O-Tetrahydropyran-2-yloxy (*O*-THP) as an *ortho*-Directing Group in the Lithiation of Pyridines

Rabah Azzouz, Laurent Bischoff,* Corinne Fruit, Francis Marsais

Laboratoire de Chimie Organique Fine et Hétérocyclique, IRCOF, INSA Rouen, CNRS UMR 6014, B.P. 08, 76131 Mont-Saint-Aignan Cedex, France
Fax +33(2)35522962; E-mail: laurent.bischoff@insa-rouen.fr
Received 30 March 2006

Abstract: Herein we report regioselective deprotonations of 3- and 4-(tetrahydropyran-2-yloxy)pyridine with *n*-butyllithium. Trapping the lithiated species with various electrophiles afforded functionalized pyridines in good yields. A one-pot procedure also allowed the double functionalization at C4 and C2 in the case of 3-*O*-THP-pyridine. The *ortho*-metallating ability of this group was examined in comparison with other well-known oxygen-based *ortho*-directing groups.

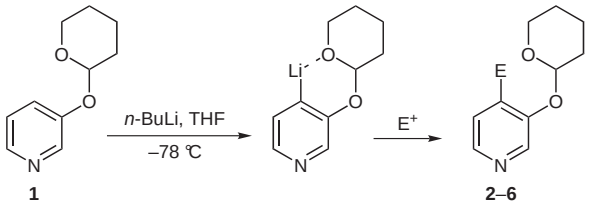
Key words: acetals, pyridines, metallations, lithium, organometallic reagents

The directed *ortho*-metallation is a powerful methodology for functionalization of aromatic and heteroaromatic compounds since lithiated derivatives display a high reactivity toward a wide range of electrophiles.[1] While numerous *ortho*-directing groups such as the methoxy group, methoxymethoxy group (MOM)[2] or *O*-carbamoyl group[3] have been widely studied in benzene series, only few examples of *ortho*-lithiated *O*-tetrahydropyran-2-yloxy (*O*-THP) group were reported. For instance, di-(*O*-THP)hydroquinone and (*O*-THP)phenol were metallated by *n*-butyllithium and trapped by carbon dioxide and ethylene oxide, respectively.[4a] *ortho*-Lithiation of (*O*-THP)phenol derivatives was also a key step in a tri-*O*-thymotide synthesis.[4b] For pyridine, the *ortho*-lithiation of the *O*-THP group still remaines unexplored. Since the easy removal of the THP group for the formation of pyridinol, which greatly enhances its synthetic application, it therefore appeared to us interesting to determine the efficiency of *O*-THP as *ortho*-directing group in metallation reaction.

In order to study the regioselectivity of the metallation reaction, 3-*O*-THP pyridine (**1**) was first studied. Because the classical DHP/H^+ pathway could not be envisaged, 3-*O*-THP pyridine (**1**) is conveniently produced from 3-hydroxypyridine by treatment with 2-hydroxytetrahydropyran under Mitsunobu conditions (triethylphosphine, diethyl azadicarboxylate in THF) as we recently described.[5] The *O*-THP group was thus tested as *ortho*-directing group in the metallation reaction.

As depicted in Scheme 1, metallation of pyridine **1** was successfully achieved. A typical procedure involved, in THF at –78 °C, the use of **1** in the presence of a slight excess of *n*-butyllithium (1.5 molar equiv). It is noteworthy that no trace of addition of the alkyllithium species on the pyridine ring was observed and the reaction led to cleanly *ortho*-metallated species. Indeed, deuteration of **1** under these conditions was achieved in 90% yield.

The lithium chelate is subsequently trapped by suitable electrophiles showing regioselectivity of the lithiation (Table 1). In all cases, only one isomer was obtained with functionalization at C4.



