ELSEVIER

Journal of Organometallic Chemistry 517 (1996) 25–36

Journal of Organometallic Chemistry

Metallation in connection with cross-coupling reactions. Coupling of hindered aryls for the synthesis of 4-phenylpyridines as part of *Streptonigrin* and *Lavendamycin* analogues

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Received 19 June 1995

Abstract

The synthesis of the C–D ring system of *Streptonigrin* and *Lavendamycin* alkaloid analogues by cross-coupling under Suzuki's conditions has been studied. Steric hindrance is the main problem. It has been solved either by using strong bases or working in a sealed tube under pressure.

Keywords: Palladium; Orthometallation; Synthesis; 4-Phenylpyridines

1. Introduction

A simple and versatile method for the synthesis of *Streptonigrin* and *Lavendamycin* models **1** and **2** via orthodirected metallation in association with palladium catalyzed coupling reactions has been previously reported by our laboratory [1]. The methodology involves the independent elaboration of the three main building blocks (benzene, pyridine and quinoline) by metallation and two cross-couplings as depicted in the retrosynthetic scheme (Scheme 1).

A key step of the synthesis is the formation of the 4-phenylpyridine moiety. The reaction was performed by a cross-coupling reaction between an arylboronic acid and a suitably substituted 4-iodopyridine in the conditions described by Suzuki and coworkers [2]. Thus, total synthesis of *Streptonigrin* and *Lavendamycin* would imply a heterobiaryl cross-coupling between a sterically hindered 3,5-disubstituted-4-iodopyridine **3** (A = NHCO^{t}Bu; R_3 = Me; R_4 = COOR and A = F; R_3 = Me; R_4 = COOR) and an orthosubstituted phenylboronic acid **4** (R_0 = OMe; R_1 = OCONEt$_2$; B = H and $R_0 = R_1$ = H; B = NHCO^{t}Bu) respectively (Scheme 2). It was in our interest to study the influence of steric and electronic factors on the course of this coupling reaction. We wish to report here some results we obtained in this field.

2. Synthesis of starting materials

2.1. Pyridine block

In order to synthesize other models of *Streptonigrin* and *Lavendamycin*, two types of 3-substituted-4-iodopyridine have been used as starting materials: 3-fluoro and 3-aminopyridine derivatives.

2.1.1. 3-Fluoropyridines

2-Chloro-3-fluoro-4-iodopyridine (**3a**) (A = F; R_3 = R_4 = H; R_5 = Cl) has been prepared by orthodirected metallation of the corresponding fluoro-compound [1b]. 2-Chloro-3-fluoro-5,6-dimethyl-4-iodopyridine (**3b**) (A = F; R_3 = R_4 = Me; R_5 = Cl) was synthesized in four steps starting from 5,6-dimethyl-3-nitro-2(1H)-pyridone (**6a**) [3,4a] as follows (Scheme 3). Chlorination of **6a** followed by reduction of the nitro group and subsequent

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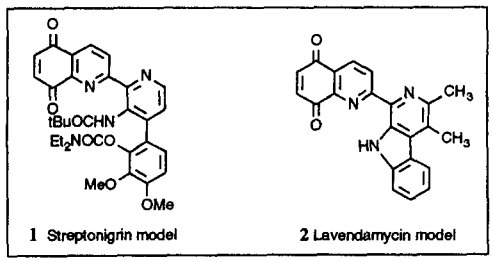
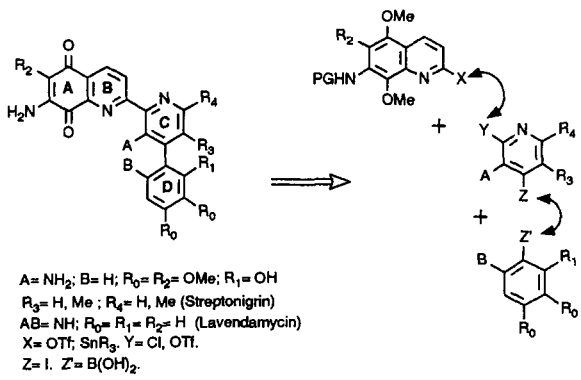
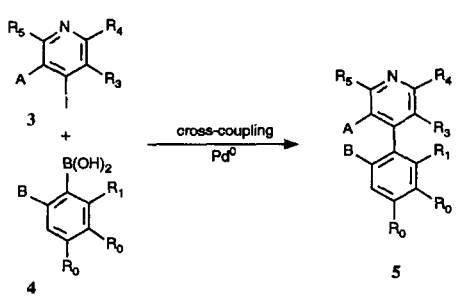




Scheme 1.

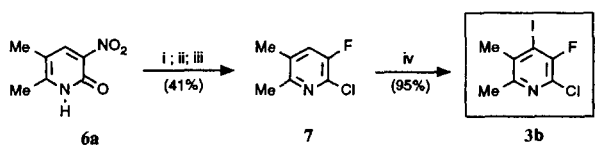


Scheme 2.

Schiemann reaction afforded the 2-chloro-3-fluoro-5,6-dimethylpyridine (**7**) in 41% overall yield. Lithiation of the tetrasubstituted pyridine (**7**) by LDA at −78°C followed by reaction of the resulting lithio species with iodine gave the expected compound **3b** in 95% yield. Noted that metallation did not occur on the methyl group at C-6 as could be expected.

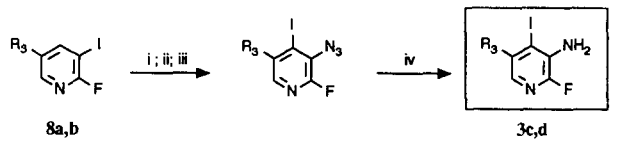
2.1.2. 3-Aminopyridines

3-Aminopyridines **3c** to **3h** (A = NHR; R_4 = H, Me; R_3 = H, Me; R_5 = F, OMe, O^{i}Pr) derivatives were obtained following two synthetic pathways



i : $POCl_3$/PhCl ; ii : Fe/HCl ; iii : 1) EtONO/ HBF_4/Et_2O . 2) Δ ;
iv: 1) LDA. 2) I_2 (overall yield 39%).

Scheme 3.



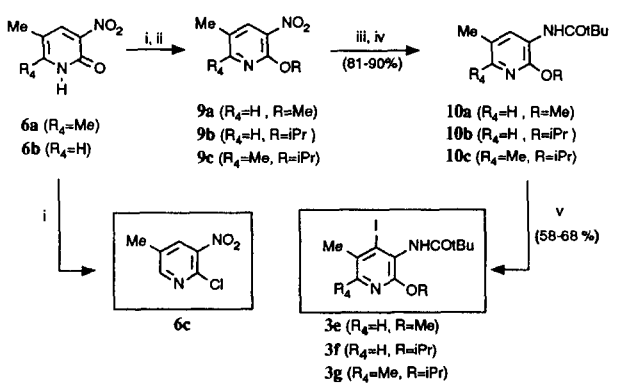
i : LDA/THF ; ii : TsN_3 ; iii : H_2O ; iv : H_2S/MeOH . (overall yield : 69% R = H; 75% R = CH_3)

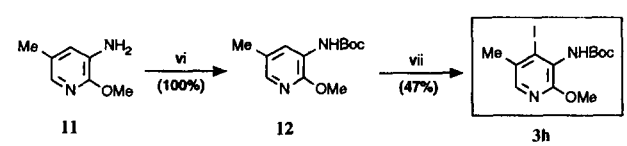
Scheme 4.

Path 1 (halogen-dance). 2-Fluoro-3-iodopyridines **8a** and **8b** were subjected to a lithiation-isomerization reaction [5] by LDA (THF/ − 78°C) before reaction with tosyl azide. Intermediary crude azides were reduced by H_2S in MeOH to give 3-amino-4-iodopyridines **3c** and **3d** in good yields (Scheme 4).

Path 2 (metallation of 3-aminopyridine derivatives). 4-Iodo-3-pivaloylaminopyridines **3e–g** were obtained by a metallation–iodination sequence of the corresponding 3-pivaloylaminopyridines **10**. Compounds **10** resulted from 2-(1H)pyridones [4] **6a** and **6b** by O-alkylation, reduction of nitro derivatives **9** and acylation of the resulted aminopyridines with pivaloyl chloride. A similar pathway was used for the synthesis of the NHBoc derivative **3h** (Scheme 5).

