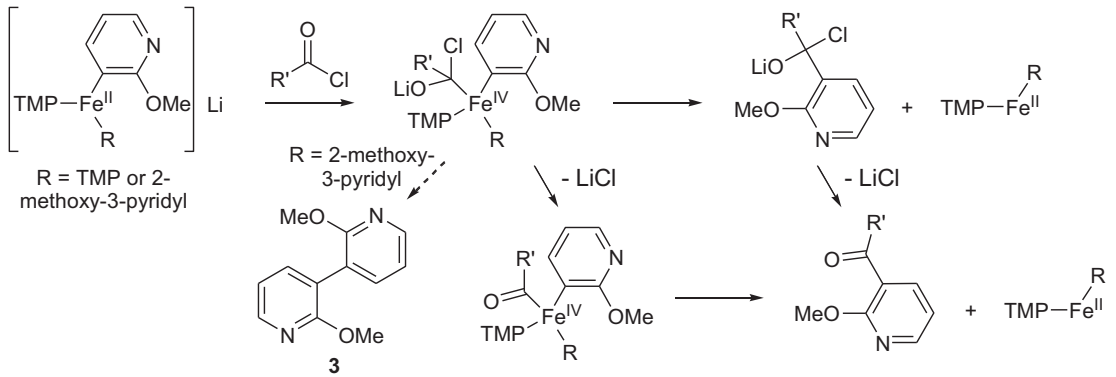
It is known that ketones are less reactive than aldehydes toward iron ate compounds. This was, for example, shown by Kauffmann and co-workers who performed competitive reactions where the reactivities of benzaldehyde and 4-methyl-2-pentanone toward Me_3FeLi and Me_4FeLi_2 were compared.[56] In our case, the alcohol **2d** was produced in a low 15% yield upon interception with benzophenone, and the dimer **3** was isolated in 28% yield (entry 4). The low reactivity of the iron ate compounds toward ketones in general allows their selective addition to aroyl chlorides.[36,48,57] In accordance, we could synthesize the corresponding ketone using benzoyl chloride in 62% yield (entry 5). Both Fe(II)/Fe(IV) and Fe(II)/Fe(III) mechanisms can be proposed (Schemes 7 and 8).



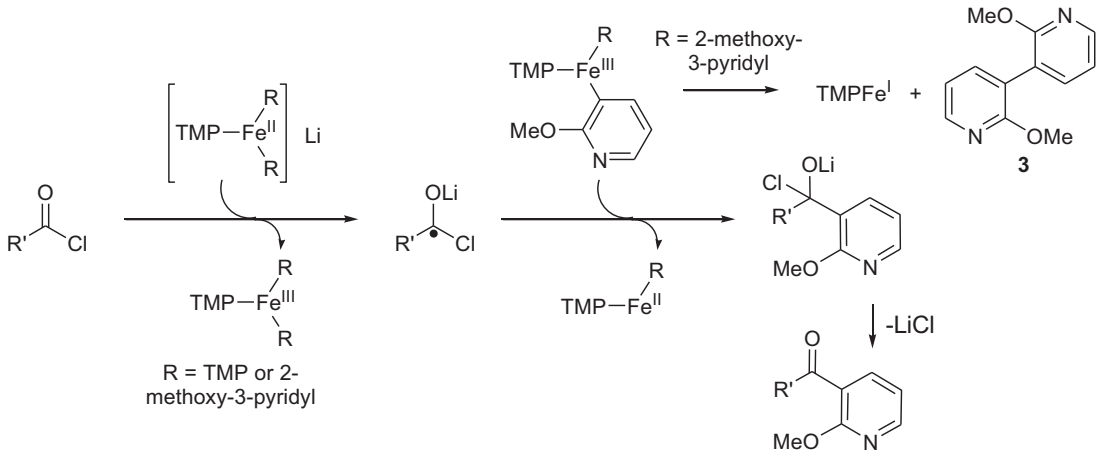
Scheme 5. Alternative Fe(II)/Fe(IV) mechanism for the trapping step using aldehydes/ketones.



Scheme 6. Alternative Fe(II)/Fe(III) mechanism for the trapping step using aldehydes/ketones.



Scheme 7. Fe(II)/Fe(IV) mechanism for the trapping step using aroyl chlorides.



Scheme 8. Fe(II)/Fe(III) mechanism for the trapping step using aroyl chlorides.

