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A Chiral Pool Strategy for the Synthesis of Enantiopure Hydroxymethyl-Substituted Pyridine Derivatives

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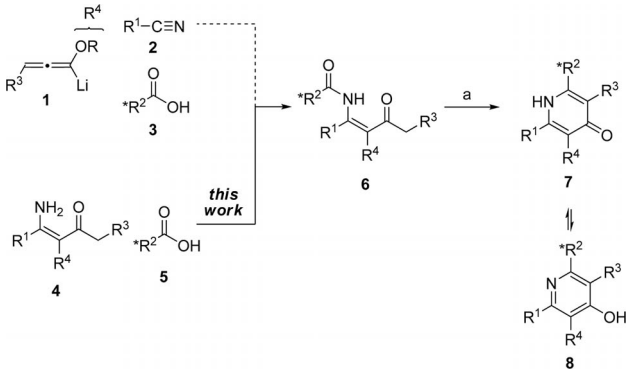
A simple procedure for the synthesis of enantiopure hydroxymethyl-substituted pyridine derivatives is presented. The developed method is based on TMSOTf-promoted cyclocondensations of β-ketoenamides, leading to differently substituted 4-hydroxypyridine/4-pyridone derivatives. The required β-ketoenamides were prepared by acylation of easily available enamino ketones with suitably protected enantiopure carboxylic chlorides. Most of the experiments were performed with D-mandelic acid as starting material. It has been shown that all steps occur essentially without racemisation. Several of the prepared 4-pyridone derivatives were transformed into the corresponding pyrid-4-yl nonaflates and subjected to a series of palladium-catalysed transformations, such as Suzuki, Heck or Sonogashira reactions. In addition, regioselective side-chain functionalisation of unsymmetrically 2,6-disubstituted pyridine derivatives was accomplished by application of Boekelheide rearrangements of the corresponding pyridine *N*-oxides. The presented methods allow a flexible, rapid and scalable approach to highly substituted, enantiopure pyridine derivatives.

Introduction

The pyridine core is ubiquitous in natural products, drugs and agrochemicals. Its ability to coordinate metal ions makes it an ideal ligand for transition-metal-catalysed processes and also for the construction of supramolecular architectures.[1] Pyridines with side chains bearing stereogenic centres are widely used in asymmetric transformations and, as a consequence, many well-established ligand frameworks feature this heteroaromatic nucleus.[2] In particular, enantiopure hydroxymethyl-substituted pyridine derivatives have attracted great attention, because they are efficient catalysts for a series of asymmetric transformations. Enantioselective additions of organometal compounds to aldehydes are efficiently catalysed by chiral pyridines of this type, for instance.[3] Moreover, structurally related phosphinites are excellent P,N ligands for asymmetric iridium-catalysed hydrogenations of olefins.[4] Further examples include palladium-catalysed allylic substitution reactions,[5] nickel-catalysed additions of organozinc compounds to enones[6] and asymmetric alkynylations of aldehydes.[7] Typically, enantiopure (hydroxymethyl)pyridine derivatives are prepared through asymmetric reductions of the corresponding ketones, diastereoselective additions of lithiated pyridine derivatives to chiral ketones or through resolution of racemic compounds.[8] De novo pyridine syntheses using chiral starting materials are rare, and only a very few examples have been reported in the literature.[9,10] Obviously, in many cases the preparation of the required enantiopure starting materials is too difficult to make this approach a competitive alternative. We have recently been able, however, to develop a new route to highly functionalised enantiopure pyridine derivatives that essentially overcomes this problem.[11] With the aid of TMSOTf-mediated cyclocondensation reactions of β-ketoenamides, leading to 4-hydroxypyridines (or their 4-pyridone tautomers), we successfully prepared a series of enantiopure 4-hydroxy-3-methoxypyridine derivatives from readily available chiral carboxylic acid or nitrile starting materials in only two steps.[11] The employed β-ketoenamides **6** (Scheme 1) were synthesised through intri-



Scheme 1. Approaches to the β-ketoenamides **6** and cyclocondensations to afford the 4-pyridones **7** or 4-hydroxypyridines **8**. (a) TMSOTf (3.0 equiv.), NEt_3 (3.0 equiv.), CH_2Cl_2 or 1,2-DCE (0.05 M), reflux, 16–48 h. TMSOTf = trimethylsilyl trifluoromethanesulfonate; NEt_3 = triethylamine; 1,2-DCE = 1,2-dichloroethane.

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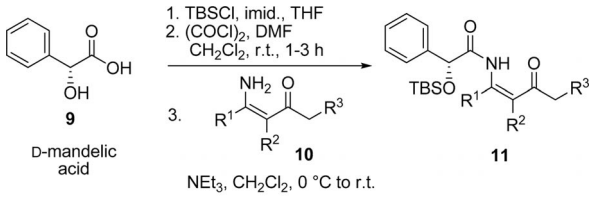
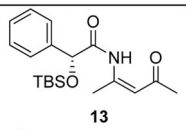
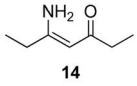
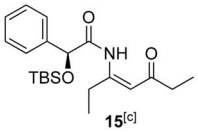
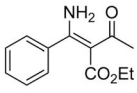
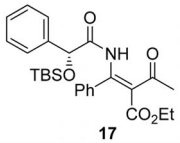
guing three-component reactions of the lithiated alkoxyallenes **1**, the nitriles **2** and the carboxylic acids **3** (Scheme 1, upper pathway).

Although this approach is highly flexible and offers rapid access to a broad range of differently substituted pyridine derivatives it suffers from the fact that in the multicomponent process the reacting carboxylic acid generally has to be used in excess. This disadvantage clearly limits the reaction scale and makes it difficult to prepare larger quantities. Alternatively, the β-ketoenamides **6** are also available through condensations between the enamino ketones **4** and the carboxylic acids **5** (Scheme 1, lower pathway), with subsequent cyclocondensation providing the pyridine derivatives **7/8** with different substitution patterns.[12] So far this method has been applied to the synthesis of a series of novel bi- and terpyridine derivatives, but more complex or chiral substrates had not been examined.

The subject of this report is the expansion of the scope of this process and the development of a practical route to enantiopure hydroxymethyl-substituted pyridine derivatives starting from readily available enantiopure α-hydroxy carboxylic acids. Moreover, we disclose our results on subsequent functionalisations of the prepared pyridine derivatives – in particular through regioselective Boekelheide rearrangements of unsymmetrically 2,6-disubstituted pyridine derivatives.

Table 1. Preparation of β-ketoenamides through acylations of enamino ketones. Variation of the enamino ketone components.



Entry	Enamino ketone	Product	Yield[a] [%]
1	 **12**	 **13**	84 (66)[b]
2	 **14**	 **15**[c]	92
3	 **16**	 **17**	13

[a] Yields of purified products. [b] 10 g scale. [c] Prepared by starting from L-mandelic acid.

Results and Discussion

As was revealed in previous investigations, silyl-ether-protected alcohols are tolerated well under the established cyclisation conditions for β-ketoenamides. To explore the scope of these reactions with respect to the enamino ketone components, a readily available silylated mandelic chloride was selected as the acyl chloride component and condensed with different enamino ketones to provide the corresponding β-ketoenamides **13**, **15** and **17** (Table 1). It is noteworthy that no prior hydrolysis of the silyl mandelate for the generation of the acyl chloride was necessary when oxalyl dichloride and catalytic amounts of *N*,*N*-dimethylformamide (DMF) were used.

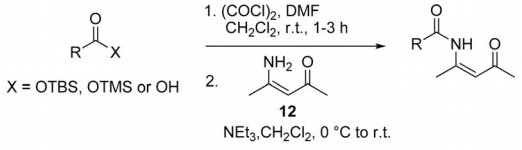
The efficacies of the coupling reactions seem to depend strongly on the electronic natures of the enamino ketone components. Whereas the reactions of the simple enamino ketones **12** and **14** provided the corresponding β-ketoenamides **13** and **15** in excellent yields (Entries 1 and 2), compound **17** was obtained in a very low yield of 13% (Entry 3). This finding might be explained by the fact that the nucleophilicity of **16** is substantially reduced by the additional electron-withdrawing ethoxycarbonyl group. In support of this result it should be noted that all peptide coupling reagents that were tried for the acylation of **12** or **16** either failed or gave only trace amounts of the desired coupling products. The nucleophilicity is apparently already fairly low even in the case of the simple enamino ketone **12**, which makes such vinylogous amides too unreactive to undergo coupling with active esters generated in situ.[13] To test the potential for scaling up of this process, the reaction between **12** and mandelic acid (**9**) was performed on a 10 g scale. Although the yield dropped significantly, the process still remained fairly efficient, and the desired coupling product could be isolated in a good yield of 66%.

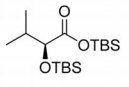
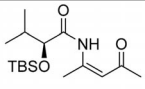
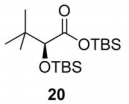
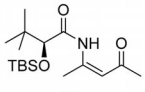
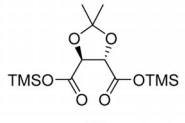
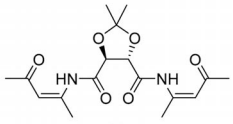
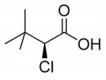
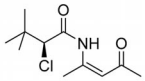
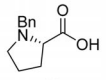
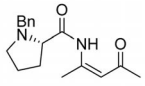
The employed enamino ketones **12** and **14** are easily accessible and were prepared by a literature procedure through treatment of the corresponding 1,3-diketones with an ammonia source.[14] The enamino ketone **16** was prepared by means of a modified Blaise reaction.[15] In the case of **16** a mixture of (*E*) and (*Z*) isomers was obtained, but, as previous results clearly demonstrate, the double bond geometries of the β-ketoenamides do not affect the outcome of the subsequent cyclocondensation reactions.[11h,15b]

Next, the scope of the coupling reactions with respect to the carboxylic acid components was investigated. Besides mandelic acid, the enantiopure α-hydroxy carboxylic acids **18** and **20** and the acetonide-protected tartaric acid derivative **22** were condensed with the enamino ketone **12** to afford the β-ketoenamides **19**, **21** and **23** in moderate to good yields (Table 2, Entries 1–3). The desired α-hydroxy carboxylic acids **18** and **20** can easily be prepared in a one-step fashion from the corresponding amino acids L-valine and L-*tert*-leucine by diazotization with $NaNO_2$ in sulfuric acid.[16] When the reaction with L-*tert*-leucine was conducted in concd. HCl in place of sulfuric acid the α-chloro carboxylic acid **24** was obtained,[17] and this could also be converted into the expected β-ketoenamide **25** (Entry 4). Unlike those of the protected α-hydroxy carboxylic acids, the preparation of the benzyl-protected pyrrolidyl-substituted β-ketoenamide **27** turned out to be more challeng-

ing.[18] When the *N*-benzyl-protected proline **26** was subjected to standard coupling conditions the desired product was isolated in only 7% yield. After tedious optimisation, however, we found that 4.7 equiv. of the sodium salt of the enamino ketone **12** (generated by deprotonation with sodium hydride) furnished the desired compound **27** in a satisfactory yield of 60% (Entry 5).