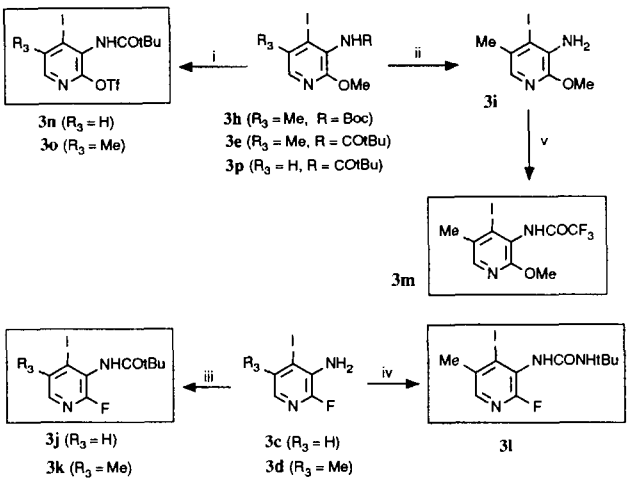
Group conversions. In order to check steric hindrance and electronic factors around the coupling site, amide and amino groups at C-3 were modified (Scheme 6). Hydrolysis of **3h** afforded 3-aminopyridine **3i**. 3-Amino-2-fluoro-4-iodopyridines **3c** and **3d** were respectively converted into the corresponding pivaloylamino derivatives **3j** and **3k**. The urethane **3l** was prepared from **3d** by reaction with LDA and *t*-butylisocyanate as





i: $POCl_3$. ii: MeONa/ MeOH or $AgCO_3$/iPrI; iii: H_2/Pd-C; iv: ClCOtBu/NEt_3/Et_2O;
v: 1) nBuLi/THF. 2) I_2/THF; vi: $(tBuCO_2)_2O$/tBuOH; vii: 1) tBuLi/THF. 2) I_2/THF.

Scheme 5.

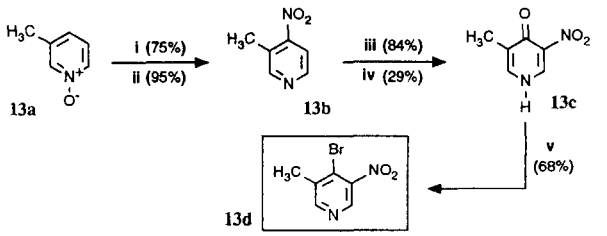


i : 1) BBr_3/CH_2Cl_2 2)Tf_2O/pyridine. ii : TFA/$ClCH_2CH_2Cl$. iii : ClCOtBu/NEt_3/toluene.
iv : 1)LDA/THF. 2) O=C=N-tBu. v : $(CF_3CO)_2O/Et_3N/Et_2O$.

Scheme 6.

electrophile. Compound **3i** reacted with trifluoroacetic anhydride to give the trifluoroacetylamide **3m**. Finally, C-2 methoxy group of 4-iodo-2-methoxypyridines **3e** and **3p** were cleaved and acylated by Tf_2O to give **3n** and **3o**.

In order to check the electronic effect of the nitro group on the course of the coupling reaction, 4-bromo-5-methyl-3-nitropyridine (**13**) was synthesized (Scheme 7). A nitro function could be easily transformed by reduction, allowing the synthesis of the required amino derivative. The methodology was adapted from the procedure described by Cheng and coworkers [6] for the preparation of 4-chloro-2,3-dimethyl-5-nitropyridine.



i: HNO_3/H_2SO_4 . ii: PCl_3/CH_2Cl_2. iii: $CH_3COOK/(CH_3CO)_2O$. iv: HNO_3/H_2SO_4.
v: $POBr_3$/ PBr_5. (Overall yield: 12%).

Scheme 7.

2.2. Phenyl blocks

Arylboronic acids **4a–e** were generally obtained by metallation of the corresponding pivaloylaminobenzene for the synthesis of *Lavendamycin* models and *N,N*-diethylcarbamoyloxybenzene for the synthesis of *Streptonigrin* models, as previously described [11] (Scheme 8).

3. Cross-coupling reactions

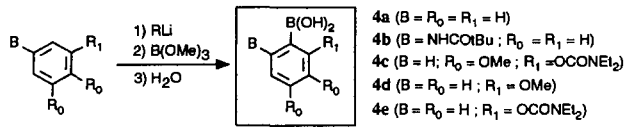
3.1. Results

Coupling reactions were carried out using the procedure described by Suzuki and coworkers [2]. 4-Iodo-

Table 1
Biaryl cross-coupling reactions with Na_2CO_3 as base

Entry	3				4				5
	A	R_3	R_4	R_5	B	R_1	R_0	Yield (%)	
1	F	H	H	Cl	NHCO^{t}Bu	H	H	94	**a**
2	F	Me	Me	Cl	NHCO^{t}Bu	H	H	75	**b**
3	NH_2	H	H	F	H	$OCONEt_2$	OMe	84	**c**
4	NH_2	Me	H	F	H	$OCONEt_2$	OMe	0	**d**
5	NH_2	Me	H	OMe	H	$OCONEt_2$	OMe	20	**e**
6	NHCO^{t}Bu	H	H	F	H	$OCONEt_2$	OMe	70	**f**
7	NHCO^{t}Bu	H	H	OMe	H	H	H	95	**g**
8	NHCO^{t}Bu	H	H	OMe	H	$OCONEt_2$	OMe	88	**h**
9	NHCO^{t}Bu	H	H	OTf	H	$OCONEt_2$	OMe	75	**i**
10	NHCO^{t}Bu	Me	H	F	H	$OCONEt_2$	OMe	0 (29) [c]	**j**
11	NHCO^{t}Bu	Me	H	OMe	H	H	H	89	**k**
12	NHCO^{t}Bu	Me	H	OMe	H	$OCONEt_2$	OMe	10 (70) [c]	**l**
13	NHCO^{t}Bu	Me	H	OMe	H	OMe	H	34	**m**
14	NHCONH^{t}Bu	Me	H	F	H	$OCONEt_2$	OMe	25	**n**
15	$NHCOCF_3$	Me	H	OMe	H	OMe	H	43 [b]	**o**
16	NO_2 [a] (**13d**)	Me	H	H	H	$OCONEt_2$	OMe	80	**p**

[a] Iodine is replaced by a bromine on pyridine ring.
[b] Yield estimated after hydrolysis of the $NHCOCF_3$ group.
[c] Temperature 180°C; pressure 8 atm.



Scheme 8.

pyridines **3** or 4-bromopyridine **13** as one part and phenylboronic acids **4** as the other part were reacted at 80°C in the presence of $Pd(PPh_3)_4$ (3%) and two equivalents of base in toluene (Scheme 2). The main results are summarised in Table 1.

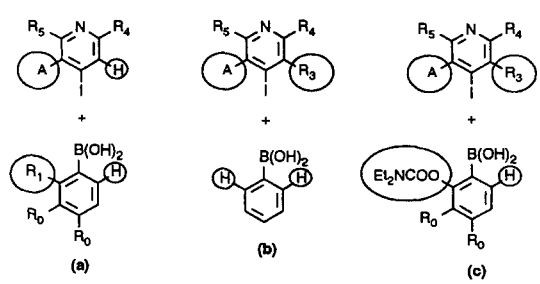
As shown in Table 1, fairly good yields were obtained when reaction was carried out with C-5 unsubtituted ($R_3 = H$) pyridine derivatives **3** and either orthosubstituted or unsubstituted arylboronic acids **4** (Table 1; entries 1, 3, 6, 7, 8, 9) (Scheme 9(a)). However, good yields were obtained when the unsubstituted phenylboronic acid **4a** ($B = R_0 = R_1 = H$) was reacted with the C-5 substituted pyridine **3e** (Table 1, entry 11) (Scheme 9(b)). A marked drop in the yields is observed when pyridine bears two large substituents ortho to iodine and, in the phenyl ring, a sterically hindering group, like $OCONEt_2$, ortho to the $B(OH)_2$ group (Table 1; entries 4, 5, 10, 12, 14) (Scheme 9(c)). Note that an improvement in the yield was observed when the NHCOtBu group was replaced by a smaller one like NH_2 (Table 1, entry 5 compared with entry 12).

Finally, 4-bromo-5-methyl-3-nitropyridine **13** was reacted with the orthosubstituted arylboronic acid **4** (B = H; $R_1 = OCONEt_2$; $R_1 = OMe$) to afford the corresponding 4-phenylpyridine in 80% yield (Table 1; entry 16).

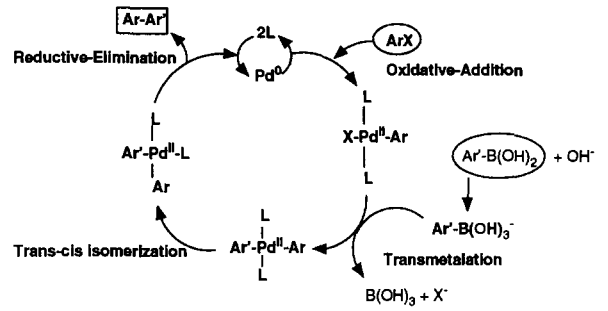
3.2. Discussion

The general proposed cyclic mechanism involves an oxidative addition in the first step. Then, transmetallation of boron for palladium takes place to form a *trans*-diarylpalladium(II) species. Finally, the *trans*-isomer is transformed into the *cis*-isomer and reductive elimination of the biaryl occurs, regenerating the catalyst (Scheme 10).

The oxidative-addition is known to be very tolerant of orthosubstitution. However, some evidence suggests



Scheme 9.



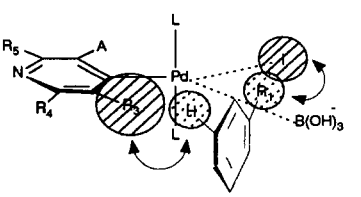
Scheme 10.

that transmetallation is the rate-determining step in most cross-coupling reactions [8].

Two main factors play a major role in biaryl cross-coupling reaction: steric hinderance around the coupling sites and electronic effects of the substituents.