A mechanism where a reduced iron catalyst enters a one-electron redox pathway, and an alkyl radical is formed from the alkyl halide, is topical to rationalize iron-catalyzed couplings of aryl Grignard reagents with alkyl halides.[58–60] When the metalated 2-methoxypyridine was reacted with methyl iodide, allyl bromide, and benzyl bromide, the main product was the dimer **3**, isolated in 27, 15 and 41% yield, respectively. The cross-functionalization was only observed significantly using benzyl bromide, which can generate a stabilized radical, affording **2h** in 18% yield (entries 6–8); it could proceed according to the pathway depicted in Scheme 9.

The attempts to use phenyl disulfide and tetramethylthiuram disulfide failed in giving the expected sulfur derivatives: only starting material was recovered with the former and the dimer **3** (36% yield) with the latter (entry 9). Ethyl phenylpropiolate and methyl methylpropiolate were tested, but similarly failed in giving the expected conjugated alkenes: only starting material was recovered with the former and also the dimer **3** with the latter (entry 10). The behavior toward chlorodiphenylphosphine proved similar, showing that the iron ate compound formed by deprotonative metalation is a bad reagent toward such soft electrophiles. Using 2-phenyloxirane led to the regioselective formation of the alcohol **2k**, albeit in a low 16% yield (entry 11); a higher yield but of the ketone corresponding to the expected product (Fig. 2) was obtained with *trans*-stilbene oxide (entry 12).

The method was then extended to other aromatic substrates (Table 3). Starting from 2,6-dimethoxypyridine (**4**) and using pivalaldehyde as electrophile, the expected alcohol **5c** was isolated in 68% yield (entry 3), a yield similar to that obtained from 2-methoxypyridine (**1**) (entry 2). In contrast, trapping with *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate did not afford

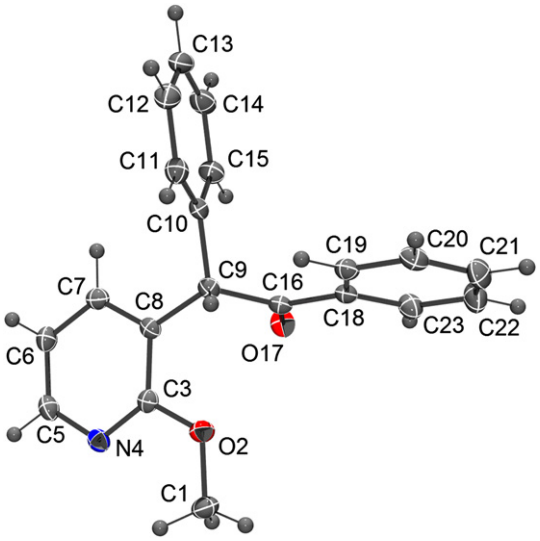
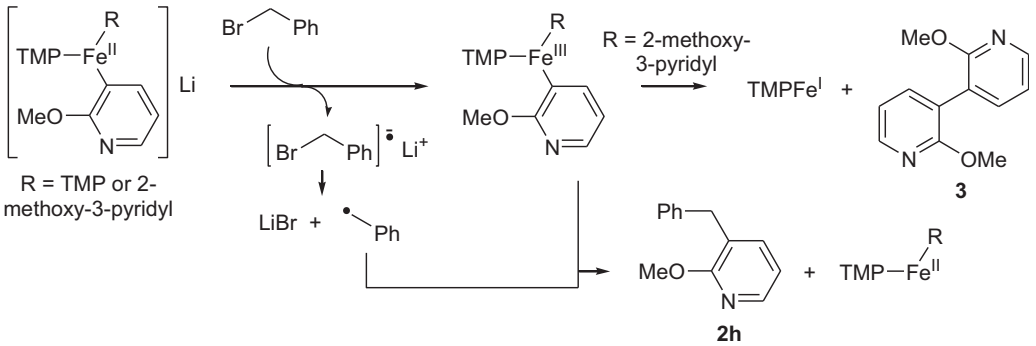


Fig. 2. ORTEP diagram (30% probability) of compound **2l**.

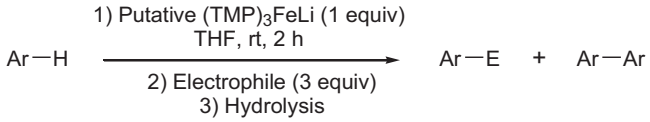
the expected fluoro derivative,[61] but instead the dimer **6** (33% yield) as well as the compound **7** (10% yield), which could result from the coupling of 3-deprotonated 2,6-dimethoxypyridine with lateral-deprotonated *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (entry 4).

