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# A synthetic approach to 2,3,4-substituted pyridines useful as scaffolds for tripeptidomimetics

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**Abstract**—The synthesis of 2,3,4-substituted pyridine derivatives useful as scaffolds in the development of peptidomimetics is described. The use of a variety of electrophiles in a halogen-dance reaction to produce 3-alkyl-2-fluoro-4-iodo-pyridine derivatives as 'functionalized scaffolds' and the possibility to differentiate between the reactivities of the two halogen handles have been explored. Coupling of amino acid derivatives in the 4-position of the pyridine was found to proceed efficiently by conversion of iodo-pyridine to a Grignard derivative, which was allowed to react with a protected amino aldehyde. Substitution of fluorine in the 2-position of the pyridine was found to be facile with alkoxide nucleophiles, whereas amines were much less reactive.


## 1. Introduction

Peptides are known to influence many vital physiological processes and thereby they constitute important lead compounds in medicinal chemistry research. However, poor pharmacokinetic properties such as low oral bioavailability and rapid enzymatic degradation make most peptides unsuitable as drugs. In addition, the conformational flexibility of peptides may reduce the receptor selectivity. These problems can be addressed by the design and synthesis of small rigid molecules known as peptidomimetics. In the interaction between a peptide and its receptor or enzyme, the peptide backbone serves as a scaffold which positions important amino acid side chains in defined spatial positions. One approach towards the development of peptidomimetics is to find rigid and physiologically stable structures that can replace the peptide backbone, i.e. providing a molecular framework to which the recognition elements can be anchored and correctly presented for the target structure.[1,2]

We have for some time been interested in the development of a general scaffold useful in mimetics of biologically active tripeptides or tripeptide sequences. A computer based design proposed a trisubstituted pyridine ring as a scaffold to which appropriate amino acids and side chain moieties should be attached in the 2-, 3- and 4-positions (Fig. 1). The suggested scaffold provides a rigid framework with a well defined geometry due to the aromaticity of the pyridine ring. There are no remaining amide bonds in the peptidomimetic; a feature that is desirable when developing new bioactive compounds. The nitrogen atom of the pyridine ring is positioned to mimic the electrostatics of the carbonyl oxygen of the original amide bond between the second and third residues of a tripeptide (Fig. 1). The middle amino acid of the tripeptide sequence is represented by the pyridine ring, which carries a side chain equivalent in position 3. The *N*-terminal amino acid moiety is attached to the 4-position of the pyridine ring via a carbonyl group, and the *C*-terminal amino acid moiety is attached to the 2-position via an amino or ether bridge. Here we report our findings towards the development of a facile synthetic strategy to produce these compounds. A main goal has been to allow the use of derivatives of the natural amino acids as building blocks,

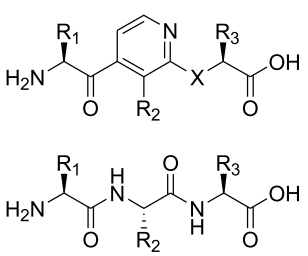


**Figure 1.** The proposed pyridine based tripeptidomimetic scaffold compared with a general tripeptide. $R_1$-$R_3$ are amino acid side-chains, X=NH or O.

*Keywords*: Peptidomimetic; Pyridine; Scaffold; Grignard reaction; Halogen-dance.

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thereby obtaining the correct stereochemistry of peptides and providing ready access to a variety of different tripeptidomimetic sequences.

## 2. Results and discussion

### 2.1. Retrosynthetic analysis

The synthetic strategy was based on an appropriately substituted pyridine derivative that should allow selective synthetic manipulations in one position without disturbing the others. This requirement was fulfilled by the 3-alkyl-2-fluoro-4-iodopyridine scaffold **1** (the 'functionalized scaffold'), as shown in the retrosynthetic analysis (Fig. 2). A fluorine atom activates the 2-position for nucleophilic substitution. For example, α-amino or α-hydroxy acid derivatives with an appropriately protected carboxylic acid functionality could be used as nucleophiles. The iodine in the 4-position of the pyridine ring could be envisioned to be useful in metal catalyzed coupling reactions with amino acid derivatives such as Weinreb's amides, amino acid chlorides or amino aldehydes. Thus, this synthetic strategy allows the use of natural amino acids as reagents for the substituents in the 2- and 4-positions of the pyridine scaffold. The side chain equivalent in the 3-position is attached by alkylation with an electrophile, which might limit the possibilities of making functionalized scaffolds corresponding to all natural amino acids. Regardless of this limitation, use of the functionalized pyridine scaffold with its two halogen handles with different reactivities seemed like a promising approach for preparation of tripeptidomimetics.

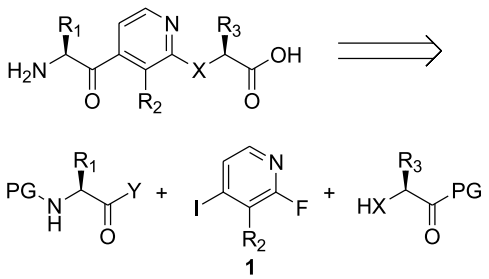


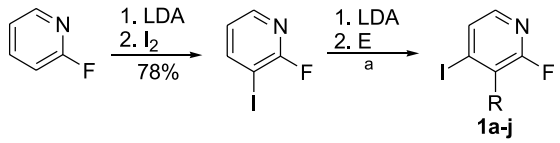

**Figure 2.** Retrosynthetic analysis of the tripeptidomimetic. $R_1$-$R_3$ are amino acid side-chains, X=NH or O, Y=N(OMe)(Me), Cl or H.

### 2.2. Synthesis of the functionalized scaffold

The functionalized scaffold **1** was obtained in two steps starting from commercially available 2-fluoropyridine according to the procedure by Queguiner.[3] 2-Fluoro-3-iodopyridine was synthesized from 2-fluoropyridine in 78% yield by reaction with LDA followed by addition of $I_2$ (Table 1).[4] In the following step, treatment with LDA is associated with a phenomenon commonly referred to as a 'halogen dance', whereby iodine migrates to the 4-position and the subsequently added electrophile is attached to the 3-position of the pyridine ring. The alkylating agents that are used should mimic the side chain of the middle amino acid of a tripeptide sequence.