Scheme 1 Lithiation and electrophilic trapping of 3-(*O*-THP)pyridine

Table 1 Deprotonation of 3-(*O*-THP)pyridine Using *n*-Butyllithium and Trapping with Various Electrophiles

Entry	Electrophile	–E	Compd	Yield (%)[a]
1	D_2O	–D	**2**	90
2	I_2	–I	**3**	88
3	PhSSPh	–SPh	**4**	65
4	4-Anisaldehyde	–CH(OH)C_6H_4-*p*-OMe	**5**	67
5	DMF	–CHO	**6**	89

[a] Isolated yield after flash chromatography.

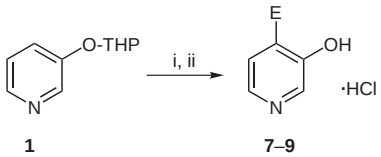
The trapping reaction led to deuteration, halogenation, sulfenylation, hydroxyalkylation or formylation. The conversion, observed by ^{1}H NMR spectroscopy on the crude reaction mixture, was >80%, very low amounts of starting material being detected. Furthermore, iodopyridine **3** would allow further substitutions or cross-coupling reaction.

The ability of the *O*-THP group for *ortho*-lithiation could be easily explained by a chelation of the lithium owing to the endocyclic oxygen atom of the heterocycle. Likewise, the acidity of the labile proton is enhancing due to the

SYNLETT 2006, No. 12, pp 1908–1912
Advanced online publication: 24.07.2006
DOI: 10.1055/s-2006-947340; Art ID: D09606ST

electron-withdrawing character of the oxygen atom. The role of this complex-induced proximity effect (CIPE) in metallation reactions was recently thoroughly discussed.[6]

The yields obtained for compounds **4** and **5** after column chromatography are lower than those expected, considering the good conversions observed before purification. This can be explained by partial hydrolysis of the THP group on silica gel. Thus, we evaluated the possibility of cleavage of the *O*-THP group after functionalization of the pyridine. We observed (Scheme 2) that an aqueous hydrolysis can be carried out under mild conditions, i.e. 3 molar HCl in a 1:1 mixture of dioxane–H_2O at room temperature. A typical procedure for a tandem functionalization–deprotection was achieved by simply hydrolyzing the crude reaction under these mild acidic conditions. In this way, the expected pyridinol hydrochloride was recovered from the aqueous layer upon lyophylization.



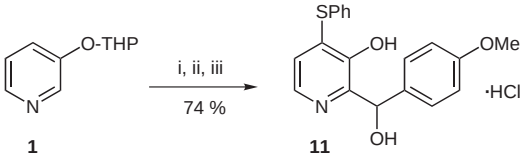
Scheme 2 One-pot lithiation, electrophilic trapping and deprotection of 3-(*O*-THP)pyridine.
Reagents and conditions: *i*) *n*-BuLi, –78 °C, then E^+, –78 °C; *ii*) 3 M HCl in dioxane–H_2O, 2 h at r.t.

Table 2 Synthesis of 3-Pyridinols Functionalized at C4

Entry	Electrophile	–E	Compd	Yield (%)
1	PhSSPh	–SPh	**7**	75
2	4-Anisaldehyde	–CH(OH)C_6H_4-*p*-OMe	**8**	67
3	MeI	–Me	**9**	96

As shown in Table 2, this one-pot methodology gave good yields of very pure pyridinol hydrochlorides, which were obtained without further purification. This was rendered feasible by a quantitative metallation, since no trace of 3-hydroxypyridine was observed. For this purpose, we used a larger excess (2 mol equiv) of *n*-BuLi.

