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New Enantioselective Synthesis of Monofluorinated Pyridines Designed for the Preparation of Chemical Libraries

Anne-Laure Blayo,[a] Stéphanie Le Meur,[b] Danielle Grée,[a,*] and René Grée[a]

[a] Université de Rennes 1, Laboratoire de Synthèse et Electrosynthèse Organiques, CNRS UMR 6510, Avenue du Général Leclerc, 35042 Rennes Cedex, France
Fax: (+33)-(0)2-2323-6978; e-mail: danielle.gree@univ-rennes1.fr
[b] Bioprojet Biotech, 4 rue du Chesnay Beauregard, BP 96205, 35762 Saint Grégoire, France

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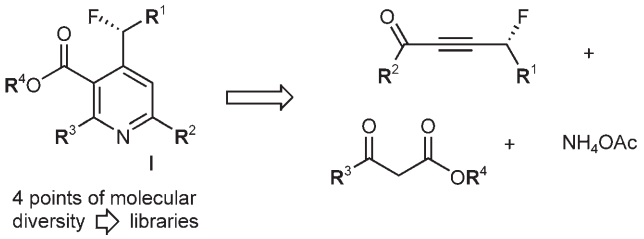
Abstract: Chiral pyridines with a fluorine atom in the benzylic position are easily accessible from optically active propargylic fluorides by using the Bohlmann–Rahtz reaction. Such pyridines, possessing four points of molecular diversity, are useful scaffolds for the preparation of chemical libraries.

Keywords: chemical libraries; fluorides; fluorination; pyridines

Introduction

The pyridine nucleus has been recognized from long time ago as an important component for biological activity in various types of natural products and for their synthetic analogues. Therefore, this skeleton is widely represented as a privileged scaffold in bioorganic and medicinal chemistry and several thousands of pyridine-containing molecules are found in drugs and in agrochemicals.[1] On the other hand, it is well known that the introduction of fluorine in organic molecules strongly modifies their physical, chemical and biological activities and this has been also of much use in fluorobiorganic chemistry.[2] Therefore pyridines bearing one or several fluorine atom(s), either on the heteroaromatic nucleus or on the side chains, appear particularly attractive and many examples of such molecules have been already described in medicinal chemistry.[1,2] As part of our research programme on the design of new strategies for the enantioselective synthesis of monofluorinated molecules,[3] we became interested in the preparation of optically active pyridines with a fluorine in benzylic position. To date, very few molecules of this sort have been synthesized and there is no general strategy to prepare them.[4] Of particular interest to us were the type **I** pyridines which possess four points of molecular diversity and therefore would be suitable for the preparation of chemical libraries.

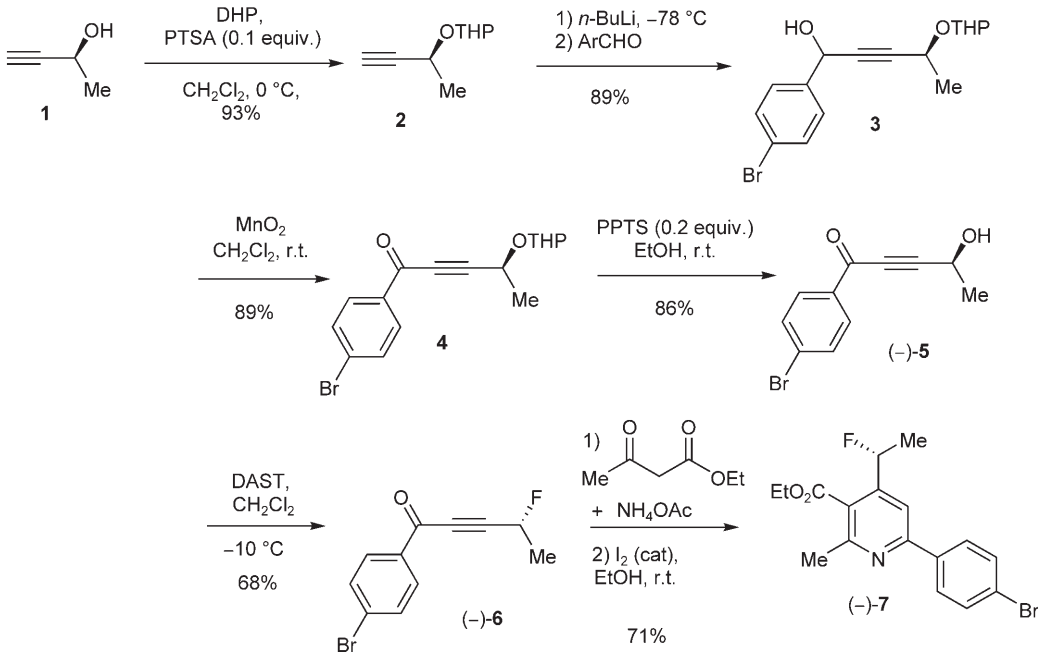
The strategy we have designed towards these target molecules, involved the Bohlman–Rahtz reaction[5] under the conditions described by Bagley (Scheme 1).[6] This approach used, as the key intermediates, optically active propargylic fluorides which are easily accessible by the routes we have reported recently.[7,8] The goal of this publication is to describe our preliminary results in this area with (i) an efficient preparation of the key pyridine (−)-**7**, selected as a model and (ii) the use of this intermediate in several organic and Pd-catalyzed coupling reactions. We will demonstrate also that all these molecules have been obtained in high *ee*s (>94%).