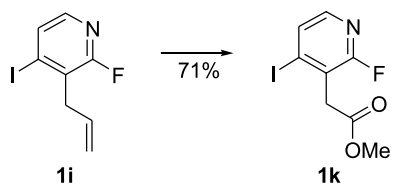
In addition to the previously reported compounds **1a**[3] and **1b**,[3] which in our application correspond to glycine (R=H) and alanine (R=Me), side chain equivalents of phenylalanine (R=Bn), leucine (R=isobutylene), threonine (R=$CH(OH)CH_3$) and the methyl ester of aspartic acid (R=$CH_2COOMe$) have successfully been introduced (Table 1 and Scheme 1). Treatment of the lithiated scaffold with benzyl bromide smoothly introduced a benzyl substituent thus producing the functionalized scaffold **1c**, corresponding to the phenylalanine side chain, in 71% yield. The direct introduction of an isobutyl group to afford the leucine mimetic **1d** proved unsuccessful using isobutyl bromide or isobutyl iodide as electrophiles, with or without the addition of TMEDA. However, when using isobutyric aldehyde, the expected alcohol **1e** was afforded in 96% yield. Removal of the hydroxyl group either directly or after modification to the tosylate[5] was not successful. Attempted catalytic hydrogenation in the presence of acid[6] or reduction with a variety of reagents ($Et_3SiH$/TFA, $NaBH_4$/TFA-AcOH,[7] HCOOH/triflic acid,[8] $NaCNBH_3/BF_3{\cdot}Et_2O$,[9] $LiAlH_4$[10] at various temperatures or $LiEt_3BH{\cdot}THF$[11]) either resulted in the isolation of unreacted starting material, or the deiodinated starting material, or gave esters formed from reactions of the alcohol with the different acids present. In one case, after refluxing the tosylate in toluene with DBU,[12] the elimination product was isolated in 55% yield. These findings indicated that the removal of the hydroxyl group would require several steps with possibilities of side reactions such as deiodination and this approach was therefore abandoned. Instead, the introduction of an isobutyl

**Table 1**. Introduction of substituents at the 3-position in the pyridine template




| Entry | Electrophile | R-group | Product | Yield (%) |
|---|---|---|---|---|
| 1 | $H_2O$ | H | **1a** | 80 |
| 2 | MeI | Me | **1b** | 89 |
| 3 | BnBr | Bn | **1c** | 71 |
| 4 | Isobutyl halide | Isobutyl | **1d** | ~0[b] |
| 5 | Isobutyric aldehyde | $Me_2CHCH(OH)$ | **1e** | 96 |
| 6 | Methallyl bromide | Isobutylene | **1f** | 93 |
| 7 | Acetaldehyde | MeCH(OH) | **1g** | 51 |
| 8 | Ethyl bromoacetate | $CH_2COOEt$ | **1h** | 13[c] |
| 9 | Allyl bromide | Allyl | **1i** | 87 |
| 10 | Ethyl acrylate | $CH_2CH_2COOEt$ | **1j** | ~0 |

[a]Reaction conditions: 2-fluoro-3-iodopyridine was reacted with LDA in THF at −78 °C for 1 h before the electrophile was added as a solution in THF.
[b] Isobutyl bromide and isobutyl iodide with or without TMEDA at −78 °C to −30 °C were used as electrophiles.
[c] See Scheme 1 for synthesis of the corresponding methyl ester.

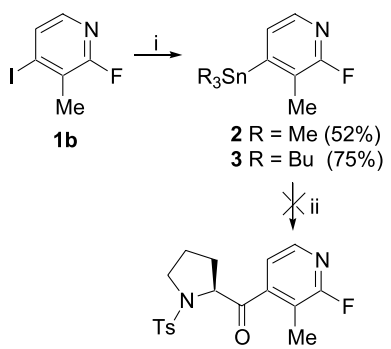



**Scheme 1.** Reagents and conditions: $O_3$, NaOH in MeOH, $CH_2Cl_2$, −78 °C, 15 min.

equivalent was performed by using 2-methyl-2-propenyl bromide as electrophile. Thereby a methallyl group was successfully introduced to afford **1f** in 93% yield. Since catalytic hydrogenation resulted in extensive deiodination of **1e**, no attempts to reduce the double bond at this stage were made. The hydrogenation is however not expected to be problematic after substitution of the iodine has been accomplished. The side chain corresponding to threonine was introduced by using acetaldehyde as electrophile to afford **1g** in 51% yield. The ester **1h**, corresponding to an aspartic acid residue, was isolated in only 13% yield after reaction with ethyl bromoacetate. To improve the yield, the desired product was instead synthesized in a two-step procedure; first an allyl group was introduced by using allyl bromide as electrophile to afford **1i** in 87% yield. The allyl group was then treated with ozone and methanolic sodium hydroxide in dichloromethane to afford the methyl ester **1k** in 71% yield (Scheme 1).[13] Attempts to introduce the side chain corresponding to glutamic acid by using ethyl acrylate as electrophile to afford **1j** were unsuccessful. However, the allyl substituent in **1i** could be useful as precursor for side chain equivalents of asparagine (via ester **1k**), glutamine and glutamate (via the primary alcohol). In subsequent studies of the reactivities of fluorine and iodine at the 2- and 4-positions of the functionalized scaffold, the methyl derivative **1b** was used.

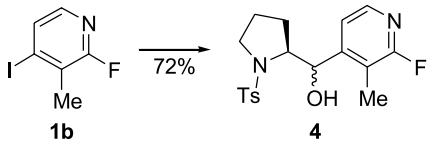
### 2.3. Introduction of the N-terminal amino acid moiety

The next step to explore was the possibility of introducing an amino acid moiety in the 4-position of the pyridine ring where the functionalized scaffold carries an iodine handle. The first approach was to perform the coupling via the corresponding tin derivative in a palladium catalyzed Stille cross-coupling reaction with an amino acid chloride.[14–16] Although this is a thoroughly explored reaction also for pyridine derivatives,[17–19] to our knowledge only one example of a Stille coupling with amino acid chlorides has previously been reported.[20] The trialkyl tin derivatives **2** and **3** were synthesized by reaction of **1b** with BuLi in THF at −78 °C followed by the addition of trialkyl tin chloride (Scheme 2). A test reaction between **2** and 3-phenyl-propionyl chloride succeeded at the first attempt using $Pd(PPh_3)_4$ as catalyst and CuI as additive producing the desired product in approximately 40% yield. Considerable effort was thereafter made to use amino acid chlorides such as Ts-Pro-COCl, Fmoc-Phe-COCl or Eoc-Phe-COCl in similar couplings. However, although a range of Pd-catalysts [$Pd(PPh_3)_4$, $Pd(OAc)_2$, $(PPh_3)_2PdCl_2$, $Pd_2(dba)_3$], ligands [dppf, dppe, $P(t\text{-}Bu)_3$, $AsPh_3$], co-catalysts and additives [CuI, CuCl, CuO, LiCl], solvents [benzene, DMSO, $CHCl_3$, DMF] and reaction temperatures [25, 60 and 80 °C] were explored, the desired coupling reaction between the pyridine scaffold and an amino acid chloride was never realized.