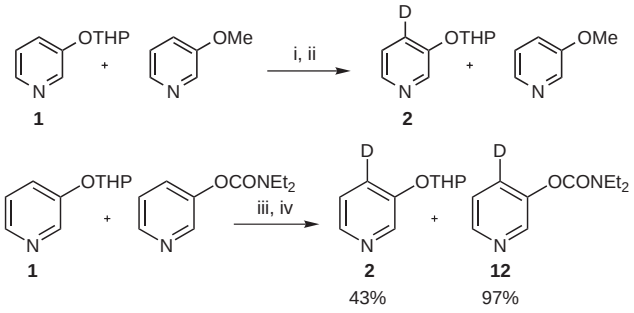
As far as the regioselectivity is concerned, according to the lithiation of 3-methoxymethyloxy pyridine with *tert*-butyllithium published earlier,[7] metallation of **1** was only effected at the C4 carbon, and no trace of the other regioisomer was observed. We then focused our attention towards the possibility of subsequent functionalization at the C2 carbon. To achieve 2-deprotonation of **1**, blocking of the 4-position is necessary. A one-pot procedure for a straight double functionalization was performed by using a slight excess of *n*-BuLi in each deprotonation step. Indeed, a first metallation-trapping sequence allowed the functionalization at the C4 position, and a subsequent, one-pot repetition of this protocol led to a second substitution at the C2 position. This was first tested by sulfenylation at C4 followed by deuteration at C2 (compound **10**), then a double functionalization was performed (Scheme 3). The pyridinol was further deprotected from the crude reaction mixture as described above. This procedure led to compound **11** with a 74% overall yield of isolated pure material.



Scheme 3 One-pot double deprotonation–electrophilic trapping sequence of 3-(*O*-THP)pyridine.
Reagents and conditions: *i*) 1.2 equiv *n*-BuLi, THF, –78 °C, then PhSSPh; *ii*) 1.5 equiv *n*-BuLi, THF, –78 °C, then anisaldehyde; *iii*) 3 M HCl, H_2O–dioxane = 1:1, r.t.

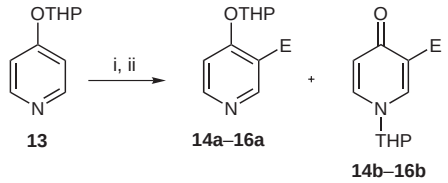
These results showed that successive metallations occurred at C4 and at subsequent C2 position, without adding *n*-BuLi onto the electron-deficient pyridine ring.

The *ortho*-directing ability of the *O*-THP group in lithiation reactions was achieved by carrying out competitive experiments. The competitive efficiencies of *ortho*-lithiations within different O-protected pyridinols were established by a series of reactions in which two different substrates (1 mmol each) were allowed to react with *n*-BuLi (2 or 3 mmol) in THF. The reactions were quenched with a deuterium source. A typical competition is shown in Scheme 4. Signifiant differences for competitive efficiencies in directed *ortho*-lithiations for O-protected pyridinol were observed. The *O*-THP-methoxy pair was allowed to compete and it was found that only *O*-THP pyridine (**1**) underwent lithiation. This is consistent with a better lithium-chelation ability of the *O*-THP compared to the OMe group. For the carbamoyl group, the deprotonation occured at 97%, while the *O*-THP group led to 43% deuteration at C4. These two experiments rank the *O*-THP group between methoxy and *O*-diethylcarbamate, in terms of *ortho*-directing ability.



Scheme 4 Competition experiments between *O*-THP and other oxygen-based *ortho*-directing groups.
Reagents and conditions: *i*) 2 mmol *n*-BuLi (for 1 mmol of **1** + 1 mmol 3-methoxypyridine), THF, –40 °C, 1 h; *ii*) D_2O; *iii*) 3 mmol *n*-BuLi (for 1 mmol of **1** + 1 mmol 3-diethylcarbamoyl pyridine), TMEDA, THF, –78 °C; iv) EtOD.

As the *O*-THP group seemed to exhibit a very good ability for directing *ortho*-metallation, we subsequently examined the possibility of deprotonating at the C3 carbon, using 4-*O*-THP pyridine **13**.[5] This position is generally more difficult to deprotonate, due to less favorable electronic effects of the nitrogen atom. We were pleased to notice that using the same reaction conditions, the lithiation only occurred at the C3 carbon. The metallated species were trapped with suitable electrophiles (Scheme 5), as listed in Table 3.