Table 2. Preparation of β-ketoenamides by acylation of the enamino ketone **12**. Variation of the carboxylic acid components.

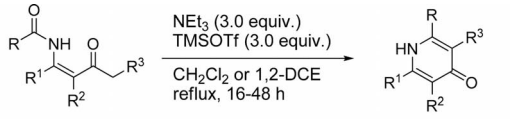


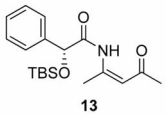
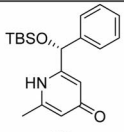
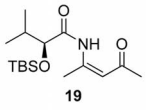
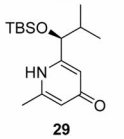
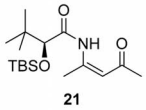
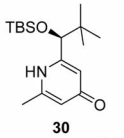
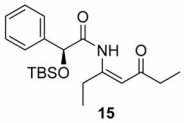
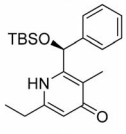
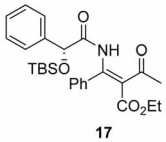
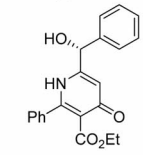
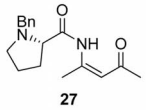
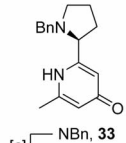
Entry	Carboxylic acid derivative	β-Ketoenamide	Yield[a] [%]
1	 **18**	 **19**	67
2	 **20**	 **21**	80
3	 **22**	 **23**	61
4	 **24**	 **25**	53
5	 **26**	 **27**	60[b]

[a] Yields of purified products. [b] The sodium salt of the enamino ketone **12** (4.7 equiv.) was used.

The prepared β-ketoenamides were then subjected to the cyclisation conditions, leading to the corresponding 4-pyridone derivatives **28**–**33** (Table 3). As the first example, the β-ketoenamide **13** was cyclised under the established conditions to provide the corresponding 4-pyridone **28** in excellent yield. No attempts to optimise the reaction conditions further were made. With the pyridone **28** we were able to demonstrate that the reaction sequence (coupling and cyclisation) proceeds without detectable racemisation (see the Supporting Information). It is therefore very likely that this holds true for all other pyridones prepared according to this method. However, the yields of the cyclisation process varied strongly when other β-ketoenamides were tried (Entries 1–3, Table 3). The efficacy of the cyclisation process is apparently strongly influenced by the steric demand of the amide substituent R. Whereas **13** could be cyclised in excellent yield with a relatively short reaction time (Entry 1), the condensation of **19** provided the corresponding 4-pyridone **29** in only 28% yield (Entry 2). This effect is even more pronounced in the case of β-ketoenamide **21** (Entry 3). When this precursor was subjected to the cyclisation conditions no product formation was observed even after prolonged reaction times. For the 4-pyridone **28** we were able to demonstrate that the cyclisation process can also be performed on a 10 g scale without any loss in efficacy, affording the product in excellent yield and perfect optical purity. In general, the purification of the 4-pyridones is easy even on large scales. Typically, simple filtration through a short silica gel pad is sufficient to provide the 4-pyridones in high purities. The cyclisation of the β-ketoenamide **15**, bearing ethyl substituents, proceeded almost as well as in the case of **13** (Entry 4), but the cyclisation of the ketoenamide **17**, with an additional ethoxycarbonyl group, was less efficient (Entry 5). This might again be the result of the electron-withdrawing effect of this substituent or of steric interactions of the phenyl substituent at C-1. Moreover, a significantly longer reaction time was required to

Table 3. Cyclisations of β-ketoenamides leading to the 4-pyridones **28**–**33**.

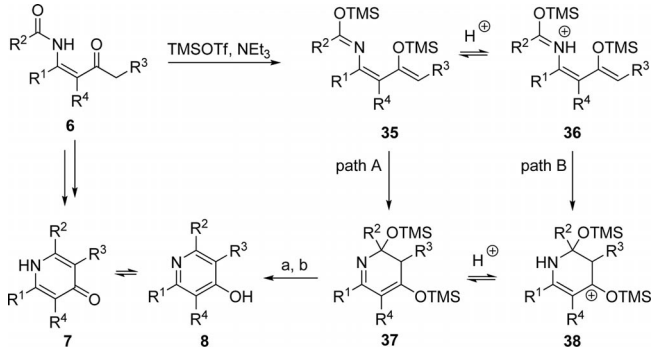


Entry	β-Ketoenamide	4-Pyridone	Yield[a] [%]
1	 **13**	 **28**	91
2	 **19**	 **29**	28
3	 **21**	 **30**	0
4	 **15**	 **31**	75
5	 **17**	 **32**	40[b]
6	 **27**	 [c] NBn, **33** → NH, **34**, 99%	53

[a] Yields of purified products. [b] The reaction time was 7 d. [c] H_2 (balloon), Pd/C (100 wt.-%), MeOH, room temp., 12 h.

achieve complete conversion of **17**, resulting in the complete desilylation of the hydroxy group. Unfortunately, all attempts to cyclise the acetonide-protected tartaric-acid-derived ketoenamide **23** failed. Presumably, the acid-labile protecting group is cleaved under the cyclisation conditions, giving rise to the formation of various unidentified products. As well as the α-hydroxy-carboxylic-acid-derived β-ketoenamides, the proline derivative **27** was also successfully cyclised to furnish the corresponding 4-pyridone **33** in moderate yield (Entry 6). Subsequent cleavage of the benzyl protective group under reductive, heterogeneous conditions afforded the debenzylated 4-pyridone derivative **34** in excellent yield.

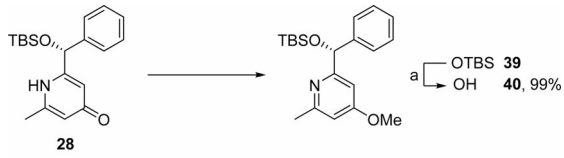
The proposed mechanism of the cyclisations is depicted in Scheme 2. In the first steps the disilylated species **35** are likely to be formed. Two different pathways (A and B) are then possible. The intermediates **35** can either cyclise directly, through formal 6π electrocyclisations, to give the dihydropyridine intermediates **37** (path A) or, after *N*-protonation leading to **36**, similar cyclisations, which can also be regarded as intramolecular Mannich reactions, will afford the cationic intermediates **38** (path B). Subsequent deprotonation should then also lead to **37**, which after elimination of trimethylsilanol followed by protodesilylation of the 4-hydroxy group would give the 4-hydroxypyridine derivatives **8** and/or the 4-pyridones **7**. In each of the examples presented (Table 3) the pyridinol/pyridone equilibrium in $CDCl_3$ solution is completely on the side of the pyridone tautomer. We speculate that intramolecular hydrogen bonds between the pyridone N–H moiety and the α-OTBS, OH or NH groups favour the pyridone tautomers.



Scheme 2. Proposed mechanism of the TMSOTf/base-mediated cyclisations of β-ketoenamides. (a) – TMSOH; (b) H_2O, – TMSOH.

With the synthesised chiral pyridine derivatives to hand we turned our attention to the further functionalisation of the prepared substrates. We have recently demonstrated that the hydroxy groups in 4-pyridinols can serve as useful handles for the introduction of high structural diversity. Modification of the C-4 substituents should allow for fine-tuning of the electronic properties and coordination abilities of the resulting pyridines in applications as ligands in metal-catalysed processes. Firstly, *O*-selective alkylation was considered and optimised for the pyridone **28**. As Table 4 shows, the efficiency of selective *O*-methylation is strongly influenced by the solvent and the base. Treatment of **28** with methyl iodide in acetonitrile did not lead to the formation of the desired product (Entry 1), and the use of Meerwein's salt as alkylating agent (Entry 2) was also unsuccessful and led only to the decomposition of **28**. The best results were obtained in aprotic polar solvents and with K_2CO_3 or Cs_2CO_3 as base (Entries 3–5). In none of these experiments were products arising from competing *N*-alkylation isolated. However, partial desilylation occurred and limited the yields of the alkylation process. Deliberate desilylation of the product **39** was smoothly achieved with tetra-*n*-butylammonium fluoride, furnishing the desired chiral pyridine derivative **40** in almost quantitative yield.

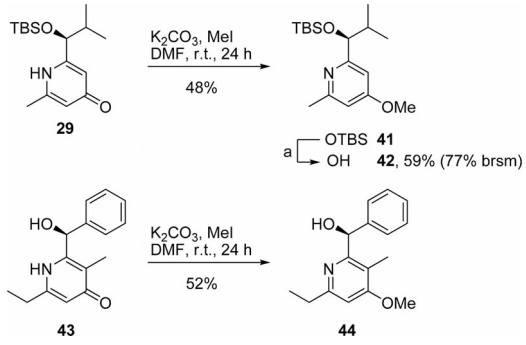
Table 4. Optimisation of the selective *O*-methylation of the 4-pyridone **28**. (a) TBAF (1.0 M in THF), THF, room temp., 2 h. TBAF = tetra-*n*-butylammonium fluoride.