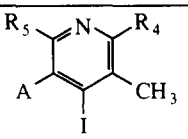
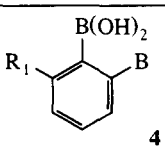
In order to take into account steric hinderance, the transmetallation transition-state could be rationalized as described in Scheme 11, in a similar conformation as previously described in Ref. [9]. It could be observed, with this model, that the conformation produces serious interactions between the orthosubstituent of the pyridine and the phenyl rings. The important hindrance between $R_3(CH_3)$ and H on the one hand, and $R_1(OCONEt_2)$ and iodine on the other hand, could explain the very low yields obtained in these cases (Table 1, entries 4, 5, 10, 12, 14).

Electronic effects are illustrated by improvement of the yield in the following reaction, for example compound **3b** ($A = F$; $R_5 = Cl$; $R_3 = R_4 = CH_3$) reacted with **4b** ($B = NHCOtBu$; $R_0 = R_1 = H$) to give the corresponding phenylpyridine **5b** in 75% yield (Table 1, entry 2). The yield was lower than that obtained with the corresponding less sterically hindered **3a** (Table 1, entry 1) but higher than the one obtained with the corresponding 4-iodo-3-methyl-5-pivaloylamino pyridines. In this case, the orthosubstituent of iodine (fluorine) is not only smaller but also possess an electron-withdrawing effect. The electron-donating effect of the amide function in the compounds **3** series was diminished by introduction of a trifluoroacetyl substituent on compound **3m** ($A = NHCOCF_3$; $R_5 = OMe$; $R_3 = Me$) (Table 1, entry 15) (note that hydrolysis of the amide function occurred). Increased yields were obtained (43%) compared with the 34% yield obtained with **3e** (Table 1, entry 13).



Scheme 11.

Table 2
Biaryl cross-coupling reactions with $Ba(OH)_2$ as base

Entry	 3			 4		Conditions	Yield (%) 5
	A	R_4	R_5	B	R_1		
17	F	CH_3	Cl	$NHCO^tBu$	H	$PhCH_3/Ba(OH)_2$ 80°C/16 h	83 (**5b**)
18						i.d./60 h	87 (B = NH_2) (**5b'**)
19	$NHCO^tBu$	CH_3	OiPr	H	$OCONEt_2$	DMF/$Ba(OH)_2$ 130°C/110 h	40 (B = OH) (**5q**)

It should be noted that a very good yield was obtained when 4-bromo-5-methyl-3-nitropyridine **13** was reacted with the sterically hindered phenyl boronic acid **4c** (yield 80%) (Table 1, entry 16).

This could be due either to the withdrawing effect of the nitro group and/or by the use of bromine instead of iodine.

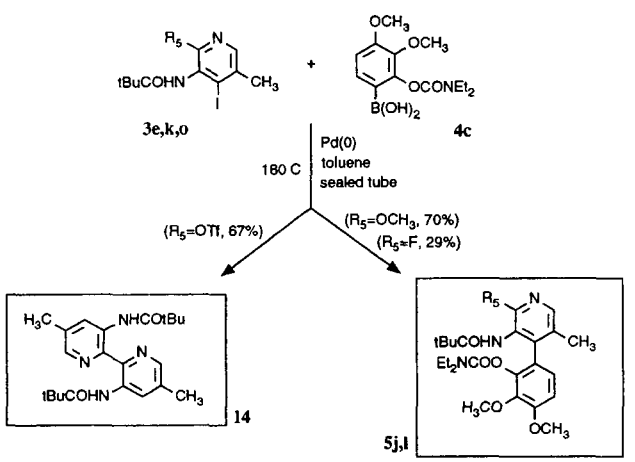
Thus, it could be advanced, in the cases studied, that the electron-withdrawing effect of substituents in the ortho position of the Ar–Pd–X bond in the transition state, make the substitution of halogen by a phenyl group easier.

Note that it has been observed that variable quantities of 4-unsubstituted pyridine is obtained when cross-coupling reaction does not occur, the explanation being a reducing procedure of the intermediate palladium complex.

As described by Suzuki and coworkers [7], yields of sterically hindered biaryls Pd(0) catalyzed cross-coupling could be improved by use of aqueous barium hydroxide as base. We observed that yields are improved by use of $Ba(OH)_2$ and different polar solvents and higher temperature (Table 2, entries 17, 18, 19). In these cases hydrolysis of carbamate or amide often occurs. Coupling reactions using fluoride anions are currently being studied.

Finally, cross-coupling of hindered reagents was carried out in a sealed tube at 180°C ($P = 8$ atm) (Scheme 12). A significant improvement in the yields was observed. Yields of 70% and 29% are obtained when $R_5 = OCH_3$ and $R_5 = F$ respectively (Table 1, entries 10 and 12). This could be compared with the 10% and 0% respective yields obtained at atmospheric pressure. However, yields are dependent on C-2 substituent on the pyridine ring. For example, triflate **3n** treated under the conditions described above afforded a reduced bipyridine **14** (Scheme 12).

Coupling reactions in a sealed tube between pyridine **3e** and phenylboronic acid **4c** to afford **5l** are particularly interesting because the methoxy groups can be subsequently transformed for the coupling of the quinoline moiety.



Scheme 12.

4. Conclusion

In conclusion, the strategy developed for the synthesis of *Streptonigrin* and *Lavendamycin* requires a heterobiaryl cross-coupling between a hindered 4-iodopyridine and an arylboronic acid. The yield of the coupling reaction was improved by use of barium hydroxide for synthesis of *Lavendamycin* models and by carrying out the reaction at higher temperature and under pressure for synthesis of *Streptonigrin* models. Substituted tricyclic molecules that are *Streptonigrin* and *Lavendamycin* are therefore more accessible.

5. Experimental

5.1. General data

The ^{1}H NMR spectra were obtained on a Varian T60 (60 MHz) spectrometer (recorded in ppm downfield from internal standard, TMS in $CDCl_3$ or HMDS in DMSO-d_6) or on a 200 MHz Bruker spectrometer (50 MHz for ^{13}C NMR spectra). Mass spectra were obtained on a Jeol D700 instrument, and elemental analyses were performed on a Carlo Erba CHN apparatus.

5.2. Solvent

Tetrahydrofuran (THF) was distilled from benzophenone/sodium and stored over 3 Å molecular sieves under argon atmosphere. The water content of the solvent was estimated by the modified Karl–Fischer method [10] to be below 45 ppm.

2-Chloro-5,6-dimethyl-3-fluoro-4-iodopyridine (3b). Compound **3b** was synthesized in four-steps starting from 5,6-dimethyl-3-nitro-2(1H)pyridone (**6a**).

2-Chloro-5,6-dimethyl-3-nitropyridine. A mixture of 5,6-dimethyl-3-nitro-2(1H)pyridone (**6a**) (2.44 g, 14.5 mmol), pyridine (0.38 g, 4.8 mmol) and phosphorus oxychloride (3.37 g, 22 mmol) in chlorobenzene (40 ml) was heated under reflux for 1 h. After cooling and evaporation in vacuo the crude product was treated with a dilute solution of Na_2CO_3. After filtration over Celite, the aqueous solution was extracted with dichloromethane. The extracts were dried over magnesium sulphate and evaporated under reduced pressure to give 2.49 g (92%) of 2-chloro-5,6-dimethyl-3-nitropyridine as a pale yellow solid.

^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, CH_3), 2.55 (s, 3H, CH_3), 8.00 (s, 1H, 4-H). Anal. Found: C, 45.31; H, 3.94; N, 14.94. $C_7H_7ClNO_2$. Calc.: C, 45.06; H, 3.78; N, 15.01. Melting point 68–69°C.

3-Amino-2-chloro-5,6-dimethylpyridine. A suspension of 2-chloro-5,6-dimethyl-3-nitropyridine (3.73 g, 20 mmols), iron dust (12 g, 0.21 mol) in ethanol (50 ml), water (10 ml) and HCl (12N) (0.5 ml) was heated in a waterbath with stirring for 1 h. The suspension was then filtered off and washed with ethanol. The organic layer was evaporated under reduced pressure and water was added. The aqueous solution was then treated with aqueous ammonia to pH = 7–8. After extraction with ethyl acetate, drying of the extracts with $MgSO_4$ and evaporation, 3-amino-2-chloro-5,6-dimethylpyridine was obtained (2.91 g, 93%) as orange crystals.

^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, 5-CH_3), 2.30 (s, 3H, 6-CH_3), 3.85 (s, 2H, NH_2), 6.80 (s, 1H, 4-H). Anal. Found:C, 53.61; H, 5.89; N, 17.92. $C_7H_9ClN_2$. Calc.: C, 53.68; H, 5.79; N, 17.89. Melting point 125–126°C.