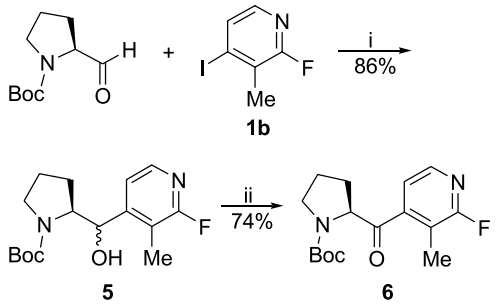

**Scheme 2.** Reagents and conditions: (i) (1) BuLi, THF, −78 °C, 1 h; (2) $R_3SnCl$, −78 °C, 1–1.5 h. (ii) Ts-ProCOCl, Pd-catalyst, co-catalyst, additive, solvent and temperature were varied as specified in the text.

The disappointing results from the Stille reactions led us to investigate the reactivity of the 4-lithiated scaffold. It was found that the Weinreb's amide of Eoc-protected phenylalanine could be coupled to **1b** by using 2 equiv. of BuLi in the presence of TMEDA. The use of TMEDA was found to be required but even so, the yield was only around 10%. An aldehyde, Ts-Pro-CHO,[21,22] showed higher reactivity and coupling under the same conditions, and by using 2 equiv. of the pyridine derivative, the reaction proceeded in approximately 60% yield. Finally, a pyridine Grignard derivative proved to be excellent for the coupling reaction in the 4-position of the pyridine.[23] Reaction of 1 equiv. of **1b** with *i*PrMgCl in THF at room temperature followed by the addition of Ts-Pro-CHO afforded the desired product **4** in 72% yield (Scheme 3). The reaction proceeded very cleanly and no additional purification was needed after work-up by extraction. $^{13}C$ NMR spectra of the crude product show signals for CH–OH at $\delta$ 71.26 and 71.22, respectively, which indicates that the two diastereomers were formed in equal amounts.




**Scheme 3.** Reagents and conditions: (1) *i*PrMgCl, THF, rt, 1.5 h; (2) Ts-Pro-CHO, rt, o.n.

Encouraged by these results, use of a Boc-protected amino aldehyde instead of the tosyl protected one was also attempted. It was found that the reaction proceeded nicely with Boc-Pro-CHO‡ providing **5** in 86% yield with a diastereomeric ratio of 1:3 according to $^1H$ NMR analysis. To afford the desired amino acid moiety in the 4-position, alcohol **5** was oxidized using Dess–Martin periodinane to give ketone **6** in 74% yield (Scheme 4). The optical purity of



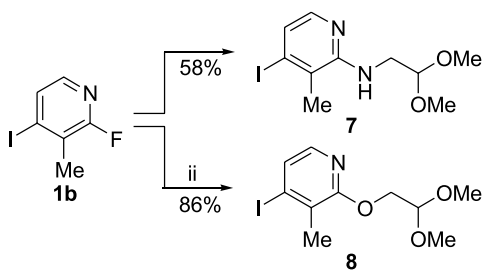

**Scheme 4.** Reagents and conditions: (i) (1) *i*PrMgCl, THF, rt, 1 h; (2) Boc-Pro-CHO, rt, o.n. (ii) Dess–Martin periodinane, $CH_2Cl_2$, rt, 3 h.

‡ Boc-Pro-CHO was synthesized according to Ref. 22 or obtained commercially from Aldrich.

**6** was confirmed by chiral HPLC analysis on a Pirkle Covalent (S,S)-Whelk-O 1 10/100 Krom Fec column using dichloromethane–isopropanol–heptane (48:4:48) as eluent. A single peak was observed in the chromatogram for **6** which was compared to a chromatogram obtained from the racemate.[§]

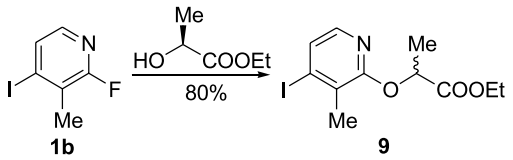
### 2.4. Introduction of the C-terminal amino acid moiety

The introduction of amino acid equivalents in the 2-position of the functionalized scaffold by nucleophilic substitution of fluorine was thereafter investigated. At first, the reactivity of nitrogen versus oxygen nucleophiles was compared using glycine aldehyde dimethyl acetal and the corresponding alcohol analogue (Scheme 5). It was found that the amine required quite harsh reaction conditions; the substitution was performed using the amino acetal as solvent at 140 °C. The reaction was stopped after 4.5 h when a byproduct was detected by TLC and the product **7** was isolated in 58% yield. The byproduct was isolated in 4% yield and found to be the 4-substituted derivative, i.e. the 4-iodo group had been substituted instead of the fluorine atom.[¶] The glycolaldehyde dimethylacetal was tested and found to react considerably faster than the amino analogue; after deprotonation by NaH the substitution went smoothly at room temperature in THF and the expected product **8** was isolated in 86% yield. The poor reactivity of amino acid analogues under these conditions was confirmed by a test reaction with the amino acid glycine in DMF. After 20 h at 140 °C the starting material was still intact according to TLC analysis.




**Scheme 5.** Reagents and conditions: (i) glycine aldehyde dimethyl acetal, 140 °C, 4.5 h. (ii) glycol aldehyde dimethyl acetal, NaH, THF, rt, o.n.

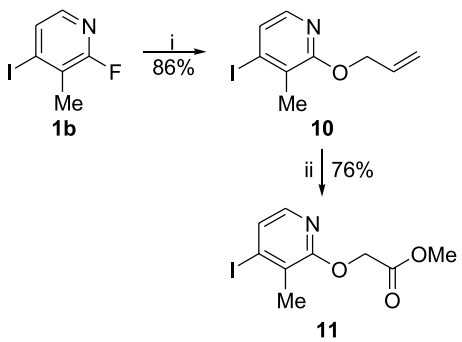
The above findings indicated that considerable problems would probably be experienced using regular amino acids as nucleophiles in the substitution at the 2-position of the scaffold. In addition, the conversion of the acetal functionality of **8** into an aldehyde or ester was unsuccessful although several different reaction conditions were explored [$CrO_3$/AcOH,[24] Oxone®/wet $Al_2O_3$,[25] trichloroisocyanuric acid,[26] AcOH/$H_2O$,[27] wet $SiO_2$/oxalic acid or $H_2SO_4$,[28,29] Amberlite® IR-120,[30] formic acid,[31] Amberlyst® 15,[30] $TiCl_4$/LiI,[32] *p*TsOH,[33] $BF_3{\cdot}Et_2O$/LiI,[34] ozone[35]]. The synthesis of derivatives with an ether bridge between the pyridine ring and the amino acid residue in the 2-position was therefore further explored. It was found that L-ethyl lactate could be used as nucleophile after deprotonation




**Scheme 6.** Reagents and conditions: NaH, THF, rt to 60 °C, o.n.

with NaH in a 0.2 M solution in THF (higher concentration caused problems with polymerization) at 60 °C (Scheme 6). It was important not to have an excess of NaH, since that resulted in deiodination of the starting material. However, even though the ether **9** was isolated in a satisfactory 80% yield, it was found both by chiral HPLC analysis and by measurement of optical rotation that the optical activity of the product was lost under these reaction conditions. To examine whether the racemization of the product was caused by the excess of nucleophile, 1 equiv. of L- and D-methyl lactate, respectively, were reacted with **1b** using KH as base. Chiral HPLC analysis (MTBE–heptane 5:95) showed that even when the reaction was stopped after 30 min at room temperature (before complete consumption of the starting material), the product was almost completely racemized (er 56:44).