Scheme 1. Retrosynthetic analysis for the preparation of type **I** pyridines.

Results and Discussion

The synthesis of the first key intermediate, the propargylic fluoride (−)-**6**, is indicated in Scheme 2. Starting from commercially available (*S*)-butynol **1**, the propargylic alcohol (−)-**5** was obtained in four straightforward steps: protection as THP ether,[9] followed by condensation of corresponding anion with *p*-bromobenzaldehyde, oxidation and THP deprotec-



Scheme 2. Synthesis of pyridine (−)-**7**.

tion. Analysis by HPLC on a chiral stationary phase demonstrated that the intermediate (−)-**5** had a very high *ee* (>98%).

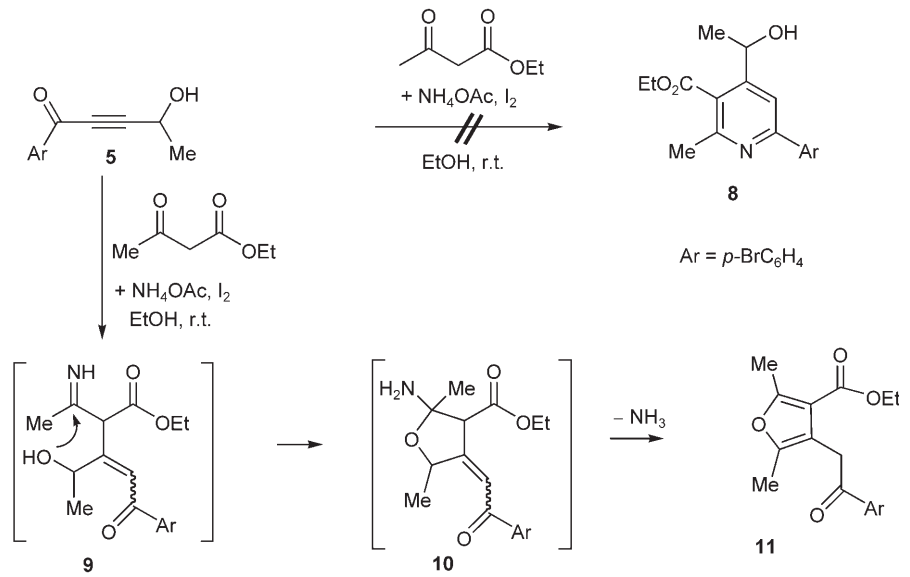
The dehydroxyfluorination step was performed using diethylaminosulfur trifluoride (DAST),[10] and after optimization of the reaction conditions (CH_2Cl_2 at −10°C), the propargylic fluoride (−)-**6** was obtained in 68% yield. It was not possible to establish the enantiomeric purity of this fluoride either by chiral HPLC or by NMR in the presence of Eu(hfc)$_3$, a common problem in this series of compounds.[11] However, since it will be demonstrated in the next part that the pyridines obtained from (−)-**6** have very high *ee*s (>94%), it is clear that this dehydroxyfluorination step occurs with inversion of configuration[12] and very little racemization, if any.