2-Chloro-5,6-dimethyl-3-fluoropyridine (7). 3-Amino-2-chloro-5,6-dimethylpyridine (2.5 g, 16 mmols) was added to fluoroboric acid (6 ml of a 34% aqueous solution) and ethanol (8 ml). Gazeous ethyl nitrite was bubbled through the cooled solution (0–5°C). (Ethyl nitrite was prepared by addition of concentrated H_2SO_4 (1.6 g), water (7.2 ml) and ethanol (0.8 ml) to a solution of sodium nitrite (2.24 g) in water (7.2 ml) and ethanol (0.8 ml).) The intermediary diazonium salt precipitated. After 2 h, Et_2O (8 ml) was added to complete the precipitation of the salt. The latter was filtered off, washed with ethanol (3.2 ml) and petroleum ether (6.4 ml). 3-Pyridyl diazonium salt was then heated at 30°C in dry petroleum ether (32 ml). The solvent was then evaporated to dryness and the residue was dissolved in water (8 ml). Diethyl ether (3.2 ml) was added and the mixture neutralized with aqueous NaOH. Extraction with Et_2O, drying on $MgSO_4$ and evaporation afforded an orange oil which was purified by flash chromatography on silica gel (eluent hexane/ethyl acetate, 8:2) to give the expected fluoropyridine **7** (1.23 g, 48%) as a pale yellow solid.

^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H, 5-CH_3), 2.40 (s, 3H, 6-CH_3), 7.20 (d, 1H, 4-H, J(4H–F) = 9.5 Hz). ^{19}F NMR ($CDCl_3$): δ −125.51 (d, J(F–4H) = 9.5 Hz). Anal. Found: C, 52.56; H, 4.36; N, 8.67. C_7H_7ClFN Calc.: C, 52.68; H, 4.42; N, 8.78. Melting point < 45°C.

2-Chloro-5,6-dimethyl-3-fluoro-4-iodopyridine (3a). To a solution of LDA prepared at −78°C from *n*-butyllithium (7.0 mmol) and diisopropylamine (7.0 mmol) in THF (40 ml) was added dropwise at −78°C a solution of 2-chloro-5,6-dimethyl-3-fluoropyridine (**7**) (1.12 g, 7.0 mmol) in THF (10 ml). After stirring for 3 h at −78°C, iodine (1.78 g, 7.0 mmol) in THF (10 ml) was added. The reaction mixture was stirred for 1 h at −78°C before hydrolysis with water (50 ml). A few drops of a saturated solution of sodium thiosulfate were added before decantation, extraction with ether and drying on $MgSO_4$. Evaporation to dryness afforded a yellow solid which was purified by sublimation (80°C per 1 mmHg) to give compound **3a** (1.9 g, 95%).

^{1}H NMR ($CDCl_3$): δ 2.45 (s, 3H, 5-CH_3), 2.55 (d, 3H, 6-CH_3, J(CH3–F) = 1.5 Hz). ^{19}F NMR ($CDCl_3$): δ −98.94 (s). Anal. Found: C, 28.63; H, 2.00; N, 4.85. C_7H_6ClFIN. Calc.: C, 28.45; H, 2.12; N, 4.91. Melting point 113–114°C.

2-Chloro-5-methyl-3-nitropyridine (6c). 3.1 g (20 mmol) of 5-methyl-3-nitro-1H-pyridone (**6b**), 4.7 g (30.8 mmol) of phosphorus oxychloride and 0.47 g (6 mmol) of pyridine were added to 50 ml of chlorobenzene. The solution was refluxed for 1 h and concentrated after

cooling. Hydrolysis in a mixture of water and sodium carbonate followed by extraction with methylene chloride, drying over $MgSO_4$ and evaporation in vacuo gave 2.6 g (76%) of the expected compound which was purified by flash chromatography on silica gel (eluent cyclohexane/ethylic ether, 8 : 2).

^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H, 5-CH_3), 8.10 (d, 1H, 4-H, $J(4-6) = 2$ Hz), 8.45 (d, 1H, 6-H, $J(6-4) = 2$ Hz). Anal. Found: C, 42.07; H, 2.82; N, 16.20. $C_6H_5ClN_2O_2$. Calc.: C, 41.76; H, 2.92; N, 16.23. Melting point < 50°C.

*2-Methoxy-5-methyl-3-nitropyridine (**9a**).* A mixture of 2-chloro-5-methyl-3-nitropyridine (0.69 g, 4 mmol) and sodium methoxide, prepared from sodium (180 mg) in methanol (25 ml), was refluxed over a period of 6 h. Methanol was evaporated in vacuo. Water (5 ml) was added to the residue and the solution was extracted with CH_2Cl_2. The combined extracts were dried over anhydrous $MgSO_4$. CH_2Cl_2 was evaporated in vacuo and the residue was purified by recrystallization from a mixture of ethanol–water to give yellow crystals of the expected 2-methoxypyridine **9a**, 0.66 g (98%).

^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, 5-CH_3), 4.10 (s, 3H, OCH_3), 8.10 (d, 1H, 4-H, $J(4-6) = 2$ Hz), 8.25 (d, 1H, 6-H, $J(6-4) = 2$ Hz). Anal. Found: C, 50.27; H, 4.52; N, 16.88. $C_7H_8N_2O_3$. Calc.: C, 50.00; H, 4.79; N, 16.73. Melting point 76°C.

*5.2.1. General procedure A: O-alkylation of nitropyridones **6a** and **6b***

A suspension of the corresponding nitropyridone (8.0 mmol), silver carbonate (1.33 g, 4.82 mmol) and 2-iodopropane (1.64 g, 9.63 mmol) in dry toluene was stirred at room temperature in total darkness over two weeks. The precipitate of the corresponding silver iodide was filtered and washed with an aqueous solution of $NaHCO_3$. Extraction by CH_2Cl_2, drying over $MgSO_4$ and solvent removal afforded a crude product which was purified by preparative flash chromatography on silica gel (eluent ethylacetate/cyclohexane, 1 : 9) to give the corresponding isopropoxypyridine (**9b** or **9c**) in 85% and 90% yield respectively as a yellow prism.

*2-Isopropoxy-5-methyl-3-nitropyridine (**9b**).* ^{1}H NMR ($CDCl_3$): δ 1.35 (d, 6H, CH_3–^{i}Pr, $J = 8$ Hz), 2.30 (s, 3H, 5-CH_3), 5.35 (m, 1H, CH–^{i}Pr), $J = 8$ Hz), 8.00 (d, 1H, 4-H, $J(4-6) = 2$ Hz), 8.20 (d, 1H, 6-H, $J(6-4) = 2$ Hz). Anal. Found: C, 50.10; H, 6.20; N, 14.30. $C_9H_{12}N_2O_3$ Calc.: C, 50.09; H, 6.16; N, 14.28. Melting point 65°C.

*2-Isopropoxy-5,6-dimethyl-3-nitropyridine (**9c**).* ^{1}H NMR ($CDCl_3$): δ 1.4 (d, 6H, CH_3–^{i}Pr, $J = 8$ Hz), 2.25 (s, 3H, 5-CH_3), 2.45 (s, 3H, 6-CH_3), 5.50 (m, 1H, CH–^{i}Pr, $J = 8$ Hz), 8.05 (s, 1H, 4-H). Anal. Found: C, 57.25; H, 6.53; N, 13.15. $C_{10}H_{14}N_2O_3$. Calc.: C, 57.13; H, 6.71; N, 13.32. Melting point 60°C.

5.2.2. General procedures for the synthesis of 3-pivaloylaminopyridines

Procedure B: Synthesis of aminopyridines by catalytic reduction. Nitropyridines **9a**, **9b** and **9c** (5.0 g) dissolved in dry ethanol (200 ml) were hydrogenated over 10% Pd/C (0.5 g) at atmospheric pressure. After absorption of the calculated quantity of hydrogen, the solution was filtered through Celite and the solvent removed by evaporation. The crude products were purified by preparative flash chromatography on silica gel (eluent ethylacetate/cyclohexane, 8 : 2).

Procedure C: Synthesis of 3-pivaloylaminopyridines. A solution of the corresponding aminopyridine (0.27 mol) and triethylamine (27 g, 0.27 mol) in anhydrous ether (150 ml) was cooled to 0°C. Trimethyl acetyl chloride (33 g, 0.29 mol) was added dropwise into the solution so that the temperature did not rise by more than 5°C. The mixture was stirred at room temperature over 1 h, water (100 ml) was added and the solution neutralized to pH = 8–9 with an aqueous solution of $NaHCO_3$. Extraction with CH_2Cl_2 and evaporation in vacuo gave a crude product which was purified by preparative flash chromatography on silica gel (eluent).

*3-Amino-2-methoxy-5-methylpyridine (**11**).* This compound was obtained from nitropyridine (**9a**) in 90% yield as a white solid.

^{1}H NMR ($CDCl_3$): δ 2.15 (s, 3H, CH_3), 3.70 (broad s, 2H, NH_2), 3.95 (s, 3H, OCH_3), 6.70 (d, 1H, 4-H, $J(4-6) = 2$ Hz), 7.35 (d, 1H, 6-H, $J(6-4) = 2$ Hz). Anal. Found: C, 60.84; H, 7.33; N, 20.45. $C_7H_{10}N_2O$ Calc.: C, 60.85; H, 7.29; N, 20.27. Melting point 59°C.

*2,2-Dimethyl-N-(2-methoxy-5-methyl-3-pyridyl)propanamide (**10a**).* Compound **10a** was obtained in 98% yield as an oil (cyclohexane/ethyl ether, 8 : 2).

