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Highly Functionalised Enantiopure 4-Hydroxypyridine Derivatives by a Versatile Three-Component Synthesis

Christian Eidamshaus[a] and Hans-Ulrich Reissig[a,*]

[a] Institut für Chemie und Biochemie, Freie Universität Berlin, Takustr. 3, 14195 Berlin, Germany
Fax: (+49)-30-838-55367; e-mail: hans.reissig@chemie.fu-berlin.de

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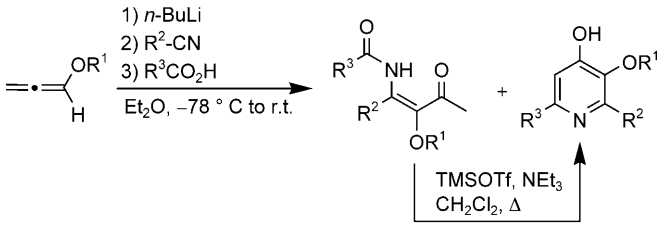
Dedicated to Professor Armin de Meijere on the occasion of his 70th birthday.

Abstract: The scope of a novel alkoxyallene-based pyridine synthesis was expanded to enantiopure carboxylic acids and nitriles as starting materials. The enantiomeric purity of the chiral α-secondary carboxylic acids and nitriles was completely preserved during this reaction sequence thus allowing the one-pot preparation of a whole range of 4-hydroxypyridines or their 4-pyridinone tautomers in good yields.

Keywords: alkoxyallenes; carboxylic acids; chiral ligands; nitriles; pyridines

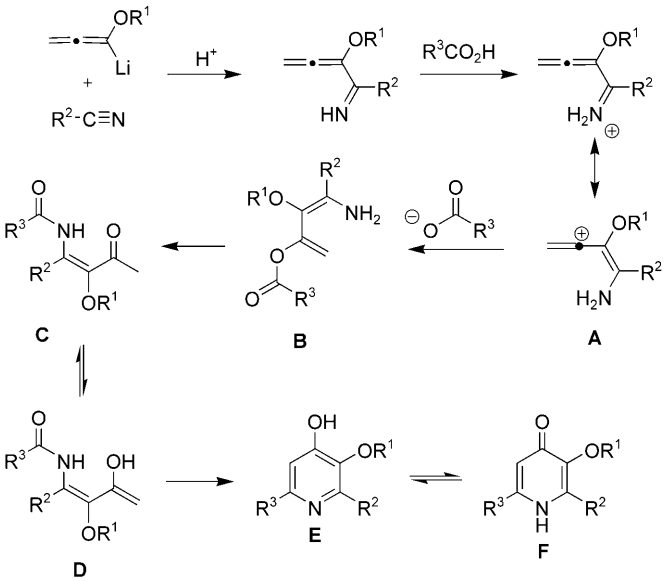
Pyridine derivatives are ubiquitous in the realms of pharmacologically active compounds, agrochemicals and natural products.[1] Moreover, ligands containing the pyridine core such as pyridine-2,6-bis(oxazolines) (pybox),[2] 1,10-phenanthrolines, 2,2′-bipyridines[3] and 2,2′:6′,2″-terpyridines[4] are of great importance in (asymmetric) catalysis. This background explains why new and efficient approaches towards enantiopure, highly functionalised pyridines are of considerable interest.[5,6] Most syntheses rely on classical condensation reactions of carbonyl compounds or thermal and metal-catalysed cycloadditions[7] but they are often restricted in terms of functional group tolerability.[8] Chirality is commonly introduced in a subsequent enantioselective transformation or by any type of chiral resolution. Incorporation of non-racemic chiral starting materials provides another convenient route for the synthesis of pyridines with stereogenic centres.

Recently, we reported a modular 4-hydroxypyridine synthesis based on the reaction of lithiated alkoxyallenes, nitriles and carboxylic acids.[9] As shown in Scheme 1, a mixture of enamides and the desired 4-hydroxypyridines is formed in this process. Subsequent treatment of the crude product with trimethylsilyl trifluoromethanesulfonate (TMSOTf) and triethylamine induces an intramolecular Mukaiyama-type aldol reaction to convert the remaining enamide intermediates into the corresponding 4-hydroxypyridines.