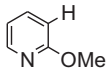
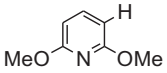
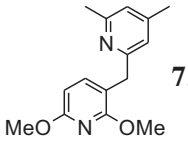
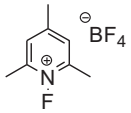
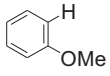
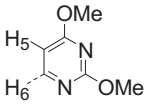
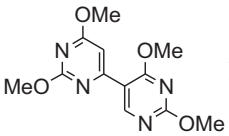
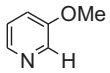
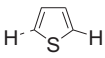
Compared with 2-methoxypyridine (**1**) (entries 1 and 2), anisole (**8**) also afforded the corresponding iodide **9a** and alcohol **9c**, but the yield of **9a** was found higher due to the absence of the



Scheme 9. Proposed pathway for the formation of **2h** and **3**.

Table 3
Extension to other aromatic substrates



Entry	Ar—H		Electrophile	Ar—E (*E*), yield (%)	Ar—Ar, yield (%)	Other products, yield (%)
1[a]	**1**:		I_2	**2a** (I), 51	**3**, 35	
2[a]			^{t}BuCHO	**2c** (CH(OH)^{t}Bu), 66	**3**, 0	
3[a]	**4**:		^{t}BuCHO	**5c** (CH(OH)^{t}Bu), 68	**6**, 0	 **7**, 10
4[a]				**5k** (F), 0	**6**, 33	
5[a]	**8**:		I_2	**9a** (I), 71	**10**, 0	
6[a]			^{t}BuCHO	**9c** (CH(OH)^{t}Bu), 47	**10**, 0	
7[a]	**11**:		^{t}BuCHO	**12c** (5-CH(OH)^{t}Bu), 50 **12c′** (6-CH(OH)^{t}Bu), 3	**13** (5,5′), 1 **13′** (6,6′), 13	 **14**, 7
8[a]	**15**:		^{t}BuCHO	**16** (CH(OH)^{t}Bu), <5	**17**, 0	
9[a]	**18**:		^{t}BuCHO	**19** (CH(OH)^{t}Bu), 64	**20**, 0	
10[a]	**21**:		^{t}BuCHO	**22** (2-CH(OH)^{t}Bu), 49 **22′** (2,5-CH(OH)^{t}Bu), 18	**17**, 0	

[a] Iron source: $FeBr_2$.

corresponding dimer **10** (entries 5 and 6). This result gives weight to the mechanism suggested in Scheme 4, with a radical anion less stable than in the pyridine case.

Compared with 2-methoxypyridine (**1**), 2,4-dimethoxypyrimidine (**11**) was converted using pivalaldehyde to the corresponding alcohols **12c** and **c′** in a slightly lower yield due to the competitive formation of different bis(pyrimidines). The reaction mainly took place at the 5-position of the pyrimidine ring (**12c** isolated in 50% yield), explaining the formation of traces (1% yield) of the 5,5′-dimer **13**. A competitive reaction at the 6-position was nevertheless evidenced by the formation of the alcohol **12c′** (3% yield); the formation of the 6,6′-dimer **13′** in 13% yield shows that the 6-metalated species is less stable than its 5-counterpart. The mixed 5,6′-dimer **14** also formed in 7% yield (entry 7).

No pyridyl alcohol was isolated when the reaction was performed from 4-methoxypyridine; with 3-methoxypyridine (**15**), the alcohol **16** was only isolated as traces (entry 8). Other 2-substituted pyridines were involved in the reaction: whereas 2-fluoropyridine (**18**) led to the alcohol **19** in 64% yield (entry 9), 2-chloropyridine did not afford any pyridine derivative when treated similarly. Deprotonation next to the heteroatom of aromatics is no more a limit with thiophene. The latter was converted into a mixture of the alcohol **22** and diol **22′**, which were isolated in 49 and 18% yield, respectively (entry 10).

3. Conclusion

Compared with the previously described 'all-TMP' lithium–zinc[18–23] and lithium–cadmium[22,24–31] combinations, the base obtained by combining $FeBr_2$ with 3 equiv of LiTMP is less efficient as far as both conversion and chemoselectivity are concerned. For example, starting from anisole (**8**), the iodide **9a** was isolated in 84% and 75% yield using 0.5 equiv of the lithium–zinc and lithium–cadmium combinations, respectively, against 71% under the same conditions but using 1 equiv of the lithium–iron combination. The efficiency of the latter more looks like those of the reported 'all-TMP' Gilman-type lithium–copper(I)[32–34] and lithium–cobalt[35] combinations. The reactivity exhibited by the generated arylmetal species is rather similar to that previously observed using the corresponding lithium–cobalt bases.[35]