^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H, ^{t}Bu), 2.25 (s, 3H, 5-Me), 4.0 (s, 3H, OMe), 7.65 (d, 1H, 6-H, $J(6-4) = 2$ Hz), 7.95 (s, 1H, NH), 8.50 (d, 1H, 4-H, $J(4-6) = 2$ Hz). Anal. Found: C, 64.75; H, 8.10; N, 12.65. $C_{12}H_{18}N_2O_2$. Calc.: C, 64.83; H, 8.16; N, 12.60.

3-Amino-2-isopropoxy-5-methylpyridine. This compound was obtained in 95% yield as a brown oil.

^{1}H NMR ($CDCl_3$): δ 1.35 (d, 6H, CH_3–^{i}Pr, $J = 8$ Hz), 2.15 (s, 3H, 5-CH_3), 3.80 (broad s, 2H, NH_2), 5.35 (m, 1H, CH–^{i}Pr, $J = 8$ Hz), 6.65 (d, 1H, 4-H, $J(4-6) = 2$ Hz), 7.35 (d, 1H, 6-H, $J(6-4) = 2$ Hz). Anal. Found: C, 65.10; H, 8.30; N, 17.00. $C_9H_{14}N_2O$. Calc.: C, 65.06; H, 8.43; N, 16.87.

*2,2-Dimethyl-N-(2-isopropoxy-5-methyl-3-pyridyl)propanamide (**10b**).* This compound was obtained in 95% yield as a white solid (eluent cyclohexane/ethylether, 8:2).

^{1}H NMR ($CDCl_3$): δ 1.35 (m, 15H, Me–^{i}Pr and Me–^{t}Bu), 2.25 (s, 3H, 5-CH_3), 5.20 (m, 1H, CH–^{i}Pr), 7.60 (d, 1H, 6-H, $J(6–4) = 2$ Hz), 8.00 (s, 1H, NH), 8.50 (d, 1H, 4-H, $J(4–6) = 2$ Hz). Anal. Found: C, 67.30; H, 8.65; N, 11.20. $C_7H_{10}N_2O$. Calc.: C, 67.20; H, 8.80; N, 11.20. Melting point 65°C.

3-Amino-5,6-dimethyl-2-isopropoxypyridine. This compound was obtained in 95% as a brown oil.

^{1}H NMR ($CDCl_3$): δ 1.30 (d, 6H, CH_3–^{i}Pr, $J = 8$ Hz), 2.10 (s, 3H, 5-CH_3), 2.30 (s, 3H, 6-CH_3), 3.55 (broad s, 2H, NH_2), 5.35 (m, 1H, CH–^{i}Pr, $J = 8$ Hz), 6.70 (s, 1H, 4-H, $J(4–6) = 2$ Hz). Anal. Found: C, 66.32; H, 8.72; N, 15.30. $C_{10}H_{16}N_2O$. Calc.: C, 66.57; H, 8.94; N, 15.55.

*2,2-Dimethyl-N-(2-isopropoxy-5,6-dimethyl-3-pyridyl)-propanamide (**10c**).* This compound was obtained in 95% yield as a white solid (eluent cyclohexane/ethyl ether, 8:2).

^{1}H NMR ($CDCl_3$): δ 1.35 (m, 15H, Me–^{i}Pr and Me–^{t}Bu), 2.17 (s, 3H, 5-CH_3), 5.35 (m, 1H, CH–^{i}Pr), 7.95 (s, 1H, NH), 8.37 (s, 1H, 4-H). Anal. Found: C, 68.00; H, 9.10; N, 10.65. $C_{15}H_{24}N_2O_2$ Calc.: C, 68.15; H, 9.15; N, 10.59. Melting point 80°C.

*2-Methoxy-5-methyl-3-tertiobutoxycarbonylaminopyridine (**12**).* A solution of ditertbutyldicarbonate (6.09 g, 27.9 mmol), 3-amino-2-methoxy-3-pivaloylaminopyridine (**11**) (3.5 g, 25.36 mmol) in *tert*-butyl alcohol (30 ml) was heated under reflux for 4 h. Hydrolysis followed by evaporation of the solvents to dryness and extraction with CH_2Cl_2 gave a crude product which was purified by flash chromatography on silica gel (eluent hexane/ether, 8:2) to afford white crystals (6,0 g, 99%).

^{1}H NMR ($CDCl_3$): δ 1.50 (s, 9H, ^{t}Bu), 2.25 (s, 3H, 5-CH_3), 3.95 (s, 3H, OCH_3), 7.0 (m, 1H, NH), 7.55 (d, 1H, 6-H, $J(6–4) = 2$ Hz), 8.15 (d, 1H, 4-H, $J(4–6) = 2$ Hz). Anal. Found: C, 60.54; H, 7.70; N, 11.86. $C_{12}H_{18}N_2O_3$ Calc.: C, 60.48; H, 7.61; N, 11.75. Melting point 61°C.

5.2.3. General procedure D: Synthesis of 4-iodo-3-pivaloylaminopyridines

A solution of the corresponding 3-pivaloylaminopyridine **10** (25 mmol) and tetramethylethylenediamine (7.25 g, 62.5 mmol) in anhydrous tetrahydrofuran (150 ml) was cooled to −78°C. *n*-Butyllithium (62.5 mmol, 39 ml of 1.6 M in hexane) was slowly added. After 15 min the mixture was stirred at −25°C over a period (T_1), cooled to −78°C and a solution of iodine (62.5 mmol, 15.9 g) in anhydrous tetrahydrofuran was added dropwise. After 15 min at −78°C, the solution was heated to −25°C and stirred over a variable time (T_2) at this temperature. A few drops of a saturated aqueous solution of sodium thiosulphate were then added at 0°C to remove excess iodine. Extraction of the reaction mixture with CH_2Cl_2 and evaporation in vacuo, gave an oil which was purified by flash chromatography on silica gel (eluent cyclohexane/ethylacetate, 9:1).

*2,2-Dimethyl-N-(4-iodo-2-methoxy-5-methyl-3-pyridyl)-propanamide (**3e**).* $T_1 = 2$ h; $T_2 = 2$ h. Compound **3e** was obtained in 68% yield as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H, ^{t}Bu), 2.35 (s, 3H, 5-CH_3), 3.90 (s, 3H, OCH_3), 6.95 (s, 1H, NH), 7.75 (s, 1H, 6-H). Anal. Found: C, 41.60; H, 5.02; N, 7.82. $C_{12}H_{17}IN_2O_2$ Calc.: C, 41.39; H, 4.92; N, 8.04. Melting point 141°C.

*2,2-Dimethyl-N-(4-iodo-2-isopropoxy-5-methyl-3-pyridyl)propanamide (**3f**).* $T_1 = 45$ min; $T_2 = 3.5$ h. Compound **3f** was obtained in a 60% yield as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.27 to 1.36 (m, 15H, (CH_3)–^{i}Pr and ^{t}Bu), 2.35 (s, 3H, 5-CH_3), 2.17 (s, 3H, 6-CH_3), 5.20 (m, 1H, CH–^{i}Pr), 7.00 (s, 1H, NH), 8.79 (s, 1H, 6-H). Anal. Found: C, 44.66; H, 5.70; N, 7.35. $C_{14}H_{21}IN_2O_2$ Calc.: C, 44.69; H, 5.58; N, 7.44. Melting point 140°C.

*2,2-Dimethyl-N-(4-iodo-2-isopropoxy-5,6-dimethyl-3-pyridyl)propanamide (**3g**).* $T_1 = 45$ min; $T_2 = 3.5$ h. Compound **3g** was obtained in a 58% yield as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.26 to 1.36 (m, 15H, (CH_3)–^{i}Pr and ^{t}Bu), 2.37 (s, 3H, 5-CH_3), 2.46 (s, 3H, 6-CH_3), 5.25 (m, 1H, CH–^{i}Pr), 6.95 (s, 1H, NH). Anal. Found: C, 46.36; H, 6.00; N, 7.30. $C_{15}H_{23}IN_2O_2$. Calc.: C, 46.16; H, 5.94; N, 7.17. Melting point 130°C.

*4-Iodo-2-methoxy-5-methyl-3-tertiobutoxycarbonylaminopyridine (**3h**).* A solution of *tert*-butyllithium (31.5 ml, 47.3 mmol, 1.5 M in pentane) was added dropwise to a solution of 2-methoxy-5-methyl-3-tertiobutoxycarbonylaminopyridine **12** (4.5 g, 18.9 mmol) in THF (80 ml) at −78°C. After stirring at −78°C for 15 min and at −20°C for 3 h, the solution was cooled again to −78°C and iodine (12 g, 47.3 mmol) in THF (50 ml) was added dropwise. The mixture was then stirred at −10°C for 2 h. Usual workup afforded the crude 4-iodopyridine which was purified by flash chromatography on silica gel (eluent hexane/ether, 7:1) to afford compound **3h** as a white solid (3.23 g, 47%).

^{1}H NMR ($CDCl_3$): δ 1.50 (s, 9H, ^{t}Bu), 2.35 (s, 3H, 5-CH_3), 3.95 (s, 3H, OCH_3), 6.05 (br s, 1H, NH), 7.80 (s, 1H, 6-H). Anal. Found: C, 39.68; H, 4.50; N, 7.56.