Entry	Conditions	Yield[a] [%]
1	MeI, Cs_2CO_3, CH_3CN, r.t.	–
2	Me_3OBF_4, CH_2Cl_2, r.t.	–
3	MeI, K_2CO_3, acetone, reflux	47
4	MeI, Cs_2CO_3, DMF, r.t.	76
5	MeI, K_2CO_3, DMF, r.t.	91

[a] Yield of purified product.

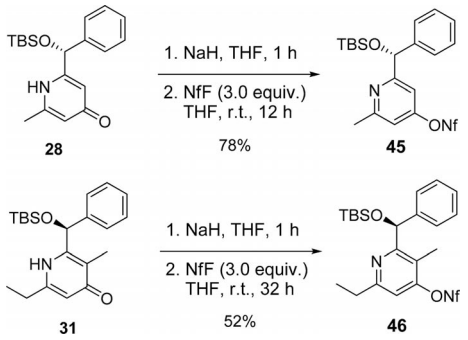
Under the optimised alkylation conditions the 4-methoxypyridines **41** and **44** were also prepared in moderate yields (Scheme 3). When the pyridine **43**, with an unprotected hydroxy group in the C-2 side chain, was alkylated the 4-methoxypyridine derivative **44** was isolated as the major product. Deprotection of the silyl ether **41** with TBAF provided the corresponding hydroxymethyl-substituted pyridine derivative **42**.



Scheme 3. *O*-Selective methylation of the 4-pyridones **29** and **43**. (a) TBAF (1.0 M in THF), THF, room temp., 2 h; brsm = based on recovered starting material.

As already demonstrated in numerous examples,[11b,11d,11f] pyrid-4-yl nonaflates are excellent reaction partners in cross-coupling reactions. Gratifyingly, our previously established nonaflation protocol for 4-hydroxypyridines could also successfully be applied to the newly syn-

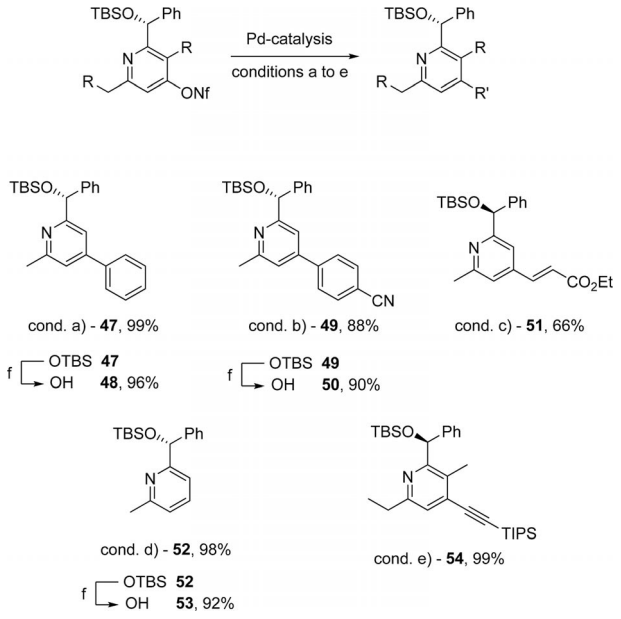
thesised tautomeric 4-pyridones **28** and **31**.[19] Deprotonation with NaH followed by treatment with nonafluorobutanesulfonyl fluoride (NfF) in THF afforded the pyrid-4-yl nonaflates **45** and **46** in good yields (Scheme 4).[20]



Scheme 4. Nonaflation of the 4-pyridones **28** and **31**.

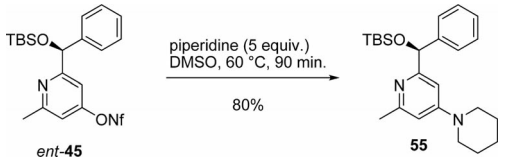
The pyrid-4-yl nonaflates **45**, *ent*-**45** (prepared as described for **45**, by starting from L-mandelic acid via *ent*-**13** and *ent*-**28**) and **46** were tested in a series of palladium-catalysed transformations to achieve facile variation of the C-4 substituent (Scheme 5). Suzuki couplings of **45** with phenylboronic acid and (*p*-cyanophenyl)boronic acid provided the desired 4-aryl-substituted pyridine derivatives **47** and **49** in excellent yields. Subsequent desilylation led to the unprotected (hydroxymethyl)pyridine derivatives **48** and **50**. Heck coupling between the pyridyl nonaflate *ent*-**45** and ethyl acrylate under Jeffery conditions afforded **51** in 66% yield.[21] Reductions of aryl triflates or nonaflates to the corresponding unsubstituted arenes under homogeneous conditions are well established.[22] We were pleased to find that these conditions can also be applied to the reduction of the pyrid-4-yl nonaflate **45**, affording the pyridine derivative **52**, unsubstituted at C-4, in excellent yield. Again, desilylation with TBAF efficiently afforded the free hydroxymethyl-substituted pyridine derivative **53**. Sonogashira coupling between the pyridyl nonaflate **46** and (triisopropylsilyl)acetylene smoothly delivered the 4-alkynylated pyridine derivative **54**. All these examples clearly demonstrate that pyrid-4-yl nonaflates of this type easily lead to a broad range of new chiral pyridine derivatives.

Chiral 4-(dialkylamino)pyridines are widely used in kinetic resolutions of racemic alcohols. We therefore addressed the question of whether or not those structures could be accessed through simple replacement of the nonaflyl groups by amines. Cacchi and co-workers had developed a protocol for the synthesis of 4-amino-substituted quinolyl derivatives through nucleophilic substitution reactions between quinol-4-yl triflates or nonaflates and various amines.[23] Gratifyingly, when *ent*-**45** and piperidine were subjected to the reported conditions, the 4-amino-substituted pyridine derivative **55** was efficiently obtained (Scheme 6). Vedejs and co-workers reported on a structurally closely related pyridine derivative that efficiently acts as an enantiopure DMAP analogue in the resolution of chiral secondary alcohols.[24] Our approach to compounds such as



Scheme 5. Palladium-catalysed transformations of the pyrid-4-yl nonaflates **45**, *ent*-**45** and **46**. (a) $C_6H_5B(OH)_2$ (1.1 equiv.), $Pd(OAc)_2$ (5%), PPh_3 (20%), K_2CO_3 (1.0 equiv.), DMF, 80 °C, 16 h; (b) *p*-$NCC_6H_4B(OH)_2$ (1.2 equiv.), $Pd(OAc)_2$ (5%), PPh_3 (20%), K_2CO_3 (1.2 equiv.), DMF, 80 °C, 16 h; (c) ethyl acrylate (2.0 equiv.), $Pd(OAc)_2$ (5%), TBAC (2.0 equiv.), $NaHCO_3$ (2.1 equiv.), DMF, 70 °C, 4 h; (d) $Pd(OAc)_2$ (16%), dppp (16%), formic acid (3.2 equiv.), NEt_3 (4.5 equiv.), DMF, 65 °C, 16 h; (e) TIPS-acetylene (1.5 equiv.), $PdCl_2(PPh_3)_2$ (5%), CuI (6%), NEt_3, 60 °C, 16 h; (f) TBAF (1.0 M in THF), THF, room temp., 1–2 h. TBAC = tetra-*n*-butylammonium chloride; dppp = 1,3-bis(diphenylphosphanyl)propane; TIPS = triisopropylsilyl.

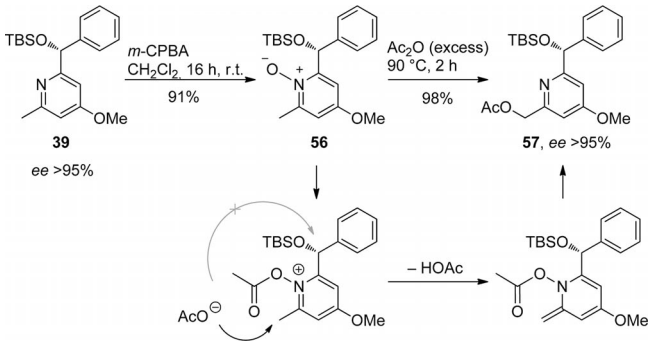
55 should allow easy variation of the substitution pattern in a highly flexible manner and might thus result in even better catalysts.



Scheme 6. Nucleophilic substitution of the pyrid-4-yl nonaflate *ent*-**45** with piperidine, leading to the chiral DMAP analogue **55**.

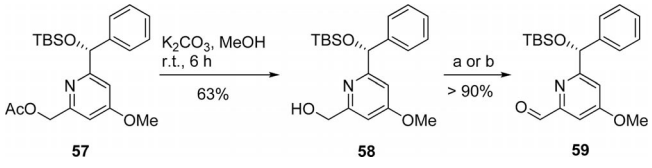
So far we had been able to vary the C-4 substituents in the prepared chiral pyridine derivatives widely, but selective transformations of the unavoidable C-6 alkyl groups in our compounds would also be highly desirable. A variety of methods for the functionalisation of 2- or 6-methyl-substituted pyridine derivatives are known in the literature. Unfortunately, our attempts to oxidise the methyl group in **28** directly with SeO_2 (Riley oxidation) gave the desired aldehyde **59** (Scheme 8, below) only in trace amounts. Furthermore, deprotonation at the methyl group followed by trapping of the resulting anion with different electrophiles also did not lead to the formation of the anticipated products. Gratifyingly, though, the C-6 methyl group in **39** can be indirectly oxidised through a Boekelheide rearrangement.[25] The required pyridine *N*-oxide **56** (Scheme 7) was

prepared in excellent yield by treatment of **39** with *m*-chloroperbenzoic acid. Heating of **56** in acetic anhydride provided the acetoxymethyl-substituted pyridine derivative **57** almost quantitatively. Surprisingly, the rearrangement proceeds with very high regioselectivity, furnishing **57** with complete preservation of the enantiopurity (>95% *ee*, see the Supporting Information). The observed regioselectivity could be due to conformational constraints, strongly lowering the kinetic acidity of the hydrogen atom in the C-2 side chain.