Scheme 1. A new three-component synthesis of highly functionalised pyridines.

The proposed mechanism of this reaction cascade leading to 4-hydroxypyridines is outlined in Scheme 2. In the first step the lithiated alkoxyallene adds to the



Scheme 2. Proposed mechanism for the formation of enamide **C**, 4-hydoxypyridine **E** and 4-pyridinone **F**.

nitrile to furnish the expected primary adduct. Protonation of the intermediate iminoallene by the carboxylic acid furnishes the resonance-stabilised cation **A**, which is attacked in the β-position by the carboxylate to give intermediate **B**. Enamide **C** is formed *via* an acyl transfer reaction and undergoes an intramolecular aldol-type condensation to afford 4-hydroxypyridine **E**. In general, **E** is in equilibrium with the corresponding 4-pyridinone **F**. In the subsequent illustrations all pyridine derivatives are depicted in their predominating tautomeric form (in $CDCl_3$ at room temperature).

So far, it could be demonstrated that a variety of substituted nitriles and carboxylic acids can successfully be converted into the corresponding 4-hydroxypyridines **E**. Besides methoxyallene, other alkoxyallenes are also suitable.[9] We were now interested to expand the scope of this unique transformation by incorporation of chiral acids and nitriles.

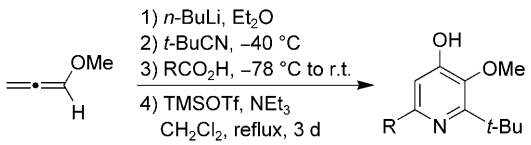
The scope of this reaction is presented in Table 1. As can be seen the protocol allows for the synthesis of a wide range of substrates. Branched alkyl- and aryl-substituted carboxylic acids (Table 1, entries 1 and 2), acids with quaternary α-carbon atoms (Table 1, entry 3), *tert*-butyldimethylsilyl (TBS)-protected mandelic acid (Table 1, entry 4) and *N,N*-dibenzylated amino acids (Table 1, entry 5) were suitable precursors.

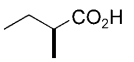
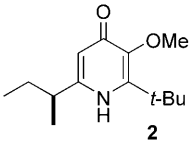
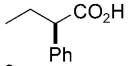
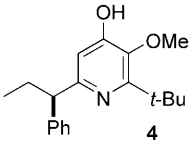
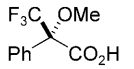
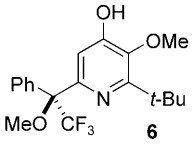
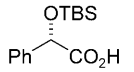
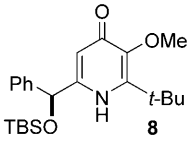
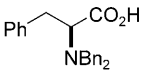
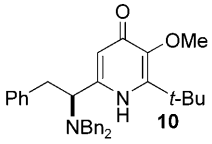
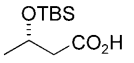
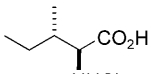
Entries 6 and 7 show limitations of the current protocol: TBS-protected β-hydroxy carboxylic acids (Table 1, entry 6) and Cbz-protected amino acids such as isoleucine (Table 1, entry 7) were not tolerated. In general, the yields obtained over both steps (without separation and purification of the enamide intermediate **C**) were fair to good.

To prove that not only chiral carboxylic acids can be successfully incorporated but also chiral nitriles, (*S*)-2-methylbutyronitrile (**13**) was treated with lithiated methoxyallene and trifluoroacetic acid to give the corresponding 4-hydroxypyridine **14** in 56% yield (Scheme 3). Unfortunately, (*S*)-tetrahydrofuran-2-carbonitrile did not afford the desired pyridine. Competitive elimination processes in the TMSOTf-promoted cyclisation step might be responsible for the failure of more sensitive compounds such as tetrahydrofuran-2-carbonitrile or compound **11** (Table 1, entry 5).