The next step was the synthesis of the pyridine (−)-**7** through the Bohlmann–Rahtz condensation.[5] This reaction, performed under the reaction conditions described by Bagley,[6] gave the desired pyridine in 71% yield. Once again, it was not possible to measure the *ee* on this intermediate by chiral HPLC since no separation of the peaks was observed on the corresponding racemic compound (±)-**7** by using five different columns. However, measurements by ^{19}F NMR in the presence of the chiral shift reagent Eu(hfc)$_3$ clearly demonstrated that this key pyridine intermediate had *ee* >94%.

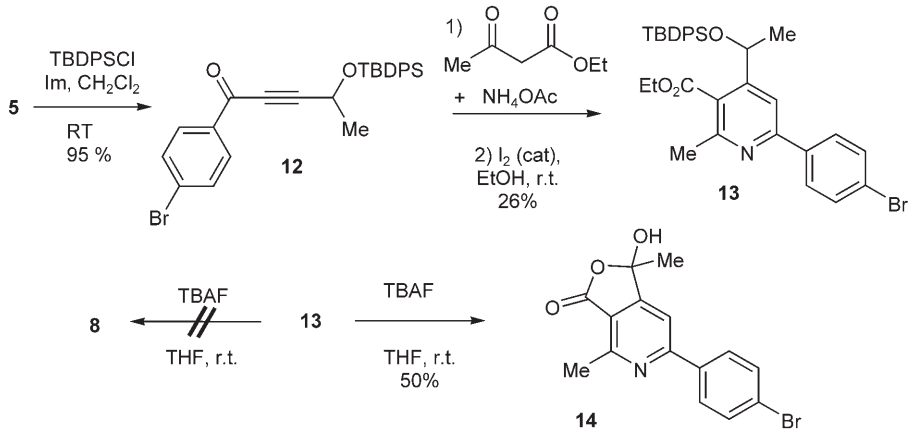
It is noteworthy that the reverse order of reactions, synthesis of the pyridine with the alcohol function followed by dehydroxyfluorination, could not be performed until now. Using the Bohlmann–Rahtz reaction under the previous conditions, the propargylic alcohol **5** did not afford the desired pyridine **8** but instead the furan **11**, albeit in low yield (22%), very likely by cyclization of intermediate **9** followed by loss of NH_3 (Scheme 3).

The propargylic alcohol function was responsible for this undesired process, therefore the corresponding silyl ether **12** was prepared in 95% yield. Starting from this intermediate the Bohlman–Ratz condensation was found to be difficult, affording a complex mixture of products from which the pyridine **13** was isolated in 26% yield only. Finally the deprotection of **13** did not give the desired pyridine **8** but the rearranged compound **14** which was isolated in 50% yield (Scheme 4). The structure of this unexpected product was clearly established from its spectral data. In particular, the NMR data were in excellent agreement with those of similar compounds.[13] Therefore, the route through the propargylic fluorides appears really advantageous.

The bromine on the aromatic ring in key intermediate (−)-**7** was a first handle to introduce the molecular diversity on this pyridine, as indicated on Scheme 5. After a careful selection and optimization of the reaction conditions, it was found that the Sonogashira coupling was best performed in aqueous medium, as reported recently.[14] When the reaction was done under argon, the desired pyridine (−)-**15** was obtained in 97% yield. The Suzuki–Miyaura coupling was also performed under aqueous reaction conditions in the presence of a phase transfer catalyst affording the desired pyridine (−)-**16** in 84% yield.[15] Finally, the Heck coupling was best performed by using triethylamine as solvent and the target pyridine



Scheme 3. Synthesis of furan **11**.



Scheme 4. Synthesis of pyridine lactol **14**.