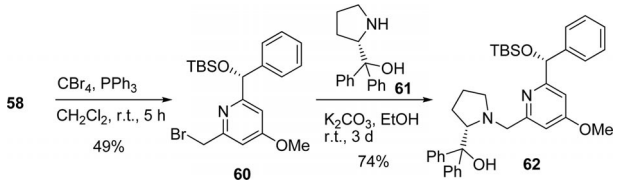
Scheme 7. Formation of the pyridine *N*-oxide **56** and Boekelheide rearrangement leading to the acetoxymethyl-substituted pyridine **57**. *m*-CPBA = *m*-chloroperbenzoic acid; Ac_2O = acetic anhydride.

For further transformations the acetoxy group in the pyridine derivative **57** was hydrolysed by treatment with K_2CO_3 in methanol (Scheme 8). Oxidation of the hydroxymethyl-substituted pyridine derivative **58** to aldehyde **59** was accomplished by Swern oxidation or alternatively by oxidation with IBX.



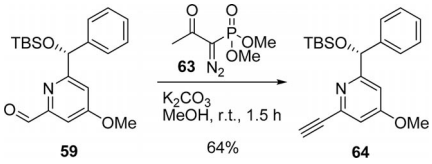
Scheme 8. Hydrolysis of **57** and subsequent oxidation of the (hydroxymethyl)pyridine **58** to the corresponding aldehyde **59**. (a) $(COCl)_2$ (1.1 equiv.), DMSO (2.0 equiv.), NEt_3 (5.0 equiv.), CH_2Cl_2, –60 °C to room temp., 97%; (b) IBX (1.1 equiv.), CH_2Cl_2/DMSO, 98%. IBX = iodooxybenzoic acid.

The new functional groups in the pyridine derivatives **58** and **59** are ideal for subsequent reactions. Compound **58**, for instance, was transformed into the corresponding bromomethyl-substituted pyridine **60** (Scheme 9) by treatment with CBr_4 and PPh_3 (Appel reaction). The reactive bromomethyl side chain may be used for the introduction of amino substituents through nucleophilic substitution reactions, as demonstrated by the reaction between **60** and (*S*)-diphenylprolinol (**61**), to afford **62** (Scheme 9). The fact that compound **62** was obtained as single diastereomer again shows that the entire sequence including the oxidation to the aldehyde **59** proceeds without (partial) racemisation.



Scheme 9. Appel reaction of the pyridyl alcohol **58** to afford the bromide **60** and subsequent reaction with (*S*)-diphenylprolinol (**61**), leading to the pyridine derivative **62** with two stereogenic centres.

The formyl group in the pyridine derivative **59** was subjected to Seyferth–Gilbert homologation[26] with the Bestmann–Ohira reagent **63**[27] to afford the alkynyl-substituted pyridine derivative **64** under mild conditions and in good yield (Scheme 10). The alkynyl group is certainly an excellent tool with which to perform cycloadditions or Sonogashira reactions and should hence allow the introduction of additional structural diversity at C-6 in these chiral pyridine derivatives.



Scheme 10. Seyferth–Gilbert homologation of the aldehyde **59**, leading to the alkynyl-substituted pyridine derivative **64**.

Conclusions

We have developed a simple approach to chiral pyridine derivatives, starting from enantiopure carboxylic acids. In particular, the use of α-hydroxy carboxylic acids, leading to (hydroxymethyl)pyridine derivatives, was investigated in great detail. A procedure for *O*-selective alkylation of the synthesised 4-pyridones was developed, and a series of 4-methoxy-substituted pyridines was prepared by this method. We were able to demonstrate that the corresponding pyrid-4-yl nonaflates are excellent reaction partners in palladium-catalysed transformations, allowing easy variation of the C-4 substituents. Moreover, we found that regioselective oxidation of the less hindered substituents in unsymmetrical 2,6-disubstituted pyridine *N*-oxides through rearrangements in the presence of acetic anhydride is possible, allowing smooth subsequent reactions of these side chains. Investigations of the prepared substrates as ligands in asymmetric transformations are ongoing and will be the subject of future reports.[28]

Experimental Section

General Methods: Reactions were generally performed under argon in flame-dried flasks. Solvents and reagents were added by syringe. Solvents were purified with the MB SPS-800-dry solvent system. NEt_3 was distilled from CaH_2 and stored over KOH under argon. Pyridine was stored over KOH under argon. Other reagents were purchased and used as received without further purification unless otherwise stated. Products were purified by flash chromatography on silica gel (230–400 mesh, Merck or Fluka). Unless otherwise stated, yields refer to analytically pure samples. NMR spectra were

recorded with Bruker (AC 250, AC 500, AVIII 700) and JOEL (ECX 400, Eclipse 500) instruments. Chemical shifts are reported relative to solvent residual peaks or TMS [^{1}H: δ = 0.00 ppm (TMS), δ = 7.26 ppm ($CDCl_3$); ^{13}C: δ = 77.0 ppm ($CDCl_3$)]. Integrals are in accordance with assignments, and coupling constants are given in Hz. All ^{13}C NMR spectra are proton-decoupled. For detailed peak assignments 2D spectra were measured (COSY, HMQC, HMBC). ^{13}C NMR signals of $CF_3(CF_2)_3$ groups are not given, because unambiguous assignment is not possible, due to strong splitting by coupling with the ^{19}F nuclei. IR spectra were measured with a Nicolet 5 SXC FT-IR spectrometer or with a Nexus FT-IR spectrometer fitted with a Nicolet Smart DuraSample IR ATR. MS and HRMS analyses were performed with Varian Ionspec QFT-7 (ESI-FT ICRMS) instruments. Elemental analyses were carried out with a CHN-Analyzer 2400 (Perkin–Elmer) or with a Vario EL or Vario EL III. Melting points were measured with a Reichert apparatus (Thermovar) and are uncorrected. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at the temperatures given.

Typical Procedure for Acylations of Enamino Ketones with α-Hydroxy Carboxylic Acids. (*R*,*Z*)-2-(*tert*-Butyldimethylsiloxy)-*N*-(4-oxopent-2-en-2-yl)-2-phenylacetamide (13): TBSCl (3.32 g, 22.0 mmol) and imidazole (1.63 g, 24.0 mmol) were added to a solution of (*R*)-mandelic acid (1.52 g, 10.0 mmol) in THF (50 mL). The resulting mixture was stirred at room temp. for 16 h. The precipitate was filtered off and thoroughly washed with THF. The combined solutions were concentrated, and the residual material was dissolved in Et_2O (50 mL) and washed with water (2 × 50 mL) and brine. The organic layer was dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure to provide the corresponding silyl ether/ester, which was used as obtained. $(COCl)_2$ (1.52 g, 12.0 mmol) was added dropwise to a solution of the silyl ether/ester (3.79 g, 9.97 mmol) in anhydrous CH_2Cl_2 (50 mL), followed by a few drops of DMF. The resulting mixture was stirred at room temp. for 4 h. All volatile components were then removed under reduced pressure to afford the crude acyl chloride, which was used in the next step without further purification. The acyl chloride was dissolved in anhydrous CH_2Cl_2 (10 mL) and added dropwise at 0 °C to a solution of (*Z*)-4-aminopent-3-en-2-one (**12**, 1.97 g, 19.9 mmol) and NEt_3 (1.38 mL, 9.97 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred under argon for 16 h, during which it was allowed slowly to reach room temp. The reaction was quenched by addition of water (30 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc, 9:1) to afford **13** (2.90 g, 84%) as a yellow oil. $[\alpha]_D^{22}$ = –248 (*c* = 1.65, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.06, 0.11, 0.94 (3 s, 3 H, 3 H, 9 H, OTBS), 2.13, 2.30 (2 s, 3 H each, 5′-H, 1′-H), 5.12 (s, 1 H, 2-H), 5.34 (s, 1 H, 3′-H), 7.31–7.33 (m, 3 H, Ph), 7.51–7.53 (m, 2 H, Ph), 12.81 (s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.9, –3.6, 18.3 (2 q, s, OTBS), 21.7 (q, C-1′), 25.8 (q, OTBS), 30.5 (q, C-5′), 76.9 (d, C-2), 106.9 (d, C-3′), 126.1, 128.1, 128.4, 139.4 (3 d, s, Ph), 153.1 (s, C-2′), 172.7 (s, C-1), 198.5 (s, C-4′) ppm. IR (ATR): $\tilde{\nu}$ = 3140 (NH), 2955–2860 (=C–H, C–H), 1710–1590 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{19}H_{29}NO_3Si$ 370.1814 [M + Na]$^+$; found 370.1812. $C_{19}H_{29}NO_3Si$ (347.5): calcd. C 65.67, H 8.41, N 4.03; found C 65.84, H 8.48, N 4.02.

(*S*,*Z*)-2-(*tert*-Butyldimethylsiloxy)-*N*-(5-oxohept-3-en-3-yl)-2-phenylacetamide (15): (*S*)-Mandelic acid (1.52 g, 10.0 mmol) was converted into the corresponding silyl ether/ester according to the typical procedure, with TBSCl (3.17 g, 21.0 mmol) and imidazole (1.44 g, 21.2 mmol). The crude product (3.81 g, 10.0 mmol) was then treated with $(COCl)_2$ (1.27 g, 10.0 mmol) and DMF in CH_2Cl_2 (50 mL) to give the desired acyl chloride. Treatment of the crude acyl chloride with the enamino ketone **14** (2.58 g, 20.3 mmol) and NEt_3 (1.39 mL, 10.0 mmol) in CH_2Cl_2 (30 mL) gave **15** (3.87 g) together with unreacted enamino ketone as a 4:1 mixture [as judged by NMR (calculated yield: 92%) after flash column chromatography (silica gel, hexane/EtOAc, 95:5)] as a colourless oil. $[\alpha]_D^{22}$ = +131 (*c* = 3.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.05, 0.11, 0.94 (3 s, 3 H, 3 H, 9 H, OTBS), 1.05 (t, X part of an ABX_3 system, J_{AX} = J_{BX} = 7.4 Hz, 3 H, 1′-H), 1.09 (t, *J* = 7.7 Hz, 3 H, 7′-H), 2.40 (dq, *J* = 1.5, 7.7 Hz, 2 H, 6′-H), 2.67, 2.77 (AB part of an ABX_3 system, J_{AX} = J_{BX} = 7.4 Hz, J_{AB} = 14.6 Hz, 2 H, 2′-H), 5.12 (s, 1 H, 2-H), 5.38 (s, 1 H, 4′-H), 7.23–7.27 (m, 1 H, Ph), 7.31–7.34, 7.50–7.54 (2 m, 2 H each, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.11, –4.96 (2 q, OTBS), 8.6 (q, C-7′), 12.5 (q, C-1′), 18.4, 25.7 (s, q, OTBS), 27.2 (q, C-2′), 36.5 (q, C-6′), 76.7 (d, C-2), 104.3 (d, C-4′), 126.1, 128.0, 128.3, 139.5 (3 d, s, Ph), 158.1 (s, C-3′), 172.1 (s, C-1), 201.9 (s, C-5′) ppm. HRMS (ESI-TOF): calcd. for $C_{21}H_{33}NO_3Si$ 376.2308 [M + H]$^+$; found 376.2312.