4. Experimental section

4.1. General procedure A (deprotonation using 1 equiv $FeBr_2$ and 3 equiv LiTMP followed by trapping using I_2)

To a stirred cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.0 mL, 6.0 mmol) in THF (5 mL) were added BuLi (1.6 M hexanes solution, 6.0 mmol) and, 5 min later, $FeBr_2$ (0.43 g, 2.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of the substrate (2.0 mmol). After 2 h at room temperature, I_2 (1.5 g, 6.0 mmol) was added. The mixture was stirred for 1 h before addition of an aq saturated solution of $Na_2S_2O_3$ (10 mL) and extraction with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

*4.1.1. 3-Iodo-2-methoxypyridine (**2a**).* Compound **2a** was obtained according to the general procedure A starting from 2-methoxypyridine (0.21 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 80:20) as a white solid (51% yield): mp 64 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (s, 3H), 6.61 (dd, 1H, J=7.5 and 4.9 Hz), 7.98 (dd, 1H, J=7.5 and 1.7 Hz), 8.10 (dd, 1H, J=4.9 and 1.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.6, 79.7, 118.1, 146.4, 147.9, 161.8. These data are analogous to those previously described.[35]

*4.1.2. 2,2′-Dimethoxy-3,3′-bipyridine (**3**).* Compound **3** was obtained according to the general procedure A starting from 2-methoxypyridine (0.21 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 80:20) as a light yellow solid (35% yield): mp 104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 6H), 6.95 (dd, 2H, J=5.0 and 7.2 Hz), 7.59 (dd, 2H, J=1.9 and 7.2 Hz), 8.18 (dd, 2H, J=1.9 and 5.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.5 (2C), 116.4 (2C), 119.8 (2C), 139.5 (2C), 146.2 (2C), 161.1 (2C). These data are analogous to those previously described.[35]

*4.1.3. 2-Iodoanisole (**9a**).* Compound **9a** was obtained according to the general procedure A starting from anisole (0.26 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 80:20) as a yellow oil (71% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 6.72 (dd, 1H, J=7.5 and 1.4 Hz), 6.83 (dd, 1H, J=8.3 and 1.3 Hz), 7.31 (ddd, 1H, J=8.3, 7.4 and 1.6 Hz), 7.77 (dd, 1H, J=7.8 and 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.3, 86.0, 111.0, 122.5, 129.6, 139.5, 158.1. These data are analogous to those previously described.[24]

4.2. General procedure B (deprotonation using 1 equiv $FeBr_2$ and 3 equiv LiTMP followed by trapping with an electrophile ≠ I_2)

To a stirred cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (1.0 mL, 6.0 mmol) in THF (5 mL) were added BuLi (1.6 M hexanes solution, 6.0 mmol) and, 5 min later, $FeBr_2$ (0.43 g, 2.0 mmol). The mixture was stirred for 15 min at 0 °C before introduction of the substrate (2.0 mmol). After 2 h at room temperature, the electrophile (6.0 mmol) was added. The mixture was stirred for 1 h before addition of H_2O (10 mL) and extraction with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

*4.2.1. α-(3,4,5-Trimethoxyphenyl)-2-methoxy-3-pyridylmethanol (**2b**).* Compound **2b** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using 3,4,5-trimethoxybenzaldehyde (0.18 g, 6.0 mmol), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 90:10 to 40:60) as a yellow oil (59% yield): IR (ATR) ν 3442, 2943, 2837, 2250, 1591, 1463, 1410, 1326, 1233, 1125, 1005, 907, 725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.83 (s, 6H), 3.84 (s, 3H), 4.00 (s, 3H), 5.93 (s, 1H), 6.62 (s, 2H), 6.89 (dd, 1H, J=7.3 and 5.0 Hz), 7.46 (dd, 1H, J=7.3 and 1.9 Hz), 8.10 (dd, 1H, J=5.0 and 1.9 Hz), OH not seen; ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.1, 55.7 (2C), 60.4, 69.9, 103.3 (2C), 116.7, 126.6, 135.3, 136.6, 138.3, 145.1, 152.7 (2C), 160.3; HRMS (ESI) calcd for $C_{16}H_{19}NNaO_5$ [(M+Na)$^+$•] 328.1161, found 328.1162.