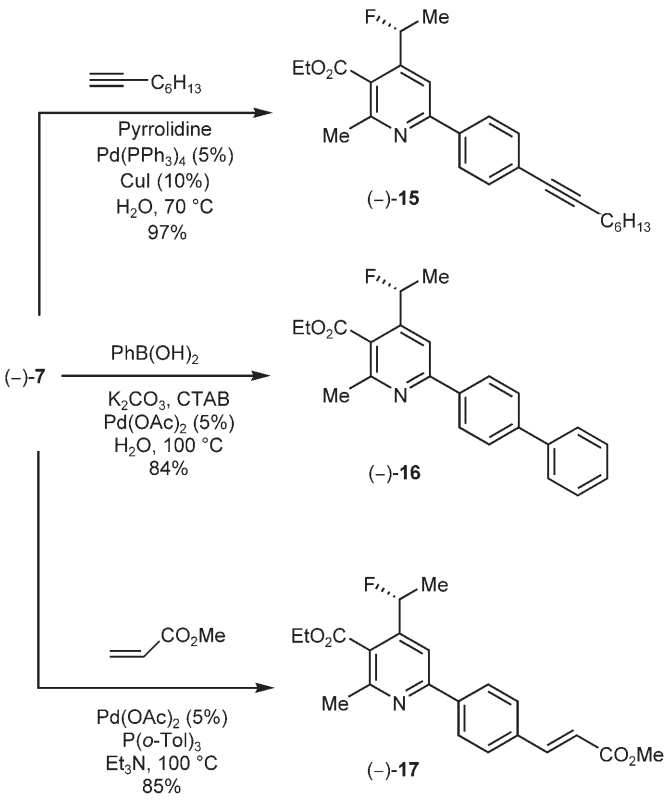
(−)-**17** was isolated in 85% yield. For all these molecules the analysis of the enantiomeric excess could be performed only by ^{19}F NMR in the presence of Eu(hfc)$_3$. In every case, very clean separations of the signals were observed for the corresponding racemic derivatives. This method allowed us to establish *ee*s >94% for pyridines (−)-**15** to (−)-**17**.

The ester function was a second place to be used for the development of the molecular diversity in these molecules. Saponification of the hindered ester in pyridine (−)-**7** was found to be difficult and could not be performed satisfactorily until now. However, reduction by LiAlH$_4$ afforded the alcohol (−)-**18** in 83% yield (Scheme 6). For this more polar compound analysis by chiral HPLC could be performed, affording a 97.3% *ee*. This result unambiguously confirms the previous data obtained by NMR in the presence of chiral shift reagents. Finally, the aldehyde (+)-**19** was obtained in 84% yield by MnO_2 oxidation of (−)-**18**.

Both compounds are very attractive intermediates for the introduction of molecular diversity on this position of the pyridine nucleus.

Conclusions

This study confirms the versatility of propargylic fluorides in the synthesis of useful building blocks for further applications in organic and medicinal chemistry. These fluorides are easily accessible in high enantiomeric purity and the Bohlmann–Rahtz reaction affords, under the conditions proposed by Bagley, interesting pyridines with several points of molecular diversity. Development of this chemistry, as well as preparation of other heterocycles starting from prop-



Scheme 5. Synthesis of pyridines (−)-**15** to (−)-**17**.

argylic fluorides, are under active study in our group and will be reported in due course.

Experimental Section

The characterization data for all compounds are available in the Supporting Information.

Synthesis of THP Ether 2

To a solution of but-3-yn-2-ol (2 g, 28.5 mmol) in anhydrous CH_2Cl_2 (50 mL) were added at 0 °C and under argon, first *para*-toluenesulfonic acid (27 mg, 0.1 mmol) and then dropwise 3,4-dihydro-2*H*-pyran (2.9 mL, 2.64 g, 31.4 mmol). The reaction mixture was magnetically stirred during 2.5 h at 0 °C. After removal of the solvent under reduced pressure, the yellow crude oil was purified by chromatography on silica gel (eluent: pentane/EtOAc, 9/1) to afford the ether **2** as a mixture of diastereoisomers; colourless oil; yield: 4.09 g (93%); R_f (pentane/EtOAc, 9/1) = 0.58 (major), R_f (pentane/EtOAc, 9/1) = 0.42 (minor).