It was not possible to use the ethyl ester of glycolic acid as a nucleophile together with NaH due to problems with polymerization. This was not unexpected as there is less steric hindrance in the glycolate compared to the lactate. Another route for the introduction of a glycolate ester was therefore employed. Use of allyl alcohol together with NaH in THF allowed a smooth reaction to take place at room temperature and the allyl ether **10** was isolated in 86% yield. The methyl ester **11** could then be afforded from the alkene in 76% yield by treatment with ozone and NaOH/MeOH in $CH_2Cl_2$ (Scheme 7).




**Scheme 7.** Reagents and conditions: (i) Allyl alcohol, NaH, THF, rt, 0.5 h. (ii) $O_3$, NaOH in MeOH, $CH_2Cl_2$, −78 °C, 1.5 h.

## 3. Conclusion

We have developed a synthetic strategy towards trisubstituted pyridine derivatives based on a functionalized scaffold that provides the possibility of selective manipulation of one position without disturbing the others. Efficient introduction of substituents in the 3- and 4-positions of the pyridine scaffold has been accomplished, whereas more work is needed to provide access to chiral amino acid derived nucleophiles suitable for substitution in the 2-position.

[§] The racemate was produced by treatment of **6** with DBU in refluxing THF.

[¶] According to $^1H$ NMR and $^{19}F$ NMR analysis.

## 4. Experimental

### 4.1. General data

THF was distilled from potassium/sodium. $^1$H and $^{13}$C NMR spectra were obtained on a Bruker DRX-400 (399.53 MHz) or a JEOL Eclipse 400 (399.78 MHz) spectrometer using residual peak of solvent as internal reference; $CDCl_3$ [$CHCl_3$ $\delta_H$ 7.26, $CDCl_3$ $\delta_C$ 77.0]. TLC analysis was performed on Silica Gel $F_{254}$ (Merck) and detection was carried out by examination under UV light and staining with phosphomolybdic acid. Flash column chromatography was performed on Silica Gel (Matrex, 60 Å, 35–70 μm, Grace Amicon). Chiral HPLC chromatography was performed on a Pirkle Covalent (S,S)-Whelk-O 1 10/100 Krom Fec column. After work-up, all organic phases were dried with $MgSO_4$. All new compounds were determined to be >95% pure by $^1$H NMR and $^{13}$C NMR spectroscopy. For the synthesis of compounds **1a** and **1b** see Ref. 3.

### 4.2. General procedure for the synthesis of 2-fluoro-4-iodo-3-substituted pyridine derivatives

LDA was prepared by the addition of diisopropylamine (0.63 mL, 4.48 mmol) to freshly distilled THF (10 mL) in a dry two-necked round bottomed flask kept under nitrogen atmosphere. The solution was cooled to −78 °C before 1.6 M *n*-BuLi in hexane (2.80 mL, 4.48 mmol) was added and the resulting clear, colorless solution was stirred for 15 min. 2-Fluoro-3-iodopyridine (1.00 g, 4.48 mmol) was added as a solution in THF (2 mL) whereby the reaction immediately turned bright yellow. The mixture was stirred for 1 h at −78 °C before the electrophile (4.48 mmol) was added with syringe (neat or as a solution in THF). After the indicated reaction times (see below), the mixture was quenched by the addition of $H_2O$ and extracted into $Et_2O$. The pooled organic phases were washed with brine, dried and evaporated to yield the crude product.

**4.2.1. 3-Benzyl-2-fluoro-4-iodo-pyridine (1c).** LDA (20 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (18 mmol) as described above. After the addition of benzyl bromide (2.4 mL, 20 mmol), the reaction was allowed to reach room temperature while stirred over night. Work-up as described above afforded a crude product which was purified by flash chromatography (EtOAc–heptane 1:10) to yield **1c** (4.0 g, 71%) as a yellow oil; $\delta$ $^1$H NMR ($CDCl_3$) 7.75–7.71 (m, 1H), 7.67–7.63 (m, 1H), 7.33–7.20 (m, 5H), 4.19 (s, 2H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.68 (d, $J_{C-F}$=242.2 Hz), 145.63 (d, $J_{C-F}$=16.2 Hz), 137.26, 132.69 (d, $J_{C-F}$=4.4 Hz), 128.53 (4 C:s), 127.12 (d, $J_{C-F}$=32.3), 126.68, 114.88 (d, $J_{C-F}$=4.0 Hz), 38.63; IR (neat) 2360 (w), 1579, 1544, 1441, 1394 cm$^{-1}$; HRMS (FAB+) calcd for $C_{12}H_9FIN$ $(M+H)^+$ 313.9842, found 313.9845.

**4.2.2. 1-(2-Fluoro-4-iodo-pyridin-3-yl)-2-methyl-propan-1-ol (1e).** LDA (4.48 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (4.48 mmol) as described above. After the addition of isobutyraldehyde (0.41 mL, 4.48 mmol), the reaction was stirred for 2 h at −78 °C. Work-up as described above afforded a crude product which was purified by flash chromatography (EtOAc–heptane 1:10 then 1:5) to yield **1e** (1.27 g, 96%) as a non-viscous, colorless oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.63 (d, 1H, *J*=5.3 Hz), 7.58 (d, 1H, *J*=5.3 Hz), 4.56 (d, 1H, *J*=9.1 Hz), 3.03 (br s, 1H), 2.24 (m, 1H), 1.11 (d, 3H, *J*=6.7 Hz), 0.75 (d, 3H, *J*=6.7 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.61 (d, $J_{C-F}$=244.5 Hz), 145.75 (d, $J_{C-F}$=16.8 Hz), 132.94 (d, $J_{C-F}$=4.0 Hz), 128.65 (d, $J_{C-F}$=27.6 Hz), 113.01 (d, $J_{C-F}$=5.4 Hz), 81.36 (d, $J_{C-F}$=3.7 Hz), 33.66 (d, $J_{C-F}$=2.7 Hz), 19.20, 18.97; IR ($CH_2Cl_2$ cast) 3389 (br), 3083 (w), 2961, 2871, 1581, 1539, 1444, 1401 cm$^{-1}$; HRMS (EI+) calcd for $C_9H_{11}FINO$ $(M)^+$ 294.9869, found 294.9871.