*4.2.2. α-(tert-Butyl)-2-methoxy-3-pyridylmethanol (**2c**).* Compound **2c** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using pivalaldehyde (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 90:10 to 70:30) as a yellow oil (66% yield): IR (ATR) ν 3404, 2956, 2909, 2873, 1587, 1463, 1412, 1248, 1265, 1046, 1021, 1009, 783, 734, 704 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (s, 9H), 3.87 (s, 3H), 4.61 (s, 1H), 6.83 (dd, 1H, J=7.3 and 5.0 Hz), 7.56 (dd, 1H, J=7.3 and 1.9 Hz), 7.99 (dd, 1H, J=5.0 and 1.9 Hz), OH not seen; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7 (3C), 36.6, 53.0, 76.0, 116.4, 124.7, 137.6, 145.1, 161.1. These data are analogous to those previously described.[62]

*4.2.3. 2-Methoxy-α,α-diphenyl-3-pyridylmethanol (**2d**).* Compound **2d** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using benzophenone (1.1 g), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/CH_2Cl_2 80:20) as a white powder (15% yield): mp 134 °C; IR (ATR) ν 3523, 3058, 3028, 2952, 1582, 1463, 1447, 1405, 1264, 1245, 1012, 755, 735, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.77–6.85 (m, 2H), 7.21–7.35 (m, 10H), 8.12 (dd, 1H, J=4.7 and 2.2 Hz), OH not seen; ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.7, 81.0, 116.8, 127.4 (2C), 127.8 (4C), 128.0 (4C), 129.4, 138.5, 145.6 (2C), 145.9, 161.0; HRMS (ESI) calcd for $C_{19}H_{17}NNaO_2$ [(M+Na)$^+$•] 314.1157, found 314.1155.

*4.2.4. 3-Benzoyl-2-methoxypyridine (**2e**).* Compound **2e** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using benzoyl chloride (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/CH_2Cl_2 40:60) as a yellow oil (62% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (s, 3H), 7.01 (dd, 1H, J=7.3 and 5.0 Hz), 7.42–7.48 (m, 2H), 7.58 (tt, 1H, J=7.4 and 1.3 Hz), 7.72 (dd, 1H, J=7.3 and 2.0 Hz), 7.78–7.81 (m, 2H), 8.32 (dd, 1H, J=5.0 and 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.8, 116.7, 122.7, 128.5 (2C), 129.9 (2C), 133.5, 137.2, 139.0, 149.4, 161.3, 194.9. These NMR data are analogous to those previously described.[33]

*4.2.5. 3-Allyl-2-methoxypyridine (**2g**).* Compound **2g** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using allyl bromide (0.52 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 80:20) as a yellow oil (<5% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.33 (br d, 2H, J=6.7 Hz), 3.95 (s, 3H), 5.05 (dq, 1H, J=7.1 and 1.6 Hz), 5.10 (t, 1H, J=1.4 Hz), 5.90–6.03 (m, 1H), 6.82 (dd, 1H, J=7.2 and 5.0 Hz) 7.38 (ddt, 1H, J=7.2, 1.9, and 0.9 Hz), 8.03 (dd, 1H, J=5.0 and 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 33.8, 53.4, 116.3, 116.7, 122.9, 135.6, 137.7, 144.4, 161.9.

*4.2.6. 3-Benzyl-2-methoxypyridine (**2h**).* Compound **2h** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using benzyl bromide (0.71 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5 to 70:30) as a yellow oil (18% yield): IR (ATR) ν 3059, 3027, 2949, 2852, 1585, 1463, 1451, 1410, 1311, 1254, 1102, 1020, 781, 731, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 2H), 3.96 (s, 3H), 6.79 (dd, 1H, J=7.3 and 5.0 Hz),

7.20–7.33 (m, 6H), 8.03 (dd, 1H, J=5.0 and 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.7, 53.5, 116.9, 124.2, 126.3, 128.6 (2C), 129.2 (2C), 138.1, 139.8, 144.7, 162.1; HRMS (ESI) calcd for $C_{13}H_{13}NNaO$ [(M+Na)$^+$•] 222.0895, found 222.0894.

*4.2.7. (E)-Methyl 3-(2-methoxy-3-pyridyl)butenoate (E-**2j**).* Compound *E*-**2j** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using methyl 2-butynoate (0.62 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 80:20) as a yellow oil (1% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.48 (d, 3H, J=1.4 Hz), 3.75 (s, 3H), 3.97 (s, 3H), 5.96 (q, 1H, J=1.3 Hz), 6.89 (dd, 1H, J=7.3 and 5.0 Hz), 7.44 (dd, 1H, J=7.3 and 1.9 Hz), 8.14 (dd, 1H, J=5.0 and 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 51.2, 53.6, 116.8, 119.7, 126.8, 137.1, 146.8, 154.4, 160.6, 167.0. These data are analogous to those previously described.[33]

*4.2.8. (Z)-Methyl 3-(2-methoxy-3-pyridyl)butenoate (Z-**2j**).* Compound *Z*-**2j** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using methyl 2-butynoate (0.62 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 80:20) as a yellow oil (1% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.15 (d, 3H, J=1.5 Hz), 3.56 (s, 3H), 3.94 (s, 3H), 5.99 (q, 1H, J=1.5 Hz), 6.90 (dd, 1H, J=7.3 and 5.1 Hz), 7.33 (dd, 1H, J=7.2 and 1.9 Hz), 8.13 (dd, 1H, J=5.0 and 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6, 51.1, 53.5, 116.4, 119.2, 124.1, 136.6, 146.1, 151.7, 159.7, 165.8. These data are analogous to those previously described.[33]