Synthesis of Propargylic Alcohol 3

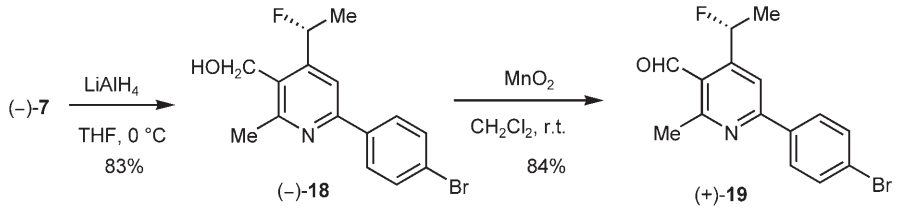
To a solution of the above ether **2** (2 g, 13.0 mmol) in anhydrous THF (50 mL) was added, dropwise under argon at −78 °C, *n*-BuLi (10.1 mL of a 1.6 N solution in hexane, 16.2 mmol). The reaction mixture was stirred during 1 h at this temperature and a solution of *p*-bromobenzaldehyde (3.12 g, 16.9 mmol) in anhydrous THF (15 mL) was added. The reaction mixture was stirred during 3 h with the temperature raising slowly to room temperature before addition of a saturated ammonium chloride solution. The aqueous phase was extracted with ethyl acetate. The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated under vacuum. The colorless oily residue was purified by chromatography on silica gel (eluent: pentane/EtOAc, 9/1 then 7/3) affording alcohol **3** as a colourless oil; yield: 3.91 g (89%). This complex mixture of four diastereoisomers was used directly for the next reaction.

Synthesis of Propargylic Ketone 4

To a solution of alcohol **3** (3.91 g, 11.5 mmol) in CH_2Cl_2 (50 mL) was added freshly prepared MnO_2 (5.01 g, 57.6 mmol). The black suspension was magnetically stirred during 1.5 h at room temperature. After filtration on silica gel and distillation under vacuum of the solvents, the crude product was pure enough to be used directly in the next step of the synthesis; yellow oil, mixture of two diastereoisomers; yield: 3.46 g (89%); R_f (pentane/EtOAc, 9/1) = 0.44 (major), R_f (pentane/EtOAc, 9/1) = 0.34 (minor).

Synthesis of Propargylic Alcohol (−)-5

To a solution of the above ketone **4** (3.18 g, 9.4 mmol) in absolute ethanol (100 mL) PPTS (474 mg, 1.9 mmol) was added and the solution was stirred at 55 °C during 4 h. After removal of the solvents under vacuum, the resulting yellow-orange oil was purified by chromatography on silica gel (eluent: pentane/EtOAc, 9/1 then 7/3) affording alcohol (−)-**5** as yellow crystals; yield: 2.06 g (86%); R_f (pentane/EtOAc, 7/3) = 0.39 R_f (pentane/EtOAc, 9/1) = 0.14. Chiral HPLC data: column Chiralcel OD, eluent hexane/2-propanol, 90/10, 1 mL min^{-1}, detection at 272 nm: retention times for (+)-**5**: 9.1 min, for (−)-**5**: 10.7 min. Using these conditions, a 98.6% *ee* was calculated for the above (−)-**5** sample.



Scheme 6. Synthesis of pyridines (−)-**18** and (−)-**19**.

Synthesis of Propargylic Fluoride (−)-6

To a solution of alcohol **5** (1.5 g, 5.9 mmol) in CH_2Cl_2 (150 mL) maintained at −10 °C was added dropwise DAST (1.55 mL, 11.8 mmol). After stirring at −10 °C during 0.5 h, the reaction mixture was washed with water (4 × 50 mL). The organic phase was dried ($MgSO_4$) and concentrated under vacuum. The yellow oil was purified by chromatography on silica gel (eluent: pentane/Et_2O, 95/5) affording fluoride (−)-**6** as pale yellow crystals; yield: 1.03 g (68%); R_f (pentane/EtOAc, 9/1) = 0.41.