**4.2.3. 2-Fluoro-4-iodo-3-(2-methyl-allyl)-pyridine (1f).** LDA (4.48 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (4.48 mmol) as described above. After the addition of 3-bromo-2-methyl-1-propene (0.47 mL, 4.48 mmol), the reaction was stirred for 2 h at −78 °C and then for 2.5 h at −45 °C. Work-up as described above afforded 1.22 g of a yellow-brown clear light crude oil. Purification by distillation at reduced pressure afforded **1f** (1.15 g, 93%) as a non-viscous, colorless oil, which solidified upon standing: mp 38–40 °C; $^1$H NMR ($CDCl_3$) $\delta$ 7.69 (dd, 1H, *J*=5.2 Hz, 0.7 Hz), 7.60 (d, 1H, *J*=5.2 Hz), 4.80 (m, 1H), 4.41 (m, 1H), 3.44 (s, 2H), 1.78 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.52 (d, $J_{C-F}$=242.5 Hz), 145.42 (d, $J_{C-F}$=15.8 Hz), 140.60, 132.46 (d, $J_{C-F}$=4.4 Hz), 125.86 (d, $J_{C-F}$=32.3 Hz), 115.13 (d, $J_{C-F}$=4.4 Hz), 112.09, 40.60 (d, $J_{C-F}$=1.3 Hz), 22.90; IR ($CH_2Cl_2$ cast) 3082 (w), 2974 (w), 1581, 1547, 1444, 1403 cm$^{-1}$; HRMS (CI) calcd for $C_9H_{10}FIN$ $(M+H)^+$ 277.9842, found 277.9837. Anal. calcd for $C_9H_9FIN$: C, 39.1; H, 3.3; N, 5.1. Found: C, 39.3; H, 3.4; N, 5.2.

**4.2.4. 1-(2-Fluoro-4-iodo-pyridin-3-yl)-ethanol (1g).** LDA (0.49 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (0.45 mmol) as described above. After the addition of acetaldehyde (0.028 mL, 0.49 mmol), the reaction was stirred for 2 h at −78 °C. Work-up as described above afforded a crude oil which was purified by flash chromatography (EtOAc–heptane 1:5) to yield **1g** (62 mg, 51%) as an oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.73 (d, 1H, *J*=5.2 Hz), 7.64 (d, 1H, *J*=5.2 Hz), 5.16 (q, 1H, *J*=6.7 Hz), 1.59 (dd, 3H, *J*=6.7, 1.2 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 159.99 (d, $J_{C-F}$=242.9 Hz), 146.14 (d, $J_{C-F}$=17.2 Hz), 132.97 (d, $J_{C-F}$=4.4 Hz), 129.72 (d, $J_{C-F}$=27.3 Hz), 110.97 (d, $J_{C-F}$=5.4 Hz), 72.92 (d, $J_{C-F}$=2.7 Hz), 22.23 (d, $J_{C-F}$=2.4 Hz); IR ($CH_2Cl_2$ cast) 3360 (br), 3084 (w), 2976, 2929, 1580, 1546, 1443, 1402 cm$^{-1}$; HRMS (FAB+) calcd for $C_7H_8FINO$ $(M+H)^+$ 267.9635, found 267.9641.

**4.2.5. 3-Allyl-2-fluoro-4-iodo-pyridine (1i).** LDA (4.93 mmol) was prepared and reacted with 2-fluoro-3-iodopyridine (4.48 mmol) as described above. After the addition of allyl bromide (0.43 mL, 4.93 mmol), the reaction was allowed to reach room temperature over night. Work-up as described above afforded a brown crude oil which was purified by distillation under reduced pressure to afford **1i** (1.03 g, 87%) as an oil; $^1$H NMR ($CDCl_3$) $\delta$ 7.70 (d, 1H, *J*=5.2 Hz), 7.62 (d, 1H, *J*=5.2 Hz), 5.86 (ddt, 1H, *J*=16.6, 10.2, 6.2 Hz), 5.15–5.07 (m, 2H), 3.55 (app dq, 2H, *J*=6.2, 1.4 Hz); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.46 (d, $J_{C-F}$=242.8 Hz), 145.46 (d, $J_{C-F}$=15.8 Hz), 132.51 (d,

$J_{C-F}$=4.7 Hz), 132.46, 125.98 (d, $J_{C-F}$=32.3 Hz), 117.19, 114.25 (d, $J_{C-F}$=4.4 Hz), 37.20 (d, $J_{C-F}$=1.4 Hz); IR ($CH_2Cl_2$ cast) 3303 (w), 3081, 2981, 2921, 1639, 1580, 1544, 1444, 1401 $cm^{-1}$; HRMS (FAB+) calcd for $C_8H_8FIN$ $(M+H)^+$ 263.9685, found 263.9697.

**4.2.6. Methyl 2-(2-fluoro-4-iodo-pyridin-3-yl)-acetate (1k).** The allyl derivative **1i** (24 mg, 0.091 mmol) was dissolved in $CH_2Cl_2$ (2 mL). NaOH (0.46 mmol) was added as a 2.5 M solution in MeOH and the reaction was cooled to −78 °C, whereafter ozone was passed through the solution which immediately turned orange. After 15 min, the solution turned blue and the ozone generator was switched off to allow oxygen to pass through the reaction mixture until the color disappeared. After addition of $H_2O$–$Et_2O$ (1:1, 2 mL) the reaction was allowed to reach room temperature. The mixture was extracted into $Et_2O$, the combined organic phases were washed with brine, dried and evaporated to afford a crude oil which was purified by flash chromatography (EtOAc–heptane 1:9) to yield **1k** (19 mg, 71%) as a white solid; $^1H$ NMR ($CDCl_3$) $\delta$ 7.78 (d, 1H, $J$=5.2 Hz), 7.65 (d, 1H, $J$=5.2 Hz), 3.87 (s, 2H), 3.74 (s, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 169.05, 160.64 (d, $J_{C-F}$= 243.5 Hz), 146.52 (d, $J_{C-F}$=15.8 Hz), 132.39 (d, $J_{C-F}$= 4.0 Hz), 121.65 (d, $J_{C-F}$=32.7 Hz), 115.16, 52.52, 38.70; IR ($CH_2Cl_2$ cast) 2951 (w), 1737 (s), 1584, 1540, 1435, 1399 $cm^{-1}$; HRMS (FAB+) calcd for $C_8H_8FINO_2$ $(M+H)^+$ 295.9584, found 295.9579.