Scheme 5 Deprotonation of 4-*O*-THP pyridine: obtention of *N*-THP by-products.
Reagents and conditions: *i*) 1.5 equiv *n*-BuLi, THF, –78 °C; *ii*) electrophile, THF, –78 °C.

Table 3 Isolated Yields for the Trapping of Lithiated 4-(*O*-THP)pyridine

Entry	Electrophile	Compd	Yield (%)	Ratio *O*-THP/*N*-THP
1	EtOD	**14a**,**b**	92	71:29
2	I_2	**15a**,**b**	50	48:52
3	4-Anisaldehyde	**16a**	68	100:0

Nevertheless, the THP protecting group is very labile, especially when linked to oxygen at the C2 or C4 on pyridinols.[5] During the course of the metallation of 4-*O*-THP pyridine, we obtained a side product resulting from a transposition of THP from the oxygen atom to the nitrogen atom of pyridine. This rearrangement should occur after the trapping, since the functionalization at C3 was quantitative in each case, according to the NMR spectra of the crude materials. Presumably, the lithiated 4-*O*-THP pyridine is stable enough to be synthesized without rearrangement, as long as the lithium is involved in the C–Li bond. Though, it may become labile and lead to *N*-THP by-products once the lithium species was trapped by the electrophile. At this time, the lithium is only chelated by the *O*-THP, without being bound to the carbon atom of the pyridine. In order to confirm this hypothesis, we used an aldehyde as the electrophile (entry 3), so as to still permit the chelation of the lithium cation by the alcoholate thus obtained. In this case, no *N*-THP by-product was observed.

In summary, we reported a new and efficient *ortho*-directing group to extend the scope of the functionalization of pyridines. This methodology used the *O*-THP both as an *ortho*-directing and protecting group, since it can be easily cleaved after the functionalization step, in much milder conditions than the methoxy group or a tertiary carbamate. The 3- and 4-(tetrahydropyran-2-yloxy)pyridines are metallated with complete regioselectivity at, respectively, C4 and C3 positions to afford products in good yields. In addition, a new one-pot procedure easily led to 2,4-disubstituted pyridin-3-ols in good yields. Further research is focused on asymmetric O-alkyl group and develops the approach into synthetically interesting methodology.

NMR spectra were recorded on a 300 MHz Bruker Avance. All chemical shifts are given in ppm. R_f given for TLC analyses were measured on silica gel Merck Kieselgel F_{254} aluminum plates. Melting points are uncorrected.

Typical Procedure for the Metallation of Compounds 1 and 13
To a solution of 300 mg (1.67 mmol) of 3-tetrahydropyran-2-yloxy pyridine (**1**) in THF (16 mL) at –78 °C were added dropwise 1.62 mL (2.51 mmol) of a 1.6 M solution of *n*-BuLi in hexanes. After 30 min stirring at this temperature, the electrophile (1 M in THF) was added dropwise. After 1 h stirring at –78 °C, 15 mL of 10% NH_4Cl were added and the crude material was obtained by extractive work-up with Et_2O. Purification was subsequently achieved by means of column chromatography through silica gel using 1% Et_3N in the eluent (compounds **2**–**6**). In the case of more acid-sensitive compounds **14**–**16**, basic alumina was used for column chromatography.

4-Deuterio-3-tetrahydropyran-2-yloxy Pyridine (2)
From 300 mg (1.67 mmol) of **1** and 150 μL (8.3 mmol) D_2O, 270 mg of compound **2** were obtained (90%) as a pale brown oil. TLC (cyclohexane–EtOAc, 1:3, 1% Et_3N): R_f = 0.65. ^{1}H NMR ($CDCl_3$): δ = 1.50–2.00 (6 H, m), 3.50–3.70 (2 H, m), 5.37 (1 H, t, *J* = 3.0 Hz), 7.14 (1 H, d, *J* = 4.7 Hz), 8.17 (1 H, d, *J* = 4.7 Hz), 8.35 (1 H, s). ^{13}C NMR: δ = 18.8, 25.4, 30.5, 62.4, 97.0, 124.2, 140.0, 143.0, 162.7. MS (CI): *m*/*z* = 97, 85, 181.