Ethyl (*R*)-2-{[2-(*tert*-Butyldimethylsiloxy)-2-phenylacetamido]phenylmethylene}-3-oxobutanoate (17): (*R*)-Mandelic acid (426 mg, 2.80 mmol) was converted into the corresponding silyl ether/ester according to the typical procedure, with TBSCl (886 mg, 5.88 mmol) and imidazole (457 mg, 6.72 mmol). The crude product (max. 2.80 mmol) was then treated with $(COCl)_2$ (391 mg, 3.08 mmol) and DMF in CH_2Cl_2 (30 mL) to give the desired acyl chloride. Treatment of the crude acyl chloride with the enamino ketone **16** (800 mg, 3.43 mmol) and NEt_3 (390 μL, 2.81 mmol) in CH_2Cl_2 (25 mL) gave **17** (172 mg, 13%) after flash column chromatography (silica gel, hexane/EtOAc, 9:1) as a colourless oil. Compound **17** was obtained as a 3:1 mixture of (*E*) and (*Z*) isomers. $[\alpha]_D^{22}$ = –57 (*c* = 0.8, $CHCl_3$). Only characteristic signals of the major isomer are given. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.00, 0.06, 0.90 (3 s, 3 H, 3 H, 9 H, OTBS), 0.81 (t, *J* = 7.2 Hz, 3 H, 3′-H), 2.31 (s, 3 H, 4-H), 3.80 (q, *J* = 7.2 Hz, 2 H, 2′-H), 5.05 (s, 1 H, C*H*Ph), 7.10–7.45 (m, 10 H, Ph) ppm. ^{13}C NMR ($CDCl_3$, 101 MHz): δ = –3.57 (q, OTBS), 14.7 (q, C-3′), 19.7, 27.1 (s, q, OTBS), 31.1 (q, C-4), 62.6 (t, C-2′), 117.7 (s, C-2), 127.4, 128.5, 129.2, 129.5, 129.8, 130.0, 135.5, 140.3 (6 d, 2 s, Ph), 154.5 (s, C-1′), 185.5, 197.9, 223.0 (3 s, CONHR, C-1, C-3) ppm. IR (ATR): $\tilde{\nu}$ = 3050–2850 (=C–H, C–H), 1720–1560 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{27}H_{35}NO_5Si$ 482.2363 [M + H]$^+$; found 482.2414.

(*S*,*Z*)-2-(*tert*-Butyldimethylsiloxy)-3-methyl-*N*-(4-oxopent-2-en-2-yl)butanamide (19): (*S*)-2-Hydroxy-3-methylbutanoic acid (7.61 g, 50.0 mmol) was converted into the corresponding silyl ether/ester according to the typical procedure, with TBSCl (15.8 g, 100 mmol) and imidazole (8.17 g, 120 mmol). This silyl ether/ester (17.5 g) was then treated with $(COCl)_2$ (6.35 g, 50.0 mmol) and DMF in CH_2Cl_2 (200 mL) to give the desired acyl chloride. Treatment of the crude acyl chloride with the enamino ketone **12** (9.70 g, 100 mmol) and NEt_3 (6.97 mL, 50.0 mmol) in CH_2Cl_2 (100 mL) gave **19** (10.5 g, 67%) after flash column chromatography (silica gel, hexane/EtOAc, 9:1) as a colourless oil. $[\alpha]_D^{22}$ = –101 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (400 MHz, $CHCl_3$): δ = 0.00, 0.05, 0.90 (3 s, 3 H, 3 H, 9 H, OTBS), 0.90 (m_c, 6 H, *i*Pr), 1.95 (m_c, 1 H, *i*Pr), 2.07, 2.31 (2 s, 3 H each, 5′-H, 1′-H), 3.86 (m_c, 1 H, 2-H), 5.28 (s, 1 H, 3′-H), 12.45 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.3, –4.9 (2 q, OTBS), 17.1, 18.2 (2 q, *i*Pr), 18.7 (s, OTBS), 21.8 (q, C-1′), 25.8 (q, OTBS), 30.4 (q, C-5′), 33.4 (d, *i*Pr), 79.3 (d, C-2), 106.3

(d, C-3′), 152.8 (s, C-2′), 174.1 (s, C-1), 198.2 (s, C-4′) ppm. IR (ATR): $\tilde{\nu}$ = 3490 (NH), 2960–2860 (=C–H, C–H), 1725–1480 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{31}NO_3Si$ 336.1965 $[M + Na]^+$; found 336.1966.

(S,*Z*)-2-(*tert*-Butyldimethylsiloxy)-3,3-dimethyl-*N*-(4-oxopent-2-en-2-yl)butanamide (21): (*S*)-2-Hydroxy-3,3-dimethylbutanoic acid (1.81 g, 13.7 mmol) was converted into the corresponding silyl ether/ester according to the typical procedure, with TBSCl (4.13 g, 27.4 mmol) and imidazole (1.87 g, 27.4 mmol). The crude product (4.78 g) was then treated with $(COCl)_2$ (1.71 g, 13.5 mmol) and DMF in CH_2Cl_2 (45 mL) to give the desired acyl chloride. Treatment of the crude acyl chloride with the enamino ketone **12** (2.00 g, 20.3 mmol) and NEt_3 (1.88 mL, 13.5 mmol) in CH_2Cl_2 (30 mL) gave **21** (3.52 g, 80%) after flash column chromatography (silica gel, hexane/EtOAc, 9:1) as a colourless oil. $[\alpha]_D^{22}$ = –52.7 (*c* = 1.25, $CHCl_3$). The NMR spectra show the presence of rotamers; for the OTBS and *t*Bu groups only characteristic signals are given. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.03, 0.85, 0.98 (3 s, 6 H, 9 H, 9 H, OTBS/*t*Bu), 2.07, 2.31 (2 s, 3 H each, 1′-H/5′-H), 3.70 (s, 1 H, 2-H), 5.27 (s, 1 H, 3′-H), 12.3 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.4, –5.1 (2 q, OTBS), 18.1 (s, OTBS), 21.9 (q, C-1′), 25.6, 25.8 (2 q, OTBS/*t*Bu), 30.3 (q, C-5′), 35.1 (s, *t*Bu), 82.6 (d, C-2), 106.1 (d, C-3′), 152.9 (s, C-2′), 173.1 (s, C-1), 198.3 (s, C-4′) ppm. IR (ATR): $\tilde{\nu}$ = 3470 (NH), 2970–2840 (=C–H, C–H), 1710–1480 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{34}NO_3Si$ 328.2302 $[M + H]^+$; found 328.2309.

(4*S*,5*S*)-2,2-Dimethyl-*N*⁴,*N*⁵-bis[(*Z*)-4-oxopent-2-en-2-yl]-1,3-dioxolane-4,5-dicarboxamide (23): Sodium (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (500 mg, 2.14 mmol) was dissolved in THF (5 mL), and TMSCl (816 µL, 6.41 mmol) was added.[29] After having been stirred under argon at room temp. for 16 h, the mixture was filtered, and the solvent was removed under reduced pressure. The obtained residue was re-dissolved in CH_2Cl_2 (7 mL), and $(COCl)_2$ (543 mg, 4.28 mmol) and DMF (catalytic amounts) were added. The mixture was stirred at ambient temperature until the gas evolution stopped. At that point, the mixture was cooled to 0 °C, and NEt_3 (0.60 mL, 4.3 mmol) and the enamino ketone **12** [445 mg, 4.49 mmol, dissolved in CH_2Cl_2 (3 mL)] were added. Stirring at room temp. was continued overnight. The reaction was quenched with H_2O (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc, 3:2) to provide **23** as a colourless solid (461 mg, 61%), m.p. 79 °C. $[\alpha]_D^{22}$ = +410 (*c* = 0.14, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.52 (s, 6 H, Me_{diox}), 2.06 (s, 6 H, 5′-H), 2.31 (s, 6 H, 1′-H), 4.63 (s, 2 H, 4-H), 5.35 (s, 2 H, 3′-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.4 (q, C-1′), 26.3 (q, Me_{diox}), 30.3 (q, C-5′), 78.3 (d, C-4/5), 107.0 (d, C-3′), 113.9 (s, C-2), 152.7 (s, C-2′), 169.7 (s, C-6), 199.1 (s, C-4′) ppm. IR (ATR): $\tilde{\nu}$ = 3130 (NH), 3000–2930 (C–H), 1720, 1650–1590 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{24}N_2O_6$: 375.1527 $[M + Na]^+$; found 375.1540. $C_{17}H_{24}N_2O_6$ (352.4): calcd. C 57.94, H 6.86, N 7.95; found C 57.83, H 6.50, N 7.90.