### 4.3. 2-Fluoro-3-methyl-4-trimethylstannyl-pyridine (2)

The pyridine derivative **1b** (3.1 g, 13 mmol) was dissolved in THF (30 mL) and the solution was cooled to −78 °C. BuLi (1.6 M, 9.1 mL) was added dropwise and the reaction was stirred for 1 h before trimethyl tin chloride (2.9 g, 14 mmol) was added as a solution in THF (15 mL). The reaction was stirred for 1 h before it was allowed to reach room temperature. $H_2O$ was added and the mixture was extracted into $Et_2O$, dried and evaporated to yield a crude yellowish oil which was purified by sublimation under vacuum to collect most of the starting material as crystals, followed by flash chromatography ($CH_2Cl_2$–MeOH–hexane 8:1:10) of the remaining oil to afford **2** (1.9 g, 52%) as an oil; $^1H$ NMR ($CDCl_3$) $\delta$ 7.95 (d, 1H, $J$=4.9 Hz), 7.17 (dd, 1H, $J$=4.9, 2.6 Hz), 2.33 (d, 3H, $J$=1.5 Hz), 0.38 (s, 9H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 161.73 (d, $J_{C-F}$=243.5 Hz), 159.44, 143.42 (d, $J_{C-F}$=12.5 Hz), 128.25 (d, $J_{C-F}$= 4.0 Hz), 125.51 (d, $J_{C-F}$=26.9 Hz), 16.91 (d, $J_{C-F}$= 1.7 Hz), −8.72 (3 C:s); HRMS (FAB+) calcd for $C_9H_{15}FNSn$ $(M+H)^+$ 276.0211, found 276.0215.

### 4.4. 2-Fluoro-3-methyl-4-tributylstannyl-pyridine (3)

The pyridine derivative **1b** (2.2 g, 8.0 mmol) was dissolved in THF (30 mL) and the solution was cooled to −78 °C. BuLi (1.6 M, 5.5 mL) was added and the reaction was stirred for 1 h before tributyl tin chloride (2.2 mL, 8.8 mmol) was added. The reaction was stirred for 1.5 h before it was quenched with $H_2O$ (50 mL) and allowed to reach room temperature. The mixture was extracted into $Et_2O$, dried and evaporated to yield a crude semi-solid which was purified by flash chromatography ($Et_2O$–hexane 1:19) to afford **3** (2.4 g, 75%) as a non-viscous, colorless oil; $^1H$ NMR ($CDCl_3$) $\delta$ 7.93 (d, 1H, $J$=4.7 Hz), 7.15 (dd, 1H, $J$=4.7, 2.6 Hz), 2.30 (d, 3H, $J$=1.6 Hz), 1.56–1.45 (m, 6H), 1.32 (sextet, 6H, $J$=7.3 Hz), 1.16–1.09 (m, 6H), 0.88 (t, 9H, $J$=7.3 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 161.78 (d, $J_{C-F}$= 243.5 Hz), 160.01 (d, $J_{C-F}$=1.0 Hz), 143.29 (d, $J_{C-F}$= 12.5 Hz), 128.89 (d, $J_{C-F}$=4.0 Hz), 125.62 (d, $J_{C-F}$= 26.6 Hz), 28.95 (3 C:s), 27.92 (3 C:s), 17.25 (d, $J_{C-F}$= 1.7 Hz), 13.56 (3 C:s), 10.29 (3 C:s); HRMS (FAB+) calcd for $C_{18}H_{33}FNSn$ $(M+H)^+$ 402.1619, found 402.1624.

### 4.5. 1-(2-Fluoro-3-methyl-pyridin-4-yl)-1-[(*S*)-1-(*p*-toluylsulfonyl)-pyrrolidin-2-yl]methanol (4)

The pyridine derivative **1b** (100 mg, 0.42 mmol) was dissolved in freshly distilled THF (1 mL) and kept under nitrogen atmosphere. Isopropyl magnesium chloride (0.21 mL, 0.42 mmol, 2.0 M in THF) was added with syringe. A white precipitate was formed immediately. After 1.5 h, Ts-Pro-CHO (0.11 g, 0.42 mmol) was added with syringe as a solution in THF (1 mL). The reaction mixture turned clear and was stirred at room temperature over night before it was quenched by the addition of $H_2O$ (2 mL). The mixture was extracted into $CH_2Cl_2$, dried and evaporated to yield **4** (111 mg, 72%) as a solid with dr 1:1 according to $^{13}C$ NMR analysis; $\delta$ $^1H$ NMR ($CDCl_3$) 7.96 (d, 1H, $J$=5.2 Hz), 7.67 (d, 2H, $J$=8.3 Hz), 7.38 (d, 1H, $J$=5.2 Hz), 7.28 (d, 2H, $J$=8.3 Hz), 5.55 (d, 1H, $J$=2.0 Hz), 3.85 (br s, 1H), 3.66–3.60 (m, 1H), 3.48–3.40 (m, 1H), 3.34–3.26 (m, 1H), 2.37 (s, 3H), 2.33 (s, 3H), 1.91–1.78 (m, 2H), 1.28–1.11 (m, 2H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 162.04 (d, $J_{C-F}$= 236.8 Hz), 153.34 (d, $J_{C-F}$=5.4 Hz), 144.02 (d, $J_{C-F}$= 15.2 Hz), 143.85, 133.67, 129.78 (2 C:s), 127.30 (2 C:s), 119.00 (d, $J_{C-F}$=3.7 Hz), 116.06 (d, $J_{C-F}$=31.7 Hz), 71.26 (CH–OH), 71.22 (CH–OH), 62.94, 50.34, 24.84, 24.71, 21.35, 10.54; IR ($CH_2Cl_2$ cast) 3297 (br), 2953, 2872, 1611, 1567, 1453, 1410, 1344, 1157 $cm^{-1}$; HRMS (FAB+) calcd for $C_{18}H_{22}FN_2O_3S$ $(M+H)^+$ 365.1335, found 365.1333.