4-Iodo-3-tetrahydropyran-2-yloxy Pyridine (3)
From 200 mg (1.12 mmol) of **1** and 426 mg (1.68 mmol) I_2, 300 mg of compound **3** were obtained (88%) as a pale brown powder; mp 90 °C; TLC (cyclohexane–EtOAc, 1:3, 1% Et_3N): R_f = 0.93. ^{1}H NMR: δ = 1.50–2.00 (6 H, m), 3.50–3.70 (2 H, m), 5.54 (1 H, dd, *J* = 2.6, 2.3 Hz), 7.65 (1 H, d, *J* = 4.9 Hz), 7.82 (1 H, d, *J* = 4.9 Hz), 8.26 (1 H, s) ^{13}C NMR ($CDCl_3$): δ = 20.1, 25.5, 30.2, 63.2, 88.8, 95.8, 132.7, 139.3, 143.0, 164.1. MS (CI): *m*/*z* = 85, 96, 222, 306.

4-Phenylsulfanyl-3-tetrahydropyran-2-yloxy Pyridine (4)
From 200 mg (1.12 mmol) of **1** and 367 mg (1.68 mmol) PhSSPh, 209 mg of **4** were obtained (65%) as a pale brown oil. TLC (CH_2Cl_2–EtOAc, 1:1, 1% Et_3N): R_f = 0.6. ^{1}H NMR ($CDCl_3$): δ = 1.50–2.00 (6 H, m), 3.50–3.70 (2 H, m), 5.52 (1 H, dd, *J* = 3.0, 2.6 Hz), 6.48 (1 H, d, *J* = 5.0 Hz), 7.40–7.50 (5 H, m), 7.92 (1 H, d, *J* = 5.0 Hz), 8.26 (1 H, s). ^{13}C NMR: δ = 20.2, 25.5, 30.2, 63.2, 96.3, 122.2, 125.6, 127.1, 129.5, 136.4, 139.0, 142.0, 157.9. MS (CI): *m*/*z* = 85, 204, 260, 288.

4-(4-Methoxyphenylhydroxymethyl)-3-tetrahydropyran-2-yloxy Pyridine (5)
From 300 mg (1.67 mmol) of **1** and 304 μL (2.5 mmol) *p*-anisaldehyde, 351 mg of **5** were obtained (67%) as a pale yellow powder; mp 102 °C; TLC (EtOAc, 1% Et_3N): R_f = 0.4. ^{1}H NMR ($CDCl_3$): δ = 1.60–2.00 (6 H, m), 3.50–3.70 (2 H, m), 3.71 (3 H, s), 5.41 (1 H, dd, *J* = 2.6, 2.3 Hz), 5.97 (1 H, s), 6.78 (2 H, d, *J* = 8.7 Hz), 7.20 (2 H, d, *J* = 8.7 Hz), 7.37 (1 H, d, *J* = 4.9 Hz), 8.22 (1 H, d, *J* = 4.9 Hz), 8.32 (1 H, s). ^{13}C NMR: δ = 19.8, 25.3, 30.4, 55.7, 62.8, 70.5, 97.5, 114.2, 127.5, 128.7, 134.8, 135.0, 137.3, 141.9, 159.6. MS (CI): *m*/*z* = 85, 232, 298, 316

4-Formyl-3-tetrahydropyran-2-yloxy Pyridine (6)
From 160 mg (0.89 mmol) of **1** and 140 μL DMF (1.78 mmol), 160 mg of compound **6** were obtained (89%) as brown oil. ^{1}H NMR ($CDCl_3$): δ = 1.50–2.00 (6 H, m), 3.65 (1 H, m), 3.90 (1 H, m), 5.66 (1 H, t, *J* = 2.9 Hz), 7.61 (1 H, d, *J* = 4.89 Hz), 8.42 (1 H, d, *J* = 4.89 Hz), 8.76 (1 H, s), 10.58 (1 H, s). ^{13}C NMR: δ = 18.8, 25.2, 30.4, 62.8, 97.6, 120.0, 130.0, 140.3, 143.7, 153.9, 189.6.