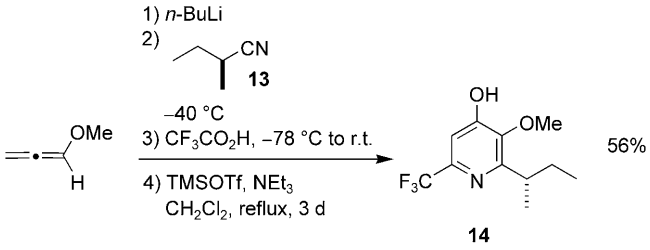
Syntheses of pyridine derivatives containing neither a *tert*-butyl group in position 2 nor bearing a trifluoromethyl group in position 6 are collected in Table 2. The 4-pyridinone **15**, which has close to C_2-symmetry, was prepared in 85% yield demonstrating that pyridines with two stereogenic centres can smoothly be prepared by our approach. The formation of diastereomers due to (partial) racemisation was not observed. Reaction between TBS-protected mandelic acid (*ent*-**7**, Table 2, entry 2) and benzonitrile afforded the desired 4-pyridinone, however, compared to the

Table 1. Scope of carboxylic acids in the synthesis of chiral 4-hydroxypyridines.



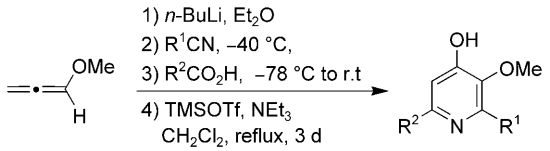
Entry	Carboxylic acid	Product	Yield[a] [%]
1	 **1**	 **2**	24
2	 **3**	 **4**	45
3	 **5**	 **6**	30
4	 **7**	 **8**	51
5	 **9**	 **10**	45
6	 **11**	-	-
7	 **12** NHCbz	-	-

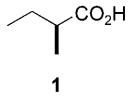
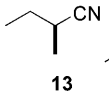
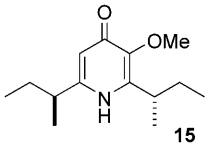
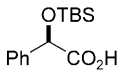
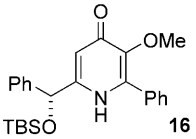
[a] All yields refer to the converted nitrile.



Scheme 3. Conversion of (*S*)-2-methylbutyronitrile into the 4-hydroxypyridine derivative **14**.

Table 2. Chiral pyridines with other substituents.

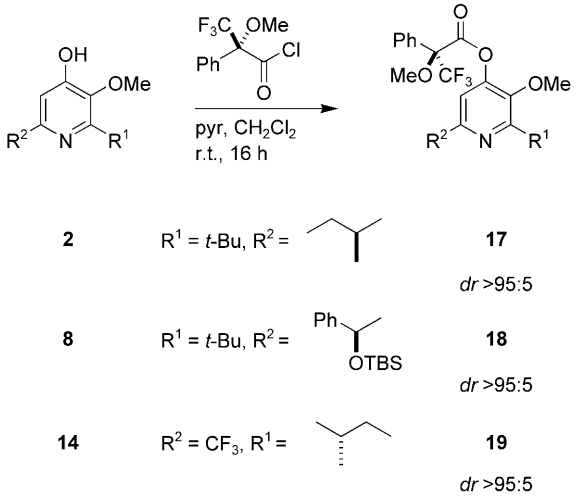


Entry	Carboxylic Acid	Nitrile	Product	Yield[a] [%]
1	 **1**	 **13**	 **15**	85
2	 *ent*-**7**	PhCN	 **16**	24

[a] All yields refer to the converted nitrile.[a] All yields refer to the converted nitrile.

reaction of **7** and pivalonitrile (Table 1, entry 4) the yield dropped significantly in this case.

To prove whether enantiopure starting materials, intermediates and products would racemise under the employed conditions, 4-hydroxypyridines **2**, **8**, and **14** were converted with Mosher's acid chloride[10,11] into the corresponding esters **17**, **18** and **19** (Scheme 4). In all cases the *dr* of the obtained products was found to be higher than 95:5 by means of ^{1}H NMR spectroscopy. Thus, the enantiomeric excess of the 4-hydroxypyridines **2**, **8** and **14** has to be higher than 90%. It can be assumed that substrates with comparable pK_a values for the protons adjacent to the cyano and carboxylate group do not lead to racemisation during this three-component synthesis of pyridines.