### 4.6. 1-((*S*)-1-*tert*-Butoxycarbonylpyrrolidin-2-yl)-1-[(2-fluoro-3-methyl-pyridin-4-yl)]-methanol (5)

The pyridine derivative **1b** (100 mg, 0.42 mmol) was dissolved in freshly distilled THF (1 mL) and kept under nitrogen atmosphere. Isopropyl magnesium chloride (0.21 mL, 0.42 mmol, 2.0 M in THF) was added with syringe. A white precipitate was formed immediately. After 1 h, Boc-Pro-CHO (84 mg, 0.42 mmol) was added as a solution in THF (0.5 mL). The reaction mixture turned clear and was stirred at room temperature over night before it was quenched by the addition of $H_2O$. The mixture was extracted into $Et_2O$, the combined organic phases were washed with brine, dried and evaporated to yield a crude yellow oil (dr 1:3 according to $^1H$ NMR analysis). Purification by flash chromatography (EtOAc–heptane 1:3 then 1:1) afforded the diastereomeric alcohols of **5** (113 mg, 86% combined yield) as a colorless oil. Partial separation allowed the isolation of respective pure isomer for characterization: *Major isomer* $[\alpha]_D$=−14.2 (*c* 1.0, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 7.99 (s, 1H), 7.26 (s, 1H), 4.84 (d, 1H, $J$=7.9 Hz), 4.18–4.09 (m, 1H), 3.50–3.23 (m, 2H), 2.26 (s, 3H), 1.83–1.57 (m, 3H), 1.47 (s, 9H), 1.38–1.26 (m, 1H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 162.24 (d, $J_{C-F}$=237.1), 158.23, 154.46 (d, $J_{C-F}$=4.7 Hz), 144.32 (d, $J_{C-F}$=

15.5 Hz), 120.17, 117.41 (d, $J_{C-F}$=31.7 Hz), 81.16, 74.12. 63.55, 47.64, 28.31 (3 C:s), 28.09, 24.02, 10.83; IR ($CH_2Cl_2$ cast) 3372 (br), 3054 (w), 2977, 2934, 2886, 2360, 2341, 1682, 1404 $cm^{-1}$; HRMS (FAB+) calcd for $C_{16}H_{24}FN_2O_3$ $(M+H)^+$ 311.1771, found 311.1768. *Minor isomer* $[\alpha]_D$=−34.8 (*c* 1.0, $CH_2Cl_2$); $^1H$ NMR ($CDCl_3$) $\delta$ 8.01 (s, 1H), 7.33 (s, 1H), 5.41 (s, 1H), 4.27–3.89 (m, 1H), 3.71–3.01 (m, 3H), 2.31 (s, 3H), 1.99–1.56 (m, 4H), 1.52–1.48 (m, 9H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 162.16 (d, $J_{C-F}$=237.8 Hz), 155.85 (br), 153.86, 143.93 (d, $J_{C-F}$=12.1 Hz), 119.46, 116.42 (br), 80.49, 70.27, 61.21 (br), 48.09, 28.52 (3 C:s), 25.76, 24.05, 10.94; IR ($CH_2Cl_2$ cast) 3371 (br), 2978, 2921, 2889, 2358, 2339, 1692, 1403 $cm^{-1}$; HRMS (FAB+) calcd for $C_{16}H_{24}FN_2O_3$ $(M+H)^+$ 311.1771, found 311.1773.

### 4.7. (*S*)-4-(1-*tert*-Butoxycarbonylpyrrolidin-2-oyl)-2-fluoro-3-methyl-pyridine (6)

The diastereomeric mixture of **5** (30 mg, 0.097 mmol) was dissolved in dry $CH_2Cl_2$ (1 mL). Dess–Martin periodinane (0.41 mL, 0.19 mmol) was added as a 15% wt solution in $CH_2Cl_2$. The reaction was stirred for 3 h at room temperature before it was quenched with $Na_2S_2O_3$ (0.28 g, 1.13 mmol) dissolved in $NaHCO_3$ (aq. sat.). The mixture was extracted into $Et_2O$, the combined organic phases were washed with $NaHCO_3$ (aq. sat.) and brine, dried and evaporated to yield **6** (22 mg, 74%) as an oil: $[\alpha]_D$=−3.5 (*c* 1.0, MeOH); $^1H$ NMR ($CDCl_3$) $\delta$ major [minor] rotamer (ratio 3:2) 8.11 [8.16] (d, 1H, *J*=5.1 Hz), 7.40 [7.27] (d, 1H, *J*=5.1 Hz), 4.94–4.85 (m, 1H), 3.71–3.39 (m, 2H), 2.31 (s, 3H), 2.23–2.11 (m, 1H), 2.03–1.76 (m, 3H), 1.44 [1.38] (s, 9H); $^{13}C$ NMR ($CDCl_3$) $\delta$ major [minor] rotamer (ratio 3:2) 202.39 [200.69], 162.72 [162.87] (d, $J_{C-F}$=239.8 Hz), 154.48 [153.52], 149.32 [148.47], 144.68 [144.94] (d, $J_{C-F}$=14.8 Hz), 119.09 [118.85], 118.40 [118.08], 80.13 [80.42], 63.85, 46.82 [46.67], 28.82 [29.37], 28.33 (3 C:s), 24.32 [23.11], 11.35 [11.54]; IR ($CH_2Cl_2$ cast) 3038 (w), 2977, 2934, 2882, 1693, 1602, 1556, 1402 $cm^{-1}$; HRMS (FAB+) calcd for $C_{16}H_{22}FN_2O_3$ $(M+H)^+$ 309.1614, found 309.1617. Chiral HPLC using $CH_2Cl_2$–*i*PrOH–heptane (48:4:48) as eluent, retention time 5.1 min.

The racemate of **6** was produced by treating **6** (2 mg, 6.5 μmol) with DBU (10 μL, 65 μmol) in refluxing THF for 7 h: Chiral HPLC using $CH_2Cl_2$–*i*PrOH–heptane (48:4:48) as eluent, retention time 4.3 and 5.1 min, respectively.

### 4.8. 2-(2,2-Dimethoxyethylamino)-4-iodo-3-methyl-pyridine (7)

The pyridine derivative **1b** (0.10 g, 0.42 mmol) was dissolved in glycine aldehyde dimethyl acetal (0.23 mL, 2.1 mmol) and heated to 140 °C. After 1.5 h, more amine (0.23 mL, 2.1 mmol) was added. The reaction was stopped after 4.5 h when the formation of a by-product was detected by TLC. After cooling, the mixture was diluted with $CH_2Cl_2$ (5 mL) and washed with 0.05 M HCl, $H_2O$ and brine. The organic phase was dried and evaporated to yield a brown solid which was purified by flash chromatography ($CH_2Cl_2$–MeOH–hexane 5:1:20) to afford **7** (79 mg, 58%) as a white semi-solid; $\delta$ $^1H$ NMR ($CDCl_3$) 7.55 (d, 1H, *J*=5.3 Hz), 7.03 (d, 1H, *J*=5.3 Hz), 4.77–4.55 (m, 1H), 4.52 (t, 1H, *J*=5.5 Hz), 3.59 (app t, 2H, *J*=5.5 Hz), 3.41 (s, 6H), 2.26 (s, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 155.72, 145.34, 123.65, 120.12, 111.87, 102.80, 54.25 (2 C:s), 43.31, 21.80; IR ($CH_2Cl_2$ cast) 3399 (w), 2978 (w), 2936 (w), 2360, 2340, 1691, 1567, 1398 $cm^{-1}$; HRMS (FAB+) calcd for $C_{10}H_{16}IN_2O_2$ $(M+H)^+$ 323.0257, found 323.0232.