(*S*,*Z*)-2-Chloro-3,3-dimethyl-*N*-(4-oxopent-2-en-2-yl)butanamide (25): $(COCl)_2$ (448 mg, 3.53 mmol) and DMF (a few drops) were added dropwise to a solution of (*S*)-2-chloro-3,3-dimethylbutanoic acid (**24**, 532 mg, 3.53 mmol) in CH_2Cl_2 (12 mL). After having been stirred at room temp. for 4 h, the reaction mixture was cooled to 0 °C, and NEt_3 (448 mg, 3.53 mmol) and the enamino ketone **12** (684 mg, 6.91 mmol) were added. The mixture was stirred under argon for 16 h, during which it was allowed to slowly reach room temp. The mixture was diluted with CH_2Cl_2, and water was added. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc, 4:1) to provide **25** (430 mg, 53%) as a colourless oil. $[\alpha]_D^{22}$ = –105 (*c* = 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 9 H, *t*Bu), 2.16 (s, 3 H, 1′-H), 2.38 (s, 3 H, 5′-H), 4.07 (s, 1 H, 2-H), 5.40 (s, 1 H, 3′-H), 12.8 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 21.6 (q, C-1′), 26.7, 35.3 (q, s, *t*Bu), 30.2 (q, C-5′), 70.8 (d, C-2), 106.6 (d, C-3′), 153.6 (s, C-2′), 167.8 (s, C-1), 199.5 (s, C-4′) ppm. IR (ATR): $\tilde{\nu}$ = 3035–2820 (=C–H, C–H), 1705–1580 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{11}H_{18}ClNO_2$: 254.0918 $[M + Na]^+$; found 254.0933. $C_{11}H_{18}ClNO_2$ (231.7): calcd. C 57.02, H 7.83, N 6.04; found C 56.34, H 7.75, N 6.09.

(*S*,*Z*)-1-Benzyl-*N*-(4-oxopent-2-en-2-yl)pyrrolidine-2-carboxamide (27): (*S*)-*N*-Benzylpyrrolidine-2-carboxylic acid (**26**, 2.06 g, 10.0 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL) in a flame-dried two-neck flask fitted with a gas outlet and a rubber septum. The mixture was cooled to –20 °C, and $(COCl)_2$ (1.40 g, 11.0 mmol) was added, followed by catalytic amounts of DMF. Stirring at –20 °C was continued for 2 h. Then, the Na salt of the enamine **12** (5.65 g, 46.7 mmol, generated by addition of an equimolar amount of NaH to a solution of **12** in THF, followed by evaporation of the solvent) was added in portions at –30 °C. Stirring under argon was continued overnight, during which the mixture was allowed to warm slowly to room temp. The reaction mixture was diluted with CH_2Cl_2 and water. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residual material was purified by flash column chromatography (neutral Al_2O_3; hexane/EtOAc, 7:3) to afford **27** (1.73 g, 60%) as a colourless oil. $[\alpha]_D^{22}$ = –196 (*c* = 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.74–1.97, 2.20–2.23 (2 m, 3 H, 1 H, 3-H/4-H), 2.17, 2.26 (2 s, 3 H, 1′-H/5′-H), 2.38–2.44 (m, 1 H, 5-H), 3.17 (dd, *J* = 10.4, 4.8 Hz, 1 H, 5-H), 3.26–3.30 (m, 1 H, 2-H), 3.67, 3.82 (AB system, J_{AB} = 13.0 Hz, 2 H, Bn), 5.31 (s, 1 H, 3′-H), 7.19–7.29 (m, 3 H, Ph), 7.38 (d, *J* = 6.9 Hz, 2 H, Ph), 12.83 (br. s, 1 H, NH) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 23.9, 30.5 (2 t, C-3/C-4), 21.7, 31.0 (2 q, C-1′/C-5′), 53.9 (t, C-5), 59.5 (t, CH_2Ph), 68.4 (d, C-2), 106.1 (d, C-3′), 127.0, 128.0, 129.2, 137.9 (3 d, s, Ph), 153.5 (s, C-2′), 175.8 (s, C-1), 198.4 (s, C-4′) ppm. IR (ATR): $\tilde{\nu}$ = 3140 (NH), 2975–2805 (=C–H, C–H), 1705–1470 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{23}N_2O_2$: 287.1760 $[M + H]^+$; found 287.1760. $C_{17}H_{23}N_2O_2$ (286.4): calcd. C 71.30, H 7.74, N 9.78; found C 71.28, H 7.44, N 9.50.

Typical Procedure for Cyclisations of the β-Ketoenamides to 4-Pyridones. (*R*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-methylpyridin-4-one (28): NEt_3 (0.24 mL, 1.71 mmol) and TMSOTf (0.31 mL, 1.71 mmol) were added to a solution of the β-ketoenamide **13** (200 mg, 0.57 mmol) in CH_2Cl_2 (12 mL). The mixture was heated to reflux for 16 h. After cooling to room temp., the reaction was quenched by addition of H_2O (10 mL), and the mixture was diluted with CH_2Cl_2. The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 90:10) to afford **28** (171 mg, 91%) as a colourless solid, m.p. 93–95 °C. $[\alpha]_D^{22}$ = –48.2 (*c* = 0.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = –0.04, 0.08, 0.92 (3 s, 3 H, 3 H, 9 H, OTBS), 2.32 (s, 3 H, Me),

5.71 (s, 1 H, PhC*H*), 6.24 (s, 1 H, 3-H), 6.40 (s, 1 H, 5-H), 7.30–7.35 (m, 5 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.2, –4.9, 18.2 (2 q, s, OTBS), 19.3 (q, Me), 25.7 (q, OTBS), 73.0 (d, Ph*C*H), 110.7 (d, C-5), 114.5 (d, C-3), 126.5, 128.7, 128.9, 140.5 (3 d, s, Ph), 150.3 (s, C-2), 156.1 (s, C-6) ppm. The signal of C-4 could not be detected. IR (KBr): $\tilde{\nu}$ = 3280 (NH), 2950–2860 (=C–H, C–H), 1630–1470 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{19}H_{27}NO_2Si$ 330.1889 [M + H]$^+$; found 330.1906.

(*S*)-2-[1-(*tert*-Butyldimethylsiloxy)-2-methylpropyl]-6-methylpyridin-4-one (29): The β-ketoenamide **19** (1.62 g, 5.18 mmol) was cyclised according to the typical procedure, with TMSOTf (2.80 mL, 15.5 mmol) and NEt_3 (2.15 mL, 15.5 mmol) in CH_2Cl_2 (100 mL) at reflux for 48 h. The pyridone **29** was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 90:10) to afford 435 mg (28%) as a colourless oil. $[\alpha]_D^{22}$ = –54.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.09, 0.10 (2 s, 3 H each, OTBS), 0.83 (d, *J* = 6.8 Hz, 3 H, *i*Pr), 0.91 (s, 9 H, OTBS), 0.94 (d, *J* = 6.8 Hz, 3 H, *i*Pr), 1.95 (dsept, *J* = 4.6, 6.8 Hz, 1 H, *i*Pr), 2.49 (s, 3 H, Me), 4.58 (d, *J* = 4.6 Hz, 1 H, 1′-H), 6.53, 6.67 (2 d, *J* = 1.9 Hz, 1 H each, 3-H/5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.3, –5.0 (2 q, OTBS), 16.1 (q, *i*Pr), 18.0 (s, OTBS), 19.0 (q, *i*Pr), 19.3 (q, Me), 25.7 (q, OTBS), 35.3 (d, *i*Pr), 74.5 (d, C-1′), 110.9, 113.9 (2 d, C-3/C-5), 150.1, 156.6 (2 s, C-2/C-6), 177.1 (s, C-4) ppm. IR (neat): $\tilde{\nu}$ = 3280 (NH), 2960–2860 (=C–H, C–H), 1630–1500 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{29}NO_2Si$ 296.2046 [M + H]$^+$; found 296.2053.

(*S*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-ethyl-3-methylpyridin-4-one (31): The β-ketoenamide **15** (3.44 g, 9.16 mmol) was cyclised according to the typical procedure, with TMSOTf (4.99 mL, 27.5 mmol) and NEt_3 (3.81 mL, 27.5 mmol) in CH_2Cl_2 (180 mL) at reflux for 48 h. The pyridone **31** was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 97:3) to afford 2.46 g (75%) as a colourless oil. $[\alpha]_D^{22}$ = +3.7 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.03, 0.08, 0.90 (3 s, 3 H, 3 H, 9 H, OTBS), 1.24 (t, *J* = 7.5 Hz, 3 H, CH_3), 1.89 (s, 3 H, CH_3), 2.54 (q, *J* = 7.5 Hz, 2 H, CH_2), 5.82 (s, 1 H, C*H*Ph), 6.18 (s, 1 H, 5-H), 7.22–7.33 (m, 5 H, Ph), 8.88 (br. s, 1 H, NH) ppm. ^{13}C NMR (127 MHz, $CDCl_3$): δ = –5.2, –5.0 (2 q, OTBS), 9.9, 12.2 (2 q, CH_3), 18.1, 25.6 (s, q, OTBS), 26.4 (t, CH_2), 71.4 (d, *C*HPh), 112.4 (d, C-5), 120.4 (s, C-3), 126.4, 128.2, 128.6, 140.1 (3 d, s, Ph), 145.7, 149.4 (2 s, C-2/C-6), 179.3 (s, C-4) ppm. IR (ATR): $\tilde{\nu}$ = 3260 (NH), 3065–2855 (=C–H, C–H), 1625 (C=O), 1520–1380 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{31}NO_2Si$ 358.2202 [M + H]$^+$; found 358.2192.

(*R*)-Ethyl 6-[Hydroxy(phenyl)methyl]-4-oxo-2-phenyl-1,4-dihydropyridine-3-carboxylate (32): The β-ketoenamide **17** (124 mg, 0.25 mmol) was cyclised according to the typical procedure, with TMSOTf (135 μL, 0.74 mmol) and NEt_3 (104 μL, 0.75 mmol) in 1,2-dichloroethane (5 mL) at 60 °C for 3 d. Because conversion was still incomplete after 3 d, additional TMSOTf (135 μL, 0.74 mmol) was added, and stirring was continued for 4 d. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 95:5) to afford the pyridone **32** (35 mg, 40%) as colourless crystals, m.p. 195 °C. $[\alpha]_D^{22}$ = –163 (*c* = 0.75, $CHCl_3$). Several signals in the NMR spectra are broadened due to the pyridinol/pyridone equilibrium, and signals for a few C atoms could not be detected. ^{1}H NMR (500 MHz, $CDCl_3$+CD_3OD): δ = 0.96 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.02 (q, *J* = 7.2 Hz, 2 H, CH_2), 5.71 (s, 1 H, C*H*Ph), 6.57 (br. s, 1 H, 5-H), 7.43–7.45 (m, 10 H, Ph) ppm. ^{13}C NMR (175 MHz, $CDCl_3$+CD_3OD): δ = 11.8 (q, CH_3), 60.2 (t, CH_2), 71.4 (br. d, *C*HPh), 112.2 (br. s, C-5), 125.8, 127.20, 127.23, 127.51, 127.53, 129.1, 140.0 (6 d, s, Ph), 166.5 (s, *C*O$_2$Et) ppm. IR (ATR): $\tilde{\nu}$ = 3340 (OH), 3065–2895 (=C–H, C–H), 1725–1560 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{18}NO_4$: 372.1206 [M + Na]$^+$; found 372.1218.