$C_{12}H_{17}N_2O_3I$. Calc.: C, 39.57; H, 4.70; N, 7.69. Melting point 134°C.

*2,2-Dimethyl-N-(2-methoxy-4-iodo-3-pyridyl)propanamide (**3p**).* $T_1 = 2$ h; $T_2 = 2$ h. Compound **3p** was obtained in a 71% yield as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.40 (s, 9H, ^{t}Bu), 3.60 (s, 3H, OMe), 7.05 (m, 1H, NH), 7.35 (d, 1H, 5-H), 7.65 (d, 1H, 4-H). Anal. Found: C, 39.94; H, 4.57; N, 8.30. $C_{11}H_{15}N_2O_2I$. Calc.: C, 39.53; H, 4.52; N, 8.38. Melting point 166°C.

*5.2.4. General procedure E: Synthesis of 2-(4-Iodo-3-pivaloylaminopyridyl)triflates (**3n** and **3o**)*

(a) *Synthesis of the intermediate substrates obtained by cleavage of alkoxy groups*

To 10 mmol of alkoxyaryles dissolved in 100 ml of methylene chloride was added slowly (under argon) a solution of boron tribromide (50 mmol, 50 ml of 1.0 M in methylene chloride) at −78°C. The mixture was allowed to stir at room temperature over 10 h, then hydrolyzed at 0° and neutralized to pH 8–9. Extraction of the reaction mixture with methylene chloride and evaporation in vacuo gave a crude product which was purified by sublimation.

*4-Iodo-3-pivaloylamino-2-(1H)pyridone (intermediate of **3n**).* The yield was 91% and the compound was obtained as a white powder.

^{1}H NMR (DMSO-d_6): δ 1.15 (s, 9H, ^{t}Bu), 6.50 (d, 1H, 5-H, $J(5-6) = 5$ Hz), 6.95 (d, 1H, 6-H, $J(6-5) = 5$ Hz), 8.65 (m, 1H, NH). Anal. Found: C, 35.31; H, 4.31; N, 8.11. $C_{10}H_{13}N_2O_2I,H_2O$. Calc.: C, 35.52; H, 4.47; N, 8.28. Melting point 210°C (dec.).

*4-Iodo-5-methyl-3-pivaloylamino-2-(1H)pyridone (intermediate of **3o**).* The yield was 80% and the compound was obtained as a white powder.

^{1}H NMR (DMSO-d_6): δ 1.15 (s, 9H, ^{t}Bu), 2.05 (s, 3H, CH_3), 7.15 (s, 1H, 6-H), 8.65 (m, 1H, NH). Anal. Found: C, 37.73; H, 4.88; N, 7.83. $C_{11}H_{15}N_2O_2I,H_2O$. Calc.: C, 37.51; H, 4.86; N, 7.95. Melting point 206°C (dec.).

(b) *Synthesis of 2-pyridyltriflates*

The corresponding pyridone (3.0 mmol) was dissolved in pyridine (15 ml). Trifluoromethanesulfonic anhydrid (0.605 ml, 1.2 equiv.) was added dropwise to the cooled solution (0°C). After stirring at room temperature for 25 h, the mixture was hydrolyzed in an ice bath, neutralized with Na_2CO_3 and extracted with CH_2Cl_2.

*2-(4-Iodo-3-pivaloylaminopyridyl)triflate (**3n**).* Purification preparative flash chromatography on silica gel (eluent hexane/ether, 1:1). The yield was 91% and compound **3n** was obtained as a white powder.

^{1}H NMR (DMSO-d_6): δ 1.2 (s, 9H, ^{t}Bu), 7.95 (d, 1H, 5-H, $J(5-6) = 5$ Hz), 8.10 (d, 1H, 6-H, $J(6-5) = 5$ Hz), 9.55 (br. s, 1H, NH). Anal. Found: C, 29.58; H, 2.55, N, 6.15. $C_{11}H_{12}N_2O_4F_3IS$. Calc.: C, 29.21; H, 2.67; N, 6.19. Melting point 220°C (dec.).

*2-(4-Iodo-5-methyl-3-pivaloylaminopyridyl)triflate (**3o**).* Purification preparative flash chromatography on silica gel (eluent hexane/ether, 6:4). The yield was 82% and compound **3o** was obtained as a white solid.

^{1}H NMR ($CDCl_3$): 1.4 (s, 9H, ^{t}Bu), 2.50 (s, 3H, 5-CH_3), 7.2 (br. s, 1H, NH), 8.05 (s, 1H, 6-H). Anal. Found: C, 30.88; H, 2.98, N, 6.05. $C_{12}H_{14}N_2O_4F_3IS$. Calc.: C, 30.92; H, 3.03; N, 6.01. Melting point 214°C.

*2,2-Dimethyl-N-(4-iodo-2-methoxy-3-pyridyl)propanamide (**3p**).* This compound was already described in a previous paper [1a].

*5.2.4. General procedure F: synthesis of 2,2-dimethyl-N-(2-fluoro-4-iodo-3-pyridyl) propanamide (**3j** and **3h**)*

This procedure is identical to procedure C except that the mixture was refluxed over a period of 20 h.

*2,2-Dimethyl-N-(2-fluoro-4-iodo-3-pyridyl)propanamide (**3j**).* This compound was obtained as a white solid in a 64% yield (eluent cyclohexane/ethyl ether, 5:5).

^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9H, ^{t}Bu), 7.50 (d, 1H, NH), 7.60 (d, 1H, 5-H, $J(5-6) = 6$Hz), 7.80 (d, 1H, 6-H, $J(6-5) = 6$ Hz). Anal. Found: C, 37.50; H, 3.70; N, 8.68. $C_{10}H_{12}FIN_2O$. Calc.: C, 37.27; H, 3.72; N, 8.69. Melting point 132°C.

*2,2-Dimethyl-N-(2-fluoro-4-iodo-5-methyl-3-pyridyl)-propanamide (**3k**).* This compound was obtained as a white solid in 79% yield (eluent diethyl ether).

^{1}H NMR ($CDCl_3$): δ 1.30 (s, 9H, ^{t}Bu), 2.40 (s, 3H, CH_3), 7.50 (s, 1H, NH), 7.80 (s, 1H, 6-H). Anal. Found: C, 39.47; H, 4.22; N, 8.16. $C_{11}H_{14}FIN_2O$. Calc.: C, 39.28; H, 4.17; N, 8.33. Melting point 158°C.

5.2.5. Synthesis of other 4-iodopyridines

*3-Amino-4-iodo-2-methoxy-5-methylpyridine (**3i**).* A mixture of 4-iodo-5-methyl-2-methoxy-3-*tert*-butoxycarbonylaminopyridine (520 mg, 1.43 mmol) and 25 ml of a solution of trifluoroacetic acid and 1,2-dichloroethane (1/1) was heated for 4 h at 80°C. The solution was cooled to room temperature and neutralized to pH 8–9. Extraction with CH_2Cl_2, drying over $MgSO_4$ and evaporation in vacuo gave a crude product which was purified by preparative flash chromatography on silica gel (eluent hexane/ether, 7:3) to yield 340 mg (90%) of **3i** as an oil.

^{1}H NMR ($CDCl_3$): δ 2.30 (s, 3H, 5-CH_3), 4.0 (s, 3H, OCH_3), 4.30 (m, 2H, NH_2), 7.35 (s, 1H, 6-H).

Anal. Found: C, 32.26; H, 3.31; N, 10.47. $C_7H_9N_2OI$. Calc.: C, 31.81; H, 3.41; N, 10.60.

N-tert-butyl-N'-(2-fluoro-4-iodo-5-methyl-3-pyridyl) urea (3l). 3-Amino-2-fluoro-4-iodo-5-methylpyridine (**3d**) (1.0 g, 4.0 mmol) in THF (20 ml) was slowly added to a cold (−78°C) solution of lithium diisopropyl amidure (4.4 mmol) in THF (100 ml). The resulting mixture was stirred for 1 h at −78°C, before addition of *tert*-butyl isocyanate (7.1 mmol) in THF (10 ml). Stirring was continued for 2 h at −78°C before hydrolysis by water (20 ml). Extraction with CH_2Cl_2 (50 ml × 3), drying over $MgSO_4$ and solvent removal afforded a crude product which was crystallized from ethanol to yield 1.1 g (78%) of **3l**.

^{1}H NMR (DMSO-d_6): δ 1.30 (s, 9H, ^{t}Bu), 2.30 (s, 3H, CH_3), 6.20 (s, 1H, N'H), 7.50 (s, 1H, NH), 7.80 (s, 1H, 6-H). Anal. Found: C, 37.80; H, 4.50; N, 11.90. $C_{11}H_{15}FIN_3$. Calc.: C, 37.60; H, 4.27; N, 11.96. Melting point 206°C.

N-(4-iodo-2-methoxy-5-methyl-3-pyridyl)trifluoroacetamide (3m). To a solution of 3-amino-4-iodo-2-methoxy-5-methylpyridine (**3i**) (0.9 g, 3.75 mmol) in 50 ml anhydrous ether was added (at 0°C) triethylamine (0.52 g, 3.75 mmol) and trifluoroacetic anhydrid (0.83 g, 3.95 mmol). The reaction mixture was stirred at 0°C for 1 h and then hydrolyzed and neutralized with an aqueous solution of $NaHCO_3$ to pH 8–9. Extraction with CH_2Cl_2, drying over $MgSO_4$ and evaporation in vacuo gave a crude product which was purified by preparative flash chromatography on silica gel (eluent cyclohexane/ethyl ether, 7:3) to yield 1.16 g (95%) of **3m** as a white solid.