*4.2.9. [2-(2-Methoxy-3-pyridyl)-2-phenyl]ethyl acetate (**2k**).* Compound **2k** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using (*R*)-styrene oxide (0.70 mL), and was isolated as its acetate after purification by flash chromatography on silica gel (eluent: heptane/CH_2Cl_2 80:20 to 80:20) as a yellow oil (15% yield): IR (ATR) ν 2950, 2168, 1737, 1584, 1462, 1451, 1411, 1223, 1018, 780, 737, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 3H), 3.93 (s, 3H), 4.57–4.67 (m, 3H), 6.84 (dd, 1H, J=7.3 and 5.0 Hz), 7.20–7.33 (m, 5H), 7.40 (dd, 1H, J=7.4 and 1.9 Hz), 8.10 (dd, 1H, J=5.0 and 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.1, 43.3, 54.1, 65.4, 116.9, 124.2, 127.1, 128.4 (2C), 128.7 (2C), 137.2, 139.9, 144.7, 161.6, 171.1; HRMS (ESI) calcd for $C_{16}H_{17}NNaO_3$ [(M+Na)$^+$•] 294.1106, found 294.1105.

*4.2.10. [(2-Methoxy-3-pyridyl)(phenyl)methyl] phenyl ketone (**2l**).* Compound **2l** was obtained according to the general procedure B starting from 2-methoxypyridine (0.21 mL), and using *trans*-stilbene oxide (1.2 g), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/CH_2Cl_2 98:2 to 80:20) as colorless crystals (60% yield): mp 128 °C, IR (ATR) ν 3063, 2949, 2252, 1687, 1595, 1464, 1449, 1407, 1258, 1212, 1103, 1021, 905, 725, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.25 (s, 1H), 6.81 (dd, 1H, J=7.4 and 5.0 Hz), 7.18 (dd, 1H, J=7.4 and 1.8 Hz), 7.54–7.29 (m, 8H), 8.02 (dt, 2H, J=6.2 and 1.2 Hz), 8.07 (dd, 1H, J=5.0 and 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.0, 53.7, 116.9, 123.4, 127.6, 128.7 (2C), 128.8 (2C), 129.1 (2C), 129.6 (2C), 133.0, 136.6, 136.9, 138.3, 145.4, 161.1, 198.1; HRMS (ESI) calcd for $C_{20}H_{17}NNaO_2$ [(M+Na)$^+$•] 326.1157, found 326.1154.

X-ray data for compound **2l**: $C_{20}H_{17}NO_2$, M=303.35, monoclinic, $P2_1/c$, a=8.3683(11), b=12.6774(19), c=14.7765(16) Å, β=97.105(6)°, V=1555.6(4) Å^3, Z=4, ρ_c=1.295 g cm^{-3}, μ=0.084 mm^{-1}. A final refinement on F^2 with 3563 unique intensities and 209 parameters converged at w$R(F^2)$=0.1021 ($R(F)$=0.0426) for 2877 observed reflections with $I>2\sigma(I)$. CCDC 862151.

*4.2.11. α-(tert-Butyl)-2,6-dimethoxy-3-pyridylmethanol (**5c**).* Compound **5c** was obtained according to the general procedure B starting from 2,6-dimethoxypyridine (0.26 mL), and using pivalaldehyde (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 90:10 to 80:20) as a yellow oil (68% yield): IR (ATR) ν 3455, 2954, 1602, 1587, 1480, 1390, 1309, 1019, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 9H), 2.44 (m, 1H), 3.84 (s, 3H), 3.85 (s, 3H), 4.52 (s, 1H), 6.23 (d, 1H, J=8.0 Hz), 7.44 (d, 1H, J=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.6 (3C), 36.6, 52.8, 53.2, 75.9, 100.2, 115.2, 140.4, 159.3, 161.6; HRMS (ESI) calcd for $C_{12}H_{19}NNaO_3$ [(M+Na)$^+$•] 248.1263, found 248.1263.