Synthesis of Pyridine (−)-7

To a solution of ammonium acetate (5.28 g, 68.5 mmol) in absolute ethanol (50 mL) was added ethyl acetoacetate (866 μL, 6.9 mmol) and this colourless solution was magnetically stirred during 2.5 h at room temperature. Then a solution of propargylic fluoride (−)-**6** (1.03 g; 4.0 mmol) in ethanol (20 mL) was added. The solution became yellow and it was stirred for further 2.5 h at room temperature before addition of iodine (205 mg, 0.8 mmol). After 1 h stirring, excess iodine was removed by addition of a 10% $Na_2S_2O_3$ aqueous solution (100 mL). Then the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were washed, dried ($MgSO_4$) and concentrated under vacuum. The crude oil was purified by chromatography on silica gel (eluent: pentane/Et_2O, 9/1) to afford pyridine (−)-**7** as a yellow oil; yield: 1.05 g (71%); R_f (pentane/Et_2O, 8/2) = 0.43.

Synthesis of Furan 11

To a solution of ammonium acetate (1.035 g, 13.4 mmol) in absolute ethanol (10 mL) was added ethyl acetoacetate (170 μL, 1.34 mmol) and this colourless solution was magnetically stirred during 3.5 h at room temperature. Then a solution of propargylic alcohol **5** (200 mg, 0.79 mmol) in ethanol (4 mL) was added. The solution became yellow and it was stirred for further 2.5 h at room temperature before addition of iodine (205 mg, 0.8 mmol). After 1 h stirring, excess iodine was removed by addition of a 10% $Na_2S_2O_3$ aqueous solution (100 mL). Then the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were washed, dried ($MgSO_4$) and concentrated under vacuum. The crude oil was purified by chromatography on silica gel (eluent: pentane/Et_2O, 9/1) to afford furan **11** as a colourless oil; yield: 64 mg (22%).

Synthesis of Ether 12

To a solution of alcohol **5** (100 mg, 0.39 mmol) in CH_2Cl_2 (2.5 mL) was added *t*-$BuPh_2SiCl$ (163 mg, 0.59 mmol) and imidazole (40 mg, 0.59 mmol). The reaction mixture was stirred at room temperature for 15 h. After addition of water the product was extracted with CH_2Cl_2 and the organic phases washed, dried ($MgSO_4$) and concentrated under vacuum. The crude oil was purified by chromatography on silica gel (eluent: pentane/EtOAc, 7/3) to afford ether **12** as a colourless oil; yield: 184 mg (95%).

Synthesis of Pyridine 13

Starting from ether **12** (184 mg, 0.37 mmol), the same procedure as for the preparation of pyridine **7** was followed with a reaction time of 14 h. After purification by chromatography on silica gel (eluent: pentane/Et_2O, 9/1 and then 8/2), the pyridine **13** was obtained as a colourless oil; yield: 58 mg (26%).

Synthesis of Lactol 14

To a solution of pyridine **13** (58 mg, 0.1 mmol) in THF (3 mL) was added, under argon, TBAF (300 μL of a 1 M solution in THF). The reaction mixture was stirred at room temperature for 2 h. After addition of water the product was extracted with CH_2Cl_2 and the organic phases washed, dried ($MgSO_4$) and concentrated under vacuum. The crude oil was purified by chromatography on silica gel (eluent: pentane/Et_2O, 1/1) to afford lactol **14** as a colourless oil; yield: 17 mg (50%).

Synthesis of Pyridine (−)-15

A suspension of pyridine (−)-**7** (160 mg, 0.4 mmol) in distilled water (1.6 mL) was degassed by bubbling argon for 10 min to eliminate oxygen. Then are successively added: pyrrolidine (76 μL, 0.9 mmol), $Pd(PPh_3)_4$ (25 mg, 5 mol%), CuI (8 mg, 10 mol%) and oct-1-yne (129 μL, 0.9 mmol). The reaction mixture was heated at 70 °C under argon during 5 h. After cooling down to room temperature the reaction mixture was extracted with ether. The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated under vacuum. The oily crude product was purified by chromatography on silica gel (eluent: pentane/Et_2O, 9/1) affording the target pyridine (−)-**15** as a yellow oil; yield: 167 mg (97%); R_f (pentane/Et_2O, 8/2) = 0.41.