^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, 5-CH_3), 3.95 (s, 3H, OCH_3), 7.65 (s, 1H, NH), 7.90 (s, 1H, 6-H). Anal. Found: C, 29.99; H, 2.15; N, 7.75. $C_9H_8F_3IN_2O_2$. Calc.: C, 30.02; H, 2.24; N, 7.78. Melting point 164°C.

Synthesis of 4-bromo-5-methyl-3-nitropyridine (13d). The procedure used for the synthesis of compound **13d** is similar to that used by Cheng and coworkers [6] for the preparation of 4-chloro-2,3-dimethyl-5-nitropyridine.

3-Methyl-4-nitropyridine-N-oxide. This compound was obtained from 3-picoline-*N*-oxide in a raw yield of 75% as a yellow solid which was not purified.

^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 8.00 (d, 2H, 5-H, 6-H, J(5–6) = 5 Hz), 8.4 (s, 1H, 2-H). EIMS M^+@154.

3-Methyl-4-nitropyridine (13b). This compound was obtained in a raw yield of 84% as an oil.

^{1}H NMR ($CDCl_3$): δ 2.40 (s, 3H, CH_3), 7.80 (d, 2H, 5-H, 6-H, J(5–6) = 5 Hz), 8.90 (d, 2H, 2-H, 6-H).

3-Methyl-4(1H)pyridone. This compound was obtained in a raw yield of 84% as a dark oil.

^{1}H NMR ($CDCl_3$): δ 2.10 (s, 3H, CH_3), 6.60 (d, 1H, 5-H, J(5–6) = 7 Hz), 7.70 (s, 2H, 6-H, 2-H), 11.30 (s, 1H, OH).

3-Methyl-5-nitro-4(1H)pyridone (13c). This compound was obtained in a raw yield of 29% as a yellow solid which was not purified.

^{1}H NMR (CF_3COOD): δ 2.10 (s, 3H, CH_3), 8.20 (s, 1H, 2-H), 9.05 (s, 1H, 6-H). EIMS M^+@154.

4-Bromo-3-methyl-5-nitropyridine (13d). This compound was obtained as a yellow solid in 68% yield after purification by preparative flash chromatography on silica gel (eluent methylene chloride).

^{1}H NMR ($CDCl_3$): δ 2.50 (s, 3H, CH_3), 8.60 (s, 1H, 2-H), 8.80 (s, 1H, 6-H). Anal. Found: C, 32.95; H, 2.03; N, 12.79. $C_6H_5BrN_2O_2$. Calc.: C, 33.18; H, 2.30; N, 12.90. Melting point 198°C.

5.2.6. General procedure G: Cross-coupling reaction under Suzuki conditions

The corresponding arylboronic acid (3.96 mmol), 0.115 g (0.1 mmol) of tetrakistriphenyl phosphine palladium(0) and ethanol (1.7 ml) were added to a solution of the corresponding 4-iodopyridine (3.30 mmol) in toluene (30 ml) and aqueous sodium carbonate (3.3 ml, 2 M). The mixture was refluxed under argon for various times *t*. The aqueous layer was separated and extracted with CH_2Cl_2, the combined organic layers were removed under reduced pressure and the residue was purified by preparative flash chromatography on silica gel (eluent).

5.2.7. General procedure H: Cross-coupling reaction under modified Suzuki conditions

This procedure is identical to procedure G except that barium hydroxide was used instead of sodium carbonate.

2,2-Dimethyl-N-(2-(2-chloro-3-fluoro-4-pyridyl)phenyl)-propanamide (5a). This compound was obtained (t = 48 h) in 94% yield (procedure G) as a white solid and has already been described in a previous paper [1b].

2,2-Dimethyl-N-(2-(2-chloro-5,6-dimethyl-3-fluoro-4-pyridyl)phenyl)propanamide (5b). This compound was obtained (t = 48 h) in 75% yield (procedure G), (eluent hexane/ethylacetate, 8:2) as a white solid and was also obtained according to procedure H (t = 16 h) in 83% yield.

^{1}H NMR ($CDCl_3$): δ 1.05 (s, 9H, ^{t}Bu), 2.03 (s, 3H, CH_3), 2.52 (s, 3H, CH_3), 6.95 (s, 1H, NH), 7.13 (d, 1H, H_6), 7.27 (t, 1H, H_5), 7.46 (t, 1H, H_4), 8.02 (d, 1H, H_3), J(3–4) = 8.1 Hz, J(5–6) = 7.0 Hz. Anal. Found:

C, 64.67; H, 6.09; N, 8.19. $C_{18}H_{20}ClFNO_2$. Calc.: C, 64.57; H, 6.02; N, 8.37. Melting point 137–138°C.

*2-(2-Chloro-5,6-dimethyl-3-fluoro-4-pyridyl)aniline (**5b'**).* This compound was obtained ($t = 60$ h) in 87% yield (procedure H), (eluent hexane/ethylacetate, 8:2) as a white solid.

^{1}H NMR ($CDCl_3$): δ 2.07 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 3.47 (s, 2H, NH_2), 6.81 to 6.97 (m, 3H), 7.27 (dt, 1H). Anal. Found: C, 62.50; H, 4.74; N, 11.06. $C_{13}H_{12}ClFN_2$. Calc.: C, 62.28; H, 4.82; N, 11.17. Melting point 164–165°C.

*3-Amino-4-(2-(N,N-diethylcarbamoyloxy)-3,4-dimethoxyphenyl)-2-fluoropyridine (**5c**).* This compound was obtained ($t = 18$ h) in 84% yield (procedure G), (ether) as brown crystals.

^{1}H NMR ($CDCl_3$): δ 1.10 (t, 6H, CH_3), 3.30 (q, 6H, CH_2 and NH_2), 3.90 (s, 6H, OCH_3), 6.85 (m, 3H, 5-H and 2H, phenyl-H)), 7.50 (d, 1H, 6-H, $J(6-5) = 5$ Hz). Anal. Found: C, 59.41; H, 6.05; N, 11.34. $C_{18}H_{22}FN_3O_4$. Calc.: C, 59.50; H, 6.06; N, 11.57. Melting point 96–98°C.

*3-Amino-4-(2-N,N-diethylcarbamoyloxy-3,4-dimethoxyphenyl)-2-methoxy-5-methylpyridine (**5e**).* This compound was obtained ($t = 24$ h) in 20% yield (procedure G), (eluent hexane/ether, 3:7) as a white solid.

^{1}H NMR ($CDCl_3$): δ 0.99 (m, 6H, CH_3), 1.90 (s, 3H, CH_3), 3.08 (m, 2H, CH_2), 3.90 (s, 3H, OMe), 3.93 (s, 3H, OMe), 3.97 (s, 3H, OMe), 6.86 (d, 1H, 5'-H, $J = 5$ Hz), 6.91 (d, 1H, 6'-H, $J = 5$ Hz), 7.41 (s, 1H, 6-H). Anal. Found: C, 61.91; H, 7.29; N, 10.56. $C_{20}H_{27}N_3O_5$. Calc.: C, 61.68; H, 6.99; N, 10.79. Melting point 128°C.

*2,2-Dimethyl-N-(2-fluoro-4-(3,4-dimethoxyphenyl)-3-pyridyl)propanamide (**5f**).* This compound was obtained ($t = 18$ h) in 70% yield (procedure G), (eluent ether/cyclohexane, 5:5) as a yellow solid.

^{1}H NMR ($CDCl_3$): δ 1.07 (m, 15H, CH_3 and ^{t}Bu), 3.40 (q, 6H, CH_2), 3.90 (s, 6H, OCH_3), 6.80 (d, 2H, phenyl-H), 7.10 (d, 1H, 5-H, $J(5-6) = 5$ Hz), 8.10 (m, 2H, 6-H and NH). Anal. Found: C, 61.95; H, 6.77; N, 9.68. $C_{23}H_{30}FN_3O_5$. Calc.: C, 61.74; H, 6.71; N, 9.39. Melting point 132°C.

*2,2-Dimethyl-N-(2-methoxy-5-methyl-4-phenyl-3-pyridyl)propanamide (**5k**).* This compound was obtained ($t = 12$ h) in 89% yield (procedure G), (eluent ether/cyclohexane, 6:4) as a yellow solid.

^{1}H NMR ($CDCl_3$): δ 1.00 (m, 9H, ^{t}Bu), 2.00 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.65 (m, 1H, NH), 7.05–7.45 (m, 5H, phenyl-H), 8.00 (s, 1H, 6-H). Anal. Found: C, 72.45; H, 7.51; N, 9.40. $C_{18}H_{22}N_2O_2$. Calc.: C, 72.45; H, 7.43; N, 9.39. Melting point 215°C.