*4.2.12. 2,2′,6,6′-Tetramethoxy-3,3′-bipyridine (**6**).* Compound **6** was obtained according to the general procedure B starting from 2,6-dimethoxypyridine (0.26 mL), and using 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (0.72 g, 3 mmol in this case), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 90:10) as a pale beige powder (33% yield): mp 145 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.91 (s, 6H), 3.94 (s, 6H), 6.36 (d, 2H, J=8.0 Hz), 7.52 (d, 2H, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.4 (2C), 53.5 (2C), 100.4 (2C), 142.5 (2C), 110.6 (2C), 159.7 (2C), 162.1 (2C). These data are analogous to those previously described.[35]

*4.2.13. 2,6-Dimethoxy-3-[(4,6-dimethyl-2-pyridyl)methyl]pyridine (**7**).* Compound **7** was obtained according to the general procedure B starting from 2,6-dimethoxypyridine (0.26 mL), and using *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate (0.72 g, 3 mmol in this case[61]), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 90:10) as a yellow oil (10% yield): IR (ATR) ν 2951, 1718, 1607, 1588, 1479, 1388, 1319, 1248, 1021, 733 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.48 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 3.95 (s, 2H), 6.23 (d, 1H, J=8.0 Hz), 6.64 (s, 1H), 6.78 (s, 1H), 7.31 (d, 1H, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 24.3, 37.1, 53.4, 54.6, 100.3, 113.0, 120.7, 121.8, 141.7, 147.8, 157.5, 159.8, 160.4, 161.8; HRMS (ESI) calcd for $C_{15}H_{18}N_2NaO_2$ [(M+Na)$^+$•] 281.1266, found 281.1266.

*4.2.14. α-(tert-Butyl)-2-methoxyphenylmethanol (**9c**).* Compound **9c** was obtained according to the general procedure B starting from anisole (0.26 mL), and using pivalaldehyde (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5) as a yellow oil (47% yield): IR (ATR) ν 3478, 2956, 1701, 1601, 1490, 1464, 1238, 1043, 1005, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (s, 9H), 2.63 (d, 1H, J=6.0 Hz), 3.81 (s, 3H), 4.73 (d, 1H, J=6.0 Hz), 6.87 (dd, 1H, J=8.3 and 0.9 Hz), 6.95 (td, 1H, J=7.4 and 1.1 Hz), 7.23 (dd, 1H, J=8.2 and 1.8 Hz), 7.29 (dd, 1H, J=7.5 and 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.2 (3C), 36.8, 55.3, 78.1, 110.7, 120.3, 128.2, 129.5, 130.2, 157.1; HRMS (ESI) calcd for $C_{12}H_{18}NaO_2$ [(M+Na)$^+$•] 217.1204, found 217.1203.

*4.2.15. α-(tert-Butyl)-2,4-dimethoxy-5-pyrimidylmethanol (**12c**).* Compound **12c** was obtained according to the general procedure B starting from 2,4-dimethoxypyrimidine (0.26 mL), and using pivalaldehyde (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5) as a yellow oil (50% yield): IR (ATR) ν 2958, 1568, 1467, 1382, 1356, 1265, 1200, 1049, 1018, 732 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 9H), 3.98 (s, 3H), 4.00 (s, 3H), 4.60 (s, 1H), 8.25 (s, 1H), OH not seen; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7 (3C), 36.8, 53.9, 54.9, 75.0, 115.5, 157.9, 164.5, 168.6; HRMS (ESI) calcd for $C_{11}H_{18}N_2NaO_3$ [(M+Na)$^+$•] 249.1215, found 249.1216.

*4.2.16. α-(tert-Butyl)-2,4-dimethoxy-6-pyrimidylmethanol (**12c′**).* Compound **12c′** was obtained according to the general procedure B starting from 2,4-dimethoxypyrimidine (0.26 mL), and using pivalaldehyde (0.70 mL), and was identified after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5)

by NMR (3% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 9H), 3.95 (s, 3H), 3.98 (s, 3H), 4.16 (s, 1H), 6.25 (s, 1H), OH not seen; ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.7 (3C), 36.8, 53.9, 54.9, 75.0, 115.5, 157.9, 164.5, 168.6.

*4.2.17. 2,2′,4,4′-Tetramethoxy-5,5′-bipyrimidine (**13**).* Compound **13** was obtained according to the general procedure B starting from 2,4-dimethoxypyrimidine (0.26 mL), and using pivalaldehyde (0.70 mL), and was identified after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5) by NMR (1% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, 6H), 4.01 (s, 6H), 8.12 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.3 (2C), 55.0 (2C), 108.3 (2C), 158.8 (2C), 165.1 (2C), 168.7 (2C). These NMR data are analogous to those previously described.[33]

*4.2.18. 2,2′,4,4′-Tetramethoxy-6,6′-bipyrimidine (**13′**).* Compound **13′** was obtained according to the general procedure B starting from 2,4-dimethoxypyrimidine (0.26 mL), and using pivalaldehyde (0.70 mL), and was identified after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5) by NMR (13% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.00 (s, 6H), 4.05 (s, 6H), 7.40 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.3 (2C), 55.0 (2C), 99,5 (2C), 162.9 (2C), 165.5 (2C), 173.1 (2C).