Scheme 4. Esterification of 4-hydroxpyridines (or their pyridinone tautomers) with Mosher's acid chloride.

In conclusion, the scope of a new alkoxyallene-based[12] three-component pyridine synthesis could successfully be expanded to more complex starting materials. We could demonstrate that enantiopure carboxylic acids or nitriles can smoothly be converted into the corresponding pyridine derivatives without detectable loss of enantiomeric purity. On the basis of three representative compounds, it was possible to show that carboxylic acids and nitriles with α-secondary stereogenic centres do not undergo racemisation under the employed conditions. The coordination chemistry of these compounds – which should be prone to fine tuning of their properties by employing the two oxy functionalities[9] – and their application as ligands in asymmetric transition metal-catalysed processes are under investigation.

Experimental Section

General Methods

Reactions involving moisture- or oxygen-sensitive reagents were performed under an atmosphere of dry argon in oven- or flame-dried glassware. Solvents and reagents were handled and added by standard Schlenk techniques. The reaction temperatures stated were those of the external bath. THF, Et_2O, CH_2Cl_2 and acetonitrile were purified using the solvent purification system SPS 800 by M. Braun. Anhydrous DMF was purchased from Aldrich and stored under an argon atmosphere in sure seal® bottles. Pyridine was distilled from calcium hydride and stored over molecular sieves 4 Å. Triethylamine was heated with calcium hydride, distilled and stored over KOH pellets. Hexane and ethyl acetate were distilled from calcium hydride. All other reagents were used as purchased without further purification unless otherwise stated.

All proton, carbon and fluorine nuclear magnetic resonance spectra (^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra) were recorded using Bruker AC 250 (250 MHz), Bruker AC 500 (500 MHz), Bruker ECP 400 (400 MHz) or Joel Eclipse 500 (500 MHz) instruments at ambient temperature. Chemical shifts (δ) for all compounds are listed in parts per million (ppm) and refer to solvent residual peaks (^{1}H NMR: $CDCl_3$ 7.26 ppm, CD_3OD 3.34 ppm; ^{13}C NMR: $CDCl_3$ 77.0 ppm, CD_3OD 49.0) as internal standards. Integrals are in accordance with assignments; coupling constants are given in Hz. All ^{13}C NMR spectra were proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMQC). Mass spectra and HR-MS analyses were recorded with Agilent 6210 (ESI-ToF, 4 kV), Varian Ionspec QFT-7 (ESI-FT ICR-MS) or Finnigan MAT 711 (EI, 80 eV, 8 kV) instruments. IR spectra were recorded as KBr pellets for solid samples or as film between KBr plates for liquid samples on a Nicolet 5 SXC FT-IR Interferometer equipped with a DTGS detector or on a Nicolet Avator 320 FT-IR spectrometer. Elemental analyses were recorded with a CHN analyzer 2400 from Perkin–Elmer. Optical rotations were recorded using a Perkin–Elmer 241 polarimeter. Melting points were measured with a melting point microscopy apparatus (Reichert Thermovar) and are uncorrected.

Typical Procedure for the Preparation of 4-Hydroxypyridine Derivatives

(*S*)-2-*tert*-Butyl-6-[(*tert*-butyldimethylsiloxy)phenylmethyl]-3-methoxypyridin-4-one (8): 250 μL (3.00 mmol) of methoxyallene were dissolved in 6.6 mL of dry Et_2O at −40 °C and 1.16 mL (2.90 mmol) of a 2.5 M solution of *n*-BuLi in hexanes were added dropwise. The resulting light yellowish solution was stirred at −40 °C for 30 min before 83 mg (1.00 mmol) of pivalonitrile were added. The mixture was stirred for additional 4 h at −40 °C and then 1.60 g (6.00 mmol, dissolved in a minimum amount of Et_2O) of (*S*)-2-(*tert*-butyldimethylsiloxy)-2-phenylacetic acid were added at −78 °C. The reaction mixture was stirred overnight during which time the mixture was allowed to warm to room temperature. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution and then extracted with Et_2O (three times). The combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was removed under vacuum. Successful conversion to the desired enamide intermediate was evaluated on the basis of ^{1}H NMR analysis.