*2,2-Dimethyl-N-(2-methoxy-4-(2-methoxyphenyl)-5-methyl-3-pyridyl)propanamide (**5m**).* This compound was obtained ($t = 12$ h) in 34% yield (procedure G), (eluent ether/cyclohexane, 4:6) as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.00 (s, 9H, CH_3, ^{t}Bu), 2.00 (s, 3H, CH_3), 3.78 (s, 6H, OCH_3), 3.96 (s, 6H, OCH_3), 6.80 (m, 1H, NH), 6.96–7.12 (m, 3H, 3',4',5'-H), 7.30–7.39 (m, 1H, 6'-H), 7.98 (s, 1H, 6-H). Anal. Found: C, 69.54; H, 7.41; N, 8.55. $C_{19}H_{24}N_2O_3$. Calc.: C, 69.49; H, 7.36; N, 8.53. Melting point 156°C.

*2,2-Dimethyl-N-(2-methoxy-4-(3,4-dimethoxyphenyl)-5-methyl-3-pyridyl)propanamide (**5l**).* This compound was obtained ($t = 12$ h) in 10% yield (procedure G), (eluent ether/cyclohexane, 8:2) as a white solid.

^{1}H NMR ($CDCl_3$): δ 0.90–1.10 (m, 15H, CH_3 and ^{t}Bu), 1.93 (s, 3H, 5-CH_3), 3.00–3.30 (s, 4H, CH_2), 3.83 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 6.76 (d, 1H, 5'-H, $J(5'-6) = 8.6$ Hz), 6.90 (d, 1H, 6'-H, $J(6'-5') = 8.6$ Hz), 7.64 (m, 1H, NH), 7.90 (s, 1H, 6-H). Anal. Found: C, 63.16; H, 7.44; N, 8.52. $C_{25}H_{35}N_3O_6$. Calc.: C, 63.40; H, 7.45; N, 8.87. Melting point 132°C.

*N-(2-Methoxy-4-(2-methoxyphenyl)-5-methyl-3-pyridyl)-trifluoroacetamide (**5o**) and 3-amino-2-methoxy-4-(2-methoxy phenyl)-5-methylpyridine (**5'o**).* Coupling reaction of 4-iodo-5-methyl-2-methoxy-3-trifluoroacetylaminopyridine (**3o**) and 2-methoxyphenylboronic acid in the conditions described in procedure G ($t = 12$ h) afforded two compounds which could not be separated by the usual procedure. A 43% yield of **5'o** was estimated after hydrolysis of the mixture by aqueous NaOH (1 M).

*2-Methoxy-4-(2-methoxyphenyl)-5-methyl-3-trifluoroacetylaminopyridine (**5o**).* ^{1}H NMR ($CDCl_3$): δ 2.00 (s, 3H, CH_3), 3.75 (s, 6H, OCH_3), 3.95 (s, 3H, OCH_3), 6.85–7.10 (m, 3H, 3',4',5'-H), 7.25–7.55 (m, 1H, 6'-H), 7.65 (s, 1H, NH), 8.00 (s, 1H, 6-H).

*3-Amino-2-methoxy-4-(2-methoxyphenyl)-5-methylpyridine (**5'o**).* ^{1}H NMR ($CDCl_3$): δ 1.90 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.95 (s, 6H, OCH_3), 6.90–7.25 (m, 3H, 3',4',5'-H), 7.35–7.45 (m, 1H, 6'-H), 7.50 (s, 1H, 6-H). Anal. Found: C, 68.61; H, 6.70; N, 11.27. $C_{14}H_{16}N_2O_2$t. Calc.: C, 68.83; H, 6.60; N, 11.46.

*N-tert-Butyl-N'-(4-(N,N-diethylcarbamoyloxy)-3,4-dimethoxyphenyl)-2-fluoro-4-iodo-5-methyl-3-pyridyl) urea (**5n**).* This compound was obtained ($t = 18$ h) in a yield of 25% (procedure G), (eluent ether/cyclohexane, 5:5) as an oil.

^{1}H NMR (DMSO-d_6): δ 0.77–0.96 (comp. 6H, CH_3), 1.14 (s, 9H, ^{t}Bu), 2.00 (s, 3H, 5-CH_3), 2.97–3.28 (comp., 4H, CH_2), 3.70 (s, 3H, OCH_3), 3.83 (s, 3H,

OCH_3), 6.38 (s, 1H, NH), 6.58(s, 1H, NH), 6.81 (d, 1H, 6'-H, $J(6'-5') = 8.6$ Hz), 7.00 (d, 1H, 6'-H, $J(5'-6') = 8.6$ Hz), 7.85 (s, 1H, 6-H). Anal. Found: C, 60.55; H, 6.90; N, 11.85. $C_{24}H_{33}N_4O_5$. Calc.: C, 60.50; H, 6.93; N, 11.76. Melting point 132°C.

*4-(2-(N,N-Diethylcarbamoyloxy)-3,4-dimethoxyphenyl)-3-methyl-5-nitropyridine (**5p**).* This compound was obtained ($t = 18$ h) in 80% yield (procedure G) (eluent ether/cyclohexane, 5:5) as a yellow solid.

^{1}H NMR ($CDCl_3$): δ 1.10 (t, 6H, CH_3), 2.35 (s, 3H, CH_3), 3.30 (q, 4H, CH_2), 4.05 (s, 3H, OCH_3), 7.05 (s, 2H, phenyl-H), 8.80 (s, 1H, 2-H), 9.10 (s, 1H, 6-H). Anal. Found: C, 58.36; H, 5.75; N, 10.61. $C_{19}H_{23}N_3O_6$. Calc.: C, 58.61; H, 5.91; N, 10.80. Melting point 72°C.

*2,2-Dimethyl-N-(2-isopropoxy-5,6-dimethyl-4-(2-hydroxyphenyl)-3-pyridyl)propanamide (**5q**).* This compound was obtained ($t = 110$ h) in 40% yield (procedure H), (eluent cyclohexane/ethyl acetate, 9:1) as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.04 (s, 9H, ^{t}Bu), 1.28 to 1.36 (dd, 6H, CH_3–^{i}Pr), 1.86 (s, 3H, CH_3), 2.44 (s, 3H, CH_3), 5.33 (sept., 1H, CH–^{i}Pr), 6.72 (s, 1H, OH), 6.78 to 7.00 (m, 4H, phenyl-H + NH), 7.20 to 7.30 (m, 1H, phenyl-H). Anal. Found: C, 70.57; H, 7.86; N, 7.93. $C_{21}H_{28}N_2O_3$. Calc.: C, 70.76; H, 7.92; N, 7.86. Melting point 170°C.

5.2.8. Procedure I: Cross-coupling reaction in sealed tubes under Suzuki conditions

The procedure used was similar to procedure G but reactions were carried out in sealed tubes at 180°C over variable time t.

*2,2-Dimethyl-N-(2-fluoro-5-methyl-3,4-dimethoxyphenyl-3-pyridyl)propanamide (**5j**).* This compound was obtained ($t = 20$ h) in 29% yield (procedure I), (eluent hexane/ether, 6:4) as a white solid.

^{1}H NMR ($CDCl_3$): δ 1.10 (m, 15H, CH_3–^{t}Bu and CH_3–NEt_2); 2.10 (s, 3H, 5-CH_3); 3.30 (q, 4H, CH_2); 3.90 (s, 6H, OMe); 6.80 (s, 2H, phenyl-H); 7.90 (s, 2H, 6-H and NH). Anal. Found: C, 62.76; H, 7.07; N, 8.93. $C_{24}H_{32}FN_3O_5$. Calc.: C, 62.47; H, 6.94; N, 9.11. Melting point 174°C.

*2,2-Dimethyl-N-(2-methoxy-5-methyl-3,4-dimethoxyphenyl-3-pyridyl)propanamide (**5l**).* This compound was obtained ($t = 48$ h) in 70% yield (procedure I), (eluent hexane/ether, 8:2) as a white powder.

^{1}H NMR ($CDCl_3$): δ 0.90 to 1.10 (m, 15H, CH_3–^{t}Bu and CH_3–NEt_2); 1.93 (s, 3H, 5-CH_3); 3.0 to 3.30 (m, 4H, CH_2); 3.83 (s, 3H, OMe); 3.87 (s, 3H, OMe); 3.90 (s, 3H, OMe); 6.76 (d, 1H, 5-H'); 6.90 (d, 1H, 6-H'); 7.64 (m, 1H, NH); 7.90 (s, 1H, 6-H). Anal. Found: C, 62.96; H, 7.04; N, 8.52. $C_{25}H_{35}N_3O_6$. Calc.: C, 63.40; H, 7.45; N, 8.87. Melting point 132°C.

*5-Methyl-3-pivaloylaminobipyridine (**14**).* This compound was obtained ($t = 48$ h) in 67% yield (procedure I), (eluent ether/hexane, 7:3) as a white powder.

^{1}H NMR ($CDCl_3$): δ 1.35 (s, 9H, ^{t}Bu), 2.40 (s, 3H, 5-CH_3), 8.12 (d, 1H, 6-H), 9.05 (d, 1H, 4-H). Anal. Found: C, 69.02; H, 8.07; N, 14.52. $C_{22}H_{30}N_4O_2$. Calc.: C, 69.08; H, 7.90; N, 14.64. Melting point 230°C.

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