Synthesis of Pyridine (−)-16

Distilled water (800 μL) was degassed by bubbling argon for 10 min to eliminate oxygen. Then were added successively: pyridine (−)-**7** (100 mg, 0.3 mmol), phenylboronic acid (67 mg, 0.6 mmol), potassium carbonate (75 mg, 0.6 mmol), CTAB (100 mg, 0.3 mmol) and palladium acetate (3 mg, 5 mol%). The reaction mixture was heated overnight to 100 °C under argon. After cooling down to room temperature the reaction mixture was extracted with ether. The combined organic phases were washed with water, filtered on celite, dried ($MgSO_4$) and concentrated under vacuum. The crude product was purified by chromatography on silica gel (eluent: pentane/Et_2O, 9/1) affording the target pyridine (−)-**16** as a white powder; yield: 83 mg (84%); R_f (pentane/Et_2O, 8/2) = 0.42.

Synthesis of Pyridine (−)-17

The pyridine (−)-**7** (200 mg, 0.6 mmol) was dissolved in triethylamine (2.7 mL) and this solution was degassed by bubbling argon for 10 min to eliminate oxygen. To this solution were successively added: tri-*o*-tolylphosphine (17 mg, 20 mol%), palladium acetate (3 mg, 5 mol%) and methylacrylate (80 μL, 0.9 mmol). The reaction mixture was heated overnight to 100 °C under argon. After cooling down to room temperature the reaction mixture was extracted with

ethyl acetate. The combined organic phases were washed with water, dried ($MgSO_4$) and concentrated under vacuum. The crude product (yellow oil) was purified by chromatography on silica gel (eluent: pentane/Et_2O, 8/2) affording the target pyridine (−)-**17** as a pale yellow oil; yield: 173 mg (85%). The corresponding racemic derivative (±)-**17** crystallized slowly in the fridge. R_f (pentane/Et_2O, 8/2) = 0.21.

Synthesis of Pyridine (−)-18

To a suspension of $LiAlH_4$ (52 mg, 1.37 mmol) in anhydrous THF (1 mL) was added, at 0 °C under argon and dropwise, a solution of pyridine (−)-**17** (100 mg, 0.27 mmol) in anhydrous THF (2 mL). The reaction mixture was stirred at 0 °C for 0.5 h and then during 3 h at room temperature. After cooling to 0 °C, a saturated aqueous solution of potassium sodium tartrate (3 mL) was first added and then CH_2Cl_2 (5 mL). After stirring for a few minutes a clear solution was obtained and the aqueous solution was extracted with CH_2Cl_2. The combined organic layers were washed, dried ($MgSO_4$) and concentrated under vacuum. The crude product (yellow oil) was purified by chromatography on silica gel (eluent: pentane/EtOAc, 6/4) affording the target pyridine (−)-**18** as a white solid; yield: 74 mg (83%); Chiral HPLC data (column Chiralpak AD-H, eluent heptane/2-propanol, 90/10, 0.6 mL min^{-1}, detection at 205 nm): retention times for (+)-**18**: 15.1 min, for (−)-**18**: 18.2 min. Using these conditions, a 97.3% *ee* was derived for the above (−)-**18** sample.

Synthesis of Pyridine (+)-19

To a solution of alcohol (−)-**18** (50 mg, 0.15 mmol) in anhydrous CH_2Cl_2 was added, portionwise, freshly prepared MnO_2 (300 mg, 30 equiv.). The reaction mixture was stirred during 4 h at room temperature and filtered over Celite. After removal of the solvent under vacuum, the crude product was purified by chromatography on silica gel (eluent: pentane/Et_2O, 2/1) affording the target pyridine (+)-**19** as a colourless oil; yield: 42 mg (84%).

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