### 4.9. 2-(2,2-Dimethoxy-ethoxy)-4-iodo-3-methyl-pyridine (8)

Glycol aldehyde dimethyl acetal (1.1 g, 10 mmol) was dissolved in THF (2.5 mL) and NaH (0.25 g, 5.8 mmol, 55% in mineral oil) was added carefully. After the gas evolution ceased, the pyridine derivative **1b** (0.50 g, 2.1 mmol) was added as a solution in THF (2.5 mL). The reaction was stirred over night before it was quenched by the addition of $H_2O$ and extracted into $CH_2Cl_2$. The combined organic phases were dried and evaporated to yield a crude oil which was purified by flash chromatography (EtOAc–heptane 1:10) to afford **8** (0.59 g, 86%) as a non-viscous, colorless oil; $^1H$ NMR ($CDCl_3$) $\delta$ 7.56 (d, 1H, *J*=5.3 Hz), 7.29 (d, 1H, *J*=5.3 Hz), 4.75 (t, 1H, *J*=5.4 Hz), 4.34 (d, 2H, *J*=5.4 Hz), 3.43 (s, 6H), 2.34 (s, 3H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 160.39, 143.85, 127.66, 125.17, 112.89, 101.74, 65.34, 53.89 (2 C:s), 20.60; IR ($CH_2Cl_2$ cast) 3042 (w), 2952, 2831, 1563, 1445, 1411, 1386, 1135, 1077 $cm^{-1}$; HRMS (FAB+) calcd for $C_{10}H_{15}INO_3$ $(M+H)^+$ 324.0097, found 324.0099.

### 4.10. (*R*,*S*)-Ethyl 2-(4-Iodo-3-methyl-pyridin-2-yloxy)-propanoate (9)

L-Ethyl lactate (2.5 g, 21 mmol) was dissolved in THF (100 mL) and 55% NaH in mineral oil (0.46 g, 10 mmol) was added carefully. The reaction was allowed to stir until the gas evolution ceased (almost 2 h) and the solution was clear with no solid particles before the pyridine derivative **1b** (1.0 g, 4.2 mmol) was added as a solution in THF (15 mL). The reaction was heated to 60 °C and allowed to stir over night before it was cooled to room temperature, quenched with $H_2O$ and extracted into $Et_2O$. The combined organic phases were washed with brine, dried and evaporated to yield a crude oil which was purified by flash chromatography ($CH_2Cl_2$–MeOH–heptane 5:1:50) to afford the racemate **9** (1.1 g, 80%) as a non-viscous, colorless oil; $\delta$ $^1H$ NMR ($CDCl_3$) 7.49 (d, 1H, *J*=5.3 Hz), 7.27 (d, 1H, *J*=5.3 Hz), 5.23 (q, 1H, *J*=7.0 Hz), 4.17 (q, 2H, *J*=7.1 Hz), 2.37 (s, 3H), 1.59 (d, 3H, *J*=7.0 Hz), 1.22 (t, 3H, *J*=7.1 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 172.15, 159.64, 143.55, 127.83, 124.87, 112.98, 70.36, 60.78, 20.45, 17.53, 14.03; IR ($CH_2Cl_2$ cast) 3044 (w), 2984, 2938, 1752, 1561, 1402, 1177, 1098 $cm^{-1}$; HRMS (FAB+) calcd for $C_{11}H_{15}INO_3$ $(M+H)^+$ 336.0097, found 336.0092.

### 4.11. 2-Allyloxy-4-iodo-3-methyl-pyridine (10)

Allyl alcohol (0.50 mL, 7.4 mmol) was dissolved in THF (4 mL) and NaH (0.14 g, 3.6 mmol, 60% in mineral oil) was added carefully. After the gas evolution ceased the pyridine derivative **1b** (0.35 g, 1.5 mmol) was added as a solution in THF (2 mL). The reaction was allowed to stir at room temperature for 0.5 h before it was quenched with $H_2O$ and extracted into EtOAc. The combined organic phases were washed with brine, dried and evaporated to yield a crude product which was purified by flash chromatography

(EtOAc–heptane 1:20) to afford **10** (0.35 g, 86%) as a colorless oil; $\delta$ $^1$H NMR ($CDCl_3$) 7.57 (d, 1H, $J$=5.3 Hz), 7.28 (d, 1H, $J$=5.3 Hz), 6.08 (ddt, 1H, $J$=17.2, 10.4, 5.2 Hz), 5.38 (ddt, 1H, $J$=17.2, 1.6, 1.6 Hz), 5.23 (ddt, 1H, $J$=10.4, 1.6, 1.6 Hz), 4.82 (ddd, 2H, $J$=5.2, 1.6, 1.6 Hz), 2.35 (s, 3H); $^{13}$C NMR ($CDCl_3$) $\delta$ 160.51, 143.86, 133.42, 127.35, 125.08, 116.94, 112.76, 66.86, 20.60; IR ($CH_2Cl_2$ cast) 3080 (w), 2988 (w), 2936, 1563, 1401, 1334, 1259, 1175, 1007 cm$^{-1}$; HRMS (FAB+) calcd for $C_9H_{11}INO$ $(M+H)^+$ 275.9885, found 275.9883.

### 4.12. Methyl (4-iodo-3-methyl-pyridin-2-yloxy)-acetate (11)

The pyridine derivative **10** (52 mg, 0.19 mmol) was dissolved in $CH_2Cl_2$ (2 mL) and NaOH in MeOH (2.5 M, 0.40 mL) was added. The solution was cooled to −78 °C before ozone was bubbled through. The reaction turned dark-yellow immediately and the color disappeared gradually until it was clear and colorless with a yellow precipitate after 80 min. The ozone generator was switched off after another 10 min when the reaction turned blue and $O_2$ was allowed to pass through until the solution was colorless. $H_2O$–$Et_2O$ (1:1, 2 mL) was added and the mixture was allowed to reach room temperature. Additional $H_2O$ was added and the reaction mixture was extracted into $Et_2O$. The combined organic phases were washed with brine, dried and evaporated to yield **11** (44 mg, 76%) as an oil; $\delta$ $^1$H NMR ($CDCl_3$) 7.53 (d, 1H, $J$=5.3 Hz), 7.32 (d, 1H, $J$=5.3 Hz), 4.88 (s, 2H), 3.75 (s, 3H), 2.39 (s, 3H); $\delta$ $^{13}$C NMR ($CDCl_3$) 169.61, 159.53, 143.65, 128.26, 125.11, 113.22, 62.74, 51.98, 20.49; IR ($CH_2Cl_2$ cast) 2998 (w), 2951, 1762, 1567, 1428, 1397, 1215, 1175, 1073 cm$^{-1}$; HRMS (FAB+) calcd for $C_9H_{11}INO_3$ $(M+H)^+$ 307.9784, found 307.9792.

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