*4.2.19. 2,2′,4′,6-Tetramethoxy-4,5′-bipyrimidine (**14**).* Compound **14** was obtained according to the general procedure B starting from 2,4-dimethoxypyrimidine (0.26 mL), and using pivalaldehyde (0.70 mL), and was identified after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5) by NMR (7% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3,98 (s, 3H), 4.02 (s, 3H), 4.04 (s, 3H), 4.09 (s, 3H), 7.07 (s, 1H), 9.24 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 54.1, 54.4, 54.8, 55.3, 100.9, 111.9, 159.5, 164.6, 164.9, 165.7, 170.6, 171.5.

*4.2.20. α-(tert-Butyl)-3-methoxy-2-pyridylmethanol (**16**).* Compound **16** was obtained according to the general procedure B starting from 3-methoxypyridine (0.21 mL), and using pivalaldehyde (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5) as a beige powder (<5% yield): mp 82 °C; IR (ATR) ν 3476, 2963, 2873, 1732, 1588, 1576, 1461, 1434, 1278, 1223, 1051, 1017, 796, 735 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 9H), 3.83 (s, 3H), 4.80 (s, 1H), 7.19–7.21 (m, 2H), 8,19 (dd, 1H, J=4.1 and 1.9 Hz), OH not seen; ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.1, 37.5, 55.5, 74.3, 118.6, 123.3, 138.6, 150.7, 153.5; HRMS (ESI) calcd for $C_{11}H_{17}NNaO_2$ [(M+Na)$^+$•] 218.1157, found 218.1159.

*4.2.21. α-(tert-Butyl)-2-fluoro-3-pyridylmethanol (**19**).* Compound **19** was obtained according to the general procedure B starting from 2-fluoropyridine (0.17 mL), and using pivalaldehyde (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 95:5) as a yellow oil (64% yield): IR (ATR) ν 3374, 2967, 1602, 1579, 1435, 1365, 1265, 1050, 1012, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.94 (s, 9H), 2.11 (m, 1H), 4.74 (s, 1H), 7.20 (dd, 1H, J=7.5 and 4.8 Hz), 7.92 (d, 1H, J=7.4 and 1.1 Hz), 8.11 (dd, 1H, J=4.8 and 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.5 (3C, d, J_F=1.1 Hz), 36.6 (s), 74,4 (d, J_F=3.3 Hz), 121.3 (d, J_F=4.2 Hz), 124.5 (d, J_F=28 Hz), 140.2 (d, J_F=5.2 Hz), 146.4 (d, J_F=15 Hz), 160.9 (d, J_F=236 Hz); ^{19}F NMR (282 MHz, $CDCl_3$): δ −69.8; HRMS (ESI) calcd for $C_{10}H_{14}FNNaO$ [(M+Na)$^+$•] 206.0957, found 206.0959.

*4.2.22. α-(tert-Butyl)-2-thienylmethanol (**22**).* Compound **22** was obtained according to the general procedure B starting from thiophene (0.17 mL), and using pivalaldehyde (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 80:20) as a yellow oil (49% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 9H), 2.11 (d, 1H, J=2.1 Hz), 4.65 (d, 1H, J=1.1 Hz), 6.94 (m, 1H), 6.97 (m, 1H), 7.23 (dd, 1H, J=4.9 and 1.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.9 (3C), 35.7, 78.9, 124.2, 125.2, 126.1, 145.9. These NMR data are in accordance with those previously described.[63]

*4.2.23. 2,5-Thienylenebis(α-(tert-butyl)methanol) (**22′**).* Compound **22′** was obtained according to the general procedure B starting from thiophene (0.17 mL), and using pivalaldehyde (0.70 mL), and was isolated after purification by flash chromatography on silica gel (eluent: heptane/AcOEt 80:20) as a yellow oil (18% yield): IR (ATR) ν 3427, 2955, 2869, 1479, 1363, 1214, 1043, 1003, 808, 734 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (s, 18H), 1.96 (d, 2H, J=3.3 Hz), 4.59 (d, 2H, J=3.3 Hz), 6.79 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.0 (6C), 35.8 (2C), 79. 2 (2C), 124.5 (2C), 144.6 (2C); HRMS (ESI) calcd for $C_{14}H_{24}NaO_2S$ [(M+Na)$^+$•] 279.1395, found 279.1394.

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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.2012.02.019. These data include MOL files and InChIKeys of the most important compounds described in this article.

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