The obtained crude material was redissolved in 6.6 mL of anhydrous CH_2Cl_2 and 1.88 mL (12.0 mmol) of NEt_3 and 2.61 mL (12.0 mmol) of TMSOTf were added. The mixture was refluxed for three days. After complete consumption of the starting material (as indicated by TLC) saturated aqueous NH_4Cl solution was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (three times). The solvent was removed under reduced pressure and the residue was redissolved in acetic acid (~5 mL) and stirred for 30 min at room temperature to ensure complete cleavage of remaining TMS groups. The solution was diluted with water, the organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (three times). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution and brine and dried with anhydrous Na_2SO_4, filtered followed by removal of the solvent under reduced pressure. The crude material was purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 50:50 to 30:70 as linear gradient) to afford **8** as a yellow oil; yield: 201 mg (51%); $[\alpha]_D^{22}$: −7.1 (*c* 10.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = -0.08$, 0.07, 0.90 (3 s, 3H, 3H, 9H, TBS), 1.40 (s, 9H, *t*-Bu), 3.89 (s, 3H, OMe), 5.56 (s, 1H, 1′-H), 6.13 (s, 1H, 5-H), 7.26–7.35 (m, 5H, Ph), 8.83 (s, 1H, NH); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta = -4.9$, −4.7, 18.2, 25.8 (2q, s, q, TBS), 28.5, 35.3 (q, s, *t*-Bu), 58.8 (q, OMe), 73.4 (d, C-1′), 113.9 (d, C-5), 126.4, 128.7, 128.9, 140.9 (3d, s, Ph), 145.6, 146.7, 147.1 (3 s, C-2, C-3, C-6), 175.5 (s, C-4); IR (film): $\tilde{\nu} = 3355$ (N−H), 2940, 2930, 2855 (C−H), 1620 (C=O), 1250 (C=C), 1000 (C−N), 840, 700 cm^{-1}; HR-MS (ESI-ToF): $m/z = 402.2472$ $[M+H]^+$, calcd. for $C_{23}H_{36}NO_2Si$: 402.2464; anal. calcd. for $C_{23}H_{35}NO_2Si$ (401.6): C 68.78, H 8.78, N, 3.49; found: C 68.48, H, 8.84, N 3.55.

Typical Procedure for the Esterification of 4-Hydroxypyridines with (*S*)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl Chloride

(*S*,*S*)-2-*tert*-Butyl-6-[(*tert*-butyldimethylsiloxy)phenylmethyl]-3-methoxypyridin-4-yl 3,3,3-trifluoro-2-methoxyphenylpropanoate (18): 22 mg (0.06 mmol) of **8** and 17 μL (0.09 mmol) of (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoyl chloride were dissolved in 0.3 mL of pyridine and 0.3 mL of CH_2Cl_2 and stirred at ambient temperature overnight. After complete consumption of the starting material (as indicated by TLC) H_2O was added, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered and the solvents were removed under reduced pressure to give spectroscopically pure **18** as a colourless oil; yield: 25 mg (68%); $[\alpha]_D^{22}$: +14 (*c* 1.0, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 0.01$, 0.02, 0.96 (s, 3H, 3H, 9H, TBS), 1.35 (s, 9H, *t*-Bu), 3.49, 3.68 (2 s, 3H each, OMe), 5.80 (s, 1H, 1′-H), 7.17 (s, 1H, 5-H), 7.19–7.22, 7.27–7.31, 7.48–7.53, 7.61–7.71 (4 m, 10H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -71.1$ (s, CF_3); IR (film): $\tilde{\nu} = 2955$, 2930 (C-H), 1775 (C=O), 1570, 1450 (C=C), 1170, 1105 (=C−H), 780, 700 (C−F) cm^{-1}; HR-MS (ESI-ToF): $m/z = 618.2896$, calcd. for $C_{33}H_{43}F_3NO_5Si$ $[M+H]^+$: 618.2857.

Acknowledgements

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