2-Deuterio-4-phenylsulfanyl-3-tetrahydropyran-2-yloxy Pyridine (10)
From 200 mg (1.12 mmol) of **1**, after successive treatments with *n*-BuLi (1.34 mmol), PhSSPh (330 mg, 1.46 mmol), then *n*-BuLi (1.68 mmol) and D_2O (0.1 mL, 5.6 mmol), 190 mg were obtained (59%) after column chromatography as a pale brown oil. ^{1}H NMR ($CDCl_3$): δ = 1.50–2.00 (6 H, m), 3.50–3.70 (2 H, m), 5.52 (1 H, t, *J* = 2.6 Hz), 6.45 (1 H, d, *J* = 4.5 Hz), 7.40–7.50 (5 H, m), 7.92 (1 H, d, *J* = 4.5 Hz). MS (CI): *m*/*z* = 85, 205, 289.

Procedure for Subsequent Deprotection
After metallation (with 2 mol equiv *n*-BuLi 45 min at –78 °C) and electrophilic trapping (45 min at –78 °C), the crude material was taken up in dioxane and an equal volume of 6 M aq HCl was added. After 2 h stirring at r.t., solvents were evaporated in vacuo and the residue was dissolved in H_2O, washed with Et_2O and lyophilized to afford pure **7**–**9** as their hydrochlorides.

3-Hydroxy-4-phenylsulfanyl Pyridine Hydrochloride (7)
From 150 mg (0.84 mmol) of **1** and 364 mg (1.67 mmol) diphenyldisulfide, 150 mg of compound **7** were obtained (75%) as a white powder; mp 238 °C. ^{1}H NMR (DMSO): δ = 6.85 (1 H, d, *J* = 6.21 Hz), 7.67 (5 H, m), 8.13 (1 H, d, *J* = 6.21 Hz), 8.19 (1 H, s). ^{13}C NMR: δ = 121.8, 125.6, 127, 131.8, 132.0, 133.7, 136.7, 150.2, 151.8. MS (FAB$^+$): *m*/*z* = 204, 185, 93, 75. HRMS: *m*/*z* calcd for $C_{11}H_9NOS$ [M]$^+$: 203.0404; found: 203.0405.

3-Hydroxy-4-(4-methoxyphenylhydroxymethyl) Pyridine Hydrochloride (8)
From 150 mg (0.84 mmol) of **1** and 200 μL 4-anisaldehyde, 150 mg of compound **8** were obtained (67%) as a light brown powder; mp 82 °C. ^{1}H NMR (D_2O): δ = 3.71 (3 H, s), 6.10 (1 H, s), 6.87 (1 H, d, *J* = 8.8 Hz), 7.25 (1 H, d, *J* = 8.8 Hz), 8.12 (1 H, d, *J* = 6.2 Hz), 8.13 (1 H, s), 8.29 (1 H, d, *J* = 6.2 Hz). ^{13}C NMR: δ = 55.6, 69.5, 114.5, 124.2, 127.9, 129.2, 132.3, 133.4, 150.6, 152.8, 159.2. MS (FAB$^+$): *m*/*z* = 232, 214, 185, 93, 75. HRMS: *m*/*z* calcd for $C_{13}H_{13}NO_3$ [M]$^+$: 231.0891; found: 231.0895.