(*S*)-2-(1-Benzylpyrrolidin-2-yl)-6-methylpyridin-4-one (33): The β-ketoenamide **27** (1.77 g, 6.18 mmol) was cyclised according to the typical procedure, with TMSOTf (3.25 mL, 18.0 mmol) and NEt_3 (2.50 mL, 18.0 mmol) in CH_2Cl_2 (120 mL) at reflux for 48 h. The crude product was purified by flash column chromatography (silica gel, CH_2Cl_2/MeOH, 80:20) to afford **33** (849 mg, 53%) as a yellow oil. $[\alpha]_D^{22}$ = –68.0 (*c* = 0.25, $CHCl_3$/MeOH, 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.70–1.93 (m, 4 H, 2-H/3-H), 2.44 (s, 3 H, Me), 3.30–3.39 (m, 1 H, 1-H/1′-H), 3.84 (s, 2 H, C*H*$_2$Ph), 4.04–4.10 (m, 1 H, 1-H/ 1′-H), 6.53, 6.81 (2 d, *J* = 1.9 Hz, 1 H each, 3-H/5-H), 7.20–7.35 (m, 5 H, Ph) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = 19.7 (q, Me), 23.1, 33.5 (2 t, C-2′/C-3′), 54.5 (t, C-4′), 59.0 (t, *C*H$_2$Ph), 65.4 (d, C-1′), 110.8, 113.9 (2 d, C-3/C-5), 128.1, 128.6, 129.2, 135.9 (3 d, s, Ph), 151.5, 154.5 (2 s, C-2/C-6), 175.8 (s, C-4) ppm. IR (ATR): $\tilde{\nu}$ = 3260 (NH), 2980–2820 (=C–H, C–H), 1625–1485 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{21}N_2O$ 269.1648 [M + H]$^+$; found 269.1624.

(*S*)-2-Methyl-6-(pyrrolidin-2-yl)pyridin-4-one (34): Compound **33** (320 mg, 1.19 mmol) was added to a suspension of palladium on charcoal (10% Pd, 330 mg) in MeOH (12 mL), and hydrogen was bubbled through the solution for 30 min. The mixture was stirred under hydrogen (balloon) at room temp. for 16 h. Filtration through a short pad of Celite and concentration of the solution to dryness afforded crude **34**, which was purified by preparative TLC (silica gel, CH_2Cl_2/MeOH, 8:2) to provide **33** (215 mg, 99%) as a yellow oil. $[\alpha]_D^{22}$ = –28.6 (*c* = 0.5, $CHCl_3$/MeOH, 1:1). ^{1}H NMR (500 MHz, CD_3OD): δ = 1.95–2.16, 2.40–2.48 (2 m, 3 H, 1 H, 3′-H/4′-H), 2.39 (s, 3 H, Me), 3.28–3.51 (m, 2 H, 5′-H), 4.54–4.56 (m, 1 H, 2′-H), 6.47, 6.54 (2 s, 1 H each, 3-H/5-H) ppm. ^{13}C NMR (176 MHz, CD_3OD): δ = 22.3 (q, Me), 24.8, 32.3 (2 t, C-3′/C-4′), 47.0 (t, C-5′), 62.4 (d, C-2′), 109.8, 113.5 (2 d, C-3/C.5), 153.2, 157.8 (2 br. s, C-2/C-6) ppm; the signal for C-4 could not be detected. IR (ATR): $\tilde{\nu}$ = 3335 (NH), 2945–2835 (=C–H), 1640–1405 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{10}H_{14}N_2O$ 179.1179 [M + H]$^+$; found 179.1166.

Typical Procedure for the *O*-Selective Methylation of 4-Pyridones. (*R*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-4-methoxy-6-methylpyridine (39): K_2CO_3 (5.80 g, 42.0 mmol) and methyl iodide (2.17 g, 15.3 mmol) were added to a solution of **28** (4.64 g, 13.3 mmol) in anhydrous DMF (50 mL). The mixture was stirred at room temp. for 48 h until the starting materials had been consumed (TLC). The mixture was diluted with EtOAc (100 mL), and water (50 mL) was added. The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with a brine/water mixture (1:1, 2 × 100 mL) and brine (100 mL), dried with Na_2SO_4 and filtered. Evaporation of the solvent afforded **39** (4.17 g, 91%) as a slightly yellow solid, m.p. 94–96 °C. $[\alpha]_D^{22}$ = +31.8 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.03, 0.04, 0.97 (3 s, 3 H, 3 H, 9 H, OTBS), 2.48 (s, 3 H, Me), 3.81 (s, 3 H, OMe), 5.85 (s, 1 H, PhC*H*), 6.52, 6.98 (2 d, *J* = 2.3 Hz, 1 H each, 3-H/5-H), 7.05–7.23, 7.29–7.31, 7.51–7.52 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (175 MHz, $CDCl_3$): δ = –4.9, 18.2 (q, s, OTBS), 24.5 (q, Me), 25.8 (q, OTBS), 54.8 (q, OMe), 77.2 (d, Ph*C*H), 102.8 (d, C-5), 107.7 (d, C-3), 126.1, 127.0, 128.0 (3 d, Ph), 143.9 (s, Ph), 158.6, 165.7 (2 s, C-6, C-2), 166.6 (s, C-4) ppm. IR (neat): $\tilde{\nu}$ = 2955–2855 (C–H), 1595–1575 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{29}NO_2Si$ 344.2040 [M + H]$^+$; found 344.2097. $C_{20}H_{29}NO_2Si$ (343.2): calcd. C 69.92, H 8.51, N 4.08; found C 69.39, H 8.39, N 4.12.

(*S*)-2-[1-(*tert*-Butyldimethylsiloxy)-2-methylpropyl]-4-methoxy-6-methylpyridine (41): The 4-pyridone **29** (435 mg, 1.47 mmol) was treated with methyl iodide (227 mg, 1.60 mmol) and K_2CO_3 (613 mg, 4.42 mmol) in DMF (5 mL) according to the typical procedure. The crude material was purified by flash column chromatography (silica gel, hexane/EtOAc, 4:1) to provide **41** (219 mg, 48%) as a colourless oil. $[\alpha]_D^{22}$ = –102 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.18, 0.03, 0.89 (3 s, 3 H, 3 H, 9 H, OTBS), 0.74, 0.90 (2 d, *J* = 6.7 Hz, 3 H each, *i*Pr), 1.95 (dsept, *J* = 4.2, 6.7 Hz, 1 H, *i*Pr), 2.43 (s, 3 H, Me), 3.77 (s, 3 H, OMe), 4.50 (d, *J* = 4.2 Hz, 1 H, 1′-H), 6.47, 6.77 (2 d, *J* = 2.2 Hz, 1 H each, 3-H/5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.1, –4.6, 18.1 (2 q, s, OTBS), 16.0, 19.8 (2 q, *i*Pr), 24.5 (q, Me), 25.9 (q, OTBS), 34.9 (d, *i*Pr), 54.8 (q, OMe), 79.9 (d, C-1′), 103.6, 107.4 (2 d, C-3/C-5), 158.2 (s, C-4), 165.7, 166.1 (2 s, C-2/C-6) ppm. IR (neat): $\tilde{\nu}$ = 2960–2855 (C–H), 1600, 1575 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{17}H_{31}NO_2Si$ 310.2202 $[M + H]^+$; found 310.2207.

(*S*)-(6-Ethyl-4-methoxy-3-methylpyridin-2-yl)(phenyl)methanol (44): The 4-pyridone **43** (590 mg, 2.42 mmol) was treated with methyl iodide (412 mg, 2.90 mmol) and K_2CO_3 (680 mg, 4.95 mmol) in DMF (6 mL) according to the typical procedure. The crude material was purified by flash column chromatography (silica gel, hexane/EtOAc, 4:1) to provide **44** (297 mg, 52%) as a colourless oil. $[\alpha]_D^{22}$ = +123.7 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.36 (t, *J* = 8.0 Hz, 3 H, Me), 1.89 (s, 3 H, 3-Me), 2.84 (q, *J* = 8.0 Hz, 2 H, CH_2), 3.82 (s, 3 H, OMe), 5.71 (s, 1 H, PhC*H*), 6.61 (s, 1 H, 5-H), 7.22–7.29 (m, 5 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 9.5, 13.6 (q, t, 6-Et), 31.1 (q, 3-Me), 55.3 (q, OMe), 72.0 (d, *C*HPh), 103.2, 115.7 (2 d, C-3/C-5), 127.3, 127.5, 128.3, 143.1 (3 d, s, Ph), 157.2, 160.1 (2 s, C-2/C-.6), 164.6 (s, C-4) ppm. IR (ATR): $\tilde{\nu}$ = 3320 (OH), 3085–2855 (=C–H, C–H), 1590–1480 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{16}H_{19}NO_2$: 240.1383 $[M – H_2O + H]^+$; found 240.1382. $C_{16}H_{19}NO_2$ (257.3): calcd. C 74.68, H 7.44, N 5.44; found C 74.60, H 7.43, N 5.47.