3-Hydroxy-4-methyl Pyridine Hydrochloride (9)
From 105 mg (0.59 mmol) of **1** and 55 μL iodomethane (0.88 mmol), 82 mg of compound **9** were obtained (96%) as a brown paste. ^{1}H NMR (DMSO): δ = 2.41 (3 H, s), 7.86 (1 H, d, *J* = 5.6 Hz), 8.34 (1 H, d, *J* = 5.6 Hz), 8.42 (1 H, s). ^{13}C NMR: δ = 17.3, 127.2, 129.3, 132.9, 146.6, 155.9.

3-Hydroxy-2-(4-methoxyphenyl)hydroxymethyl-4-phenylsulfanyl Pyridine Hydrochloride (11)
From 100 mg (0.56 mmol) of **1**, *n*-BuLi (1.12 mmol, 45 min at –78 °C), 244 mg diphenyldisulfide (1.12 mmol, 45 min at –78 °C), 135 μL 4-anisaldehyde (1.12 mmol, 45 min at –78 °C), then hydrolyzing as described for **7**–**9**, 156 mg of compound **11** were obtained (74%) as a white powder; mp 112 °C. ^{1}H NMR (DMSO): δ = 3.65 (3 H, s), 6.17 (1 H, s), 6.48 (1 H, d, *J* = 5.8 Hz), 6.83 (1 H, d, *J* = 8.7 Hz), 7.28 (1 H, d, *J* = 8.7 Hz), 7.43 (1 H, s), 7.50 (5 H, m), 7.82 (1 H, d, *J* = 5.8 Hz). ^{13}C NMR: δ = 55.4, 70.9, 113.9, 114, 119.9, 128.2, 128.4, 130.6, 130.8, 134, 135.6, 136, 145.4, 147.4, 159.1. HRMS: *m*/*z* calcd for $C_{19}H_{18}NO_3S$ [M]$^+$: 340.0991; found: 340.1007.

Competition Experiments
Competition experiment involving 3-methoxy and 3-(*O*-THP)pyridine was conducted using the experimental conditions described for **2**.

Competition Experiment with the Carbamate
From 100 mg (0.56 mmol) of **1** and 110 mg (0.56 mmol) of 3-*O*-diethylcarbamoylpyridine, 150 mg of the following mixture were obtained as a colorless oil. ^{1}H NMR ($CDCl_3$): δ = 1.23 (6 H, 2 t, *J* = 7.1 Hz), 1.50–2.00 (6 H, m), 3.42 (4 H, 2q, *J* = 7.0 Hz), 3.61 (1 H, m), 3.86 (1 H, m), 5.44 (1 H, t, *J* = 2.9 Hz), 7.20 (1 H, dd, *J* = 8.5, 4.5 Hz), 7.30 (1 H, d, *J* = 4.3 Hz), 7.38 (0.57 H, H4 of the THP ether, ddd, *J* = 8.3, 2.8, 1.3 Hz), 7.52 (0.03 H, H4 of the carbamate, ddd, *J* = 8.1, 4.3, 1.1 Hz), 8.10 (1 H, d, *J* = 4.2 Hz), 8.41 (1 H, s), 8.43 (1 H, s), 8.43 (1 H, d, *J* = 4.3 Hz).

3-Deuterio-4-tetrahydropyran-2-yloxy Pyridine (14a)
From 100 mg (0.56 mmol) of **13** and 160 μL (2.79 mmol) EtOD, 65 mg of **14a** (65%) were obtained. ^{1}H NMR: δ = 1.50–2.00 (6 H, m), 3.50–3.70 (2 H, m), 5.46 (1 H, t, *J* = 2.8 Hz), 6.88 (1 H, d, *J* = 5.6 Hz), 8.36 (1 H, s), 8.37 (1 H, d, *J* = 5.6 Hz). ^{13}C NMR: δ = 18.7, 25.5, 30.2, 69.3, 93.7, 131.6, 153.1, 164.0.

3-Deuterio-1-tetrahydropyran-2-yloxy Pyridin-4-one (14b)
From the previous experiment, 27 mg of **14b** (27%) were obtained by crystallization as a white solid. ^{1}H NMR ($CDCl_3$): δ = 1.50–2.00 (6 H, m), 3.60–4.10 (2 H, m), 4.78 (1 H, dd, *J* = 10.0, 2.2 Hz), 6.32 (1 H, d, *J* = 8.1 Hz), 7.41 (2 H, m). ^{13}C NMR: δ = 22.9, 24.9, 32.3, 69.3, 91.7, 118.5, 118.7, 137.4, 137.5, 180.2.

3-Iodo-4-tetrahydropyran-2-yloxy Pyridine (15a)
From 100 mg (0.56 mmol) of **13** and 210 mg (0.83 mmol) I_2, 40 mg of **15a** were obtained (24%) as a brown oil. ^{1}H NMR ($CDCl_3$): δ = 1.50–2.00 (6 H, m), 3.50–3.70 (2 H, m), 5.61 (1 H, t, *J* = 2.9 Hz), 6.94 (1 H, d, *J* = 5.6 Hz), 8.28 (1 H, d, *J* = 5.6 Hz), 8.71 (1 H, s).

3-Iodo-1-tetrahydropyran-2-yloxy Pyridin-4-one (15b)
From the previous experiment, 45 mg of **15b** (26%) were obtained by crystallization as a yellow solid. ^{1}H NMR ($CDCl_3$): δ = 1.50–2.00 (6 H, m), 3.60 (1 H, m), 4.11 (1 H, m), 4.79 (1 H, dd, *J* = 10.0, 2.1 Hz), 6.33 (1 H, d, *J* = 7.5 Hz), 7.41 (1 H, dd, *J* = 7.5, 2.4 Hz), 8.00 (1 H, d, *J* = 2.4 Hz). ^{13}C NMR: δ = 21.5, 23.5, 31.1, 68, 90.1, 91.9, 113, 135.8, 141.4, 174.3. MS (CI): *m*/*z* = 306, 222, 180, 96, 85, 73.

3-(4-Methoxyphenylhydroxymethyl)-4-tetrahydropyran-2-yloxy Pyridine (16a)
From 100 mg (0.56 mmol) of **13** and 100 μL (0.83 mmol) of 4-anisaldehyde, 120 mg of **16a** were obtained (68%) as a white oil. ^{1}H NMR ($CDCl_3$): δ = 1.50–2.00 (6 H, m), 3.47 (2 H, m), 3.71 (3 H, s), 5.44 (1 H, m), 5.90 (1 H, s), 6.78 (2 H, d, *J* = 8.8 Hz), 6.94 (1 H, d, *J* = 5.6 Hz), 7.22 (2 H, d, *J* = 8.8 Hz), 8.34 (1 H, d, *J* = 5.6 Hz), 8.56 (1 H, s). ^{13}C NMR: δ = 19.3, 25.9, 30, 55.7, 65.3, 69.2, 96, 103, 114.1, 118.1, 128.5, 130.3, 148,150.6, 159, 172.7.

References

(1) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059.
(2) (a) Schlosser, M. In *Organometallics in Synthesis*, 2nd ed.; Schlosser, M., Ed.; Wiley: Chichester UK, **2002**, 1–352. (b) Clayden, J. In *The Chemistry of Organolithium Compounds*; Rappoport, Z.; Marek, I., Eds.; Wiley: Chichester UK, **2004**, 495–646.
(3) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5438.
(4) (a) Stern, R.; English, J. Jr.; Cassidy, H. G. *J. Am. Chem. Soc.* **1957**, *79*, 5797. (b) Harris, T. D.; Oruganti, S. R.; Davis, L. M.; Keehu, P. M.; Green, B. S. *Tetrahedron* **1987**, *43*, 1519.
(5) Azzouz, R.; Bischoff, L.; Fouquet, M.-H.; Marsais, F. *Synlett* **2005**, 2808.
(6) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206.
(7) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101.