Typical Procedure for the Nonaflation of 4-Pyridones. (*R*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-methylpyridin-4-yl Nonaflate (45): NaH (60 wt.-% in mineral oil, 103 mg, 2.57 mmol) was added to a solution of the 4-pyridone **28** (706 mg, 2.14 mmol) in THF (21 mL). After the mixture had been stirred at room temp. under argon for 30 min, NfF (785 mg, 2.60 mmol) was added, and stirring was continued for 12 h. The reaction was quenched by slow addition of methanol (10 mL). All volatile components were evaporated, and the residue was purified by flash column chromatography (silica gel, gradient elution hexane to hexane/EtOAc, 9:1) to provide **45** (1.02 g, 78%) as a colourless oil. $[\alpha]_D^{22}$ = –7.4 (*c* = 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00, 0.03, 0.94 (3 s, 3 H, 3 H, 9 H, OTBS), 2.55 (s, 3 H, Me), 5.88 (s, 1 H, C*H*Ph), 6.90, 7.41 (2 d, *J* = 2.0 Hz, 1 H each, 3-H/5-H), 7.17–7.19, 7.29–7.31, 7.48–7.50 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.2, –4.9, 18.1 (2 q, s, OTBS), 24.6 (q, Me), 25.6 (q, OTBS), 77.2 (d, *C*HPh), 109.3, 113.6 (2 d, C-3/5), 126.3, 127.5, 128.3, 142.9 (3 d, s, Ph), 157.5, 160.8, 167.8 (3 s, C-2/C-4/C-6) ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –125.7, –120.8, –108.6, –80.6 ppm. IR (neat): $\tilde{\nu}$ = 2955–2860 (C–H), 1595–1550 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{23}H_{25}F_9NO_4SSi$ 612.1286 $[M + H]^+$; found 612.1280. $C_{23}H_{25}F_9NO_4SSi$ (611.6): calcd. C 45.17, H 4.28, N 2.33; found C 45.29, H 4.28, N 2.23.

(*S*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-ethyl-3-methylpyridin-4-yl Nonaflate (46): The pyridone **31** (254 mg, 0.71 mmol) was treated with NaH (85 mg, 2.13 mmol) and NfF (634 mg, 2.10 mmol) in THF (7 mL) according to the typical procedure. After 16 h, additional NfF (393 mg, 1.30 mmol) was added, and stirring was continued for 16 h. Flash column chromatography (silica gel, gradient elution hexane to hexane/EtOAc, 9:1) provided **46** (236 mg, 52%) as a colourless oil. $[\alpha]_D^{22}$ = –55.8 (*c* = 0.52, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.14, 0.11, 0.92 (3 s, 3 H, 3 H, 9 H, OTBS), 1.43 (t, X part of an ABX_3 system, J_{AX} = J_{BX} = 7.7 Hz, 3 H, Me), 2.10 (s, 3 H, Me), 2.85, 2.89 (AB part of an ABX_3 system, J_{AB} = 2.3 Hz, 1 H each, CH_2), 6.14 (s, 1 H, C*H*Ph), 7.01 (s, 1 H, 5-H), 7.20–7.35 (m, 5 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.3, –5.0 (2 q, OTBS), 10.6 (q, 3-Me), 13.8 (q, Me), 18.2, 25.8 (s, q, OTBS), 31.0 (t, CH_2), 79.7 (d, *C*HPh), 112.8 (d, C-5), 122.5 (s, C-3), 125.2, 126.9, 128.0, 141.9 (3 d, s, Ph), 156.8 (s, C-4), 161.1 (s, C-6), 163.8 (s, C-2) ppm. ^{19}F NMR (376 MHz): δ = –128.0, –120.7, –109.5, –80.5 ppm. IR (ATR): $\tilde{\nu}$ = 2960–2860 (C–H), 1600–1430 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{25}H_{30}F_9NO_4SSi$ 640.1594 $[M + H]^+$; found 640.1596.

(*R*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-methyl-4-phenylpyridine (47): Phenylboronic acid (77 mg, 0.63 mmol), $Pd(OAc)_2$ (7 mg, 0.03 mmol), PPh_3 (31 mg, 0.12 mmol) and K_2CO_3 (88 mg, 0.62 mmol) were added to a solution of the pyrid-4-yl nonaflate **45** (380 mg, 0.62 mmol) in anhydrous DMF (2 mL). The mixture was heated to 80 °C under argon for 16 h. The mixture was filtered, and EtOAc (15 mL) and water (15 mL) were added to the filtrate. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed consecutively with a brine/water mixture (1:1) and brine, dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (SiO_2, hexane/EtOAc, 90:10) to provide **47** (243 mg, 99%) as a colourless solid, m.p. 98 °C. $[\alpha]_D^{22}$ = –2.5 (*c* = 0.08, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.03, 0.04, 0.96 (3 s, 3 H, 3 H, 9 H, OTBS), 2.58 (s, 3 H, Me), 5.93 (s, 1 H, C*H*Ph), 7.18–7.21 (m, 2 H, Ph, 5-H), 7.27–7.30 (m, 2 H, Ph), 7.40–7.47 (m, 3 H, Ph), 7.52–7.54 (m, 2 H, Ph), 7.60–7.63 (m, 3 H, Ph, 3-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = –4.8, 18.3 (q, s, OTBS), 24.5 (q, Me), 25.9 (q, OTBS), 77.8 (d, *C*HPh), 115.2, 119.7 (2 d, C-3/C-5), 126.1, 127.0, 128.1, 128.7, 128.9 (5 d, Ph)*, 138.9, 144.0 (2 s, Ph), 149.2, 157.5, 164.4 (3 s, C-2/C-4/C-6) ppm; * the signal of one carbon atom could not be detected. IR (ATR): $\tilde{\nu}$ = 3085–2855 (=C–H, C–H), 1600–1570 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{25}H_{31}NOSi$ 390.2253 $[M + H]^+$; found 390.2244.

(*R*)-4-{2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-methylpyridin-4-yl}benzonitrile (49): *p*-Cyanophenylboronic acid (302 mg, 2.04 mmol), $Pd(OAc)_2$ (18 mg, 0.08 mmol), PPh_3 (84 mg, 0.32 mmol) and K_2CO_3 (284 mg, 2.04 mmol) were added to a solution of the pyrid-4-yl nonaflate **45** (1.04 g, 1.69 mmol) in anhydrous DMF (8 mL). The mixture was heated at 80 °C under argon for 16 h. The mixture was filtered, and EtOAc (30 mL) and water (30 mL) were added to the filtrate. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed consecutively with a brine/water mixture (1:1) and brine, dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (SiO_2, hexane/EtOAc, 85:15) to provide **49** (619 mg, 88%) as a colourless oil. $[\alpha]_D^{22}$ = –43.2 (*c* = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.03, 0.04, 0.95 (3 s, 3 H, 3 H, 9 H, OTBS), 2.59 (s, 3 H, Me), 5.93 (s, 1 H, C*H*Ph), 7.16 (s, 1 H, 3-H or 5-H), 7.18–7.20, 7.27–7.31, 7.51–7.54 (3 m, 1 H, 2 H, 2 H, Ar), 7.59 (s, 1 H, 3-H or 5-H), 7.65–7.67, 7.73–7.75 (2 m, 2 H, 2 H, Ar) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.7, 18.4 (q, s, OTBS), 24.6 (q, Me), 25.9 (q, OTBS), 77.8 (d, *C*HPh), 112.5 (s, C-4′), 115.1 (d, C-3 or C-5), 118.6 (s, C≡N), 119.6 (d, C-3 or C-5), 126.2, 127.3, 127.8, 128.2, 132.8 (5 d, Ar), 143.5, 143.8, 147.3, 158.2, 165.1 (5 s, Ar, C-2/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3020–2860

(=C–H, C–H), 2360–2280 (CN), 1710–1600 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{26}H_{31}N_2OSi$ 415.2200 $[M + H]^+$; found 415.2194.

Ethyl (*S*,*E*)-3-{2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-methylpyridin-4-yl}acrylate (51): $Pd(OAc)_2$ (5 mg, 0.02 mmol), tetra-*n*-butylammonium chloride (137 mg, 0.98 mmol), $NaHCO_3$ (90 mg, 1.03 mmol) and ethyl acrylate (98 mg, 0.98 mmol) were added to a solution of the pyrid-4-yl nonaflate *ent*-**45** (300 mg, 0.49 mmol) in DMF (4 mL). The resulting mixture was heated at 70 °C under argon for 4 h. The mixture was filtered through a short plug of silica, and all volatile components were removed under reduced pressure. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc, 9:1) to afford **51** (133 mg, 66%) as a colourless solid, m.p. 55–58 °C. $[\alpha]_D^{22}$ = +50.4 (*c* = 0.75, $CHCl_3$, 80% *ee*).[30] ^1H NMR (500 MHz, $CDCl_3$): δ = 0.02, 0.01, 0.93 (3 s, 3 H, 3 H, 9 H, OTBS), 1.33 (t, *J* = 7.0 Hz, 3 H, Me), 2.52 (s, 3 H, Me), 4.26, 4.27 (2 q, *J* = 7.0 Hz, 1 H each, CH_2), 5.86 (s, 1 H, C*H*Ph), 7.03 (s, 1 H, 3-H or 5-H), 6.52, 7.54 (2 d, *J* = 16.0 Hz, 1 H each, =CH), 7.18–7.21, 7.26–7.29 (2 m, 1 H, 2 H, Ph), 7.44–7.49 (m, 3 H, Ph, 3-H or 5-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.89 (q, OTBS), 14.2 (q, Me), 18.3, 25.8 (s, q, OTBS), 24.4 (q, 6-Me), 60.8 (t, CH_2), 77.6 (d, *C*HPh), 115.4, 119.7 (2 d, C-3/C-5), 122.1 (d, =CH), 126.0, 127.1, 128.1, 142.5 (3 d, s, Ph), 143.7 (d, =CH), 158.0, 164.9 (2 s, C-2/C-6), 166.3 (s, CO_2R) ppm; the C-4 signal could not be detected. IR (ATR): $\tilde{\nu}$ = 3065–2855 (=C–H, C–H), 1775–1470 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{24}H_{33}NO_3Si$ 434.2122 $[M + Na]^+$; found 434.2208. $C_{24}H_{33}NO_3Si$ (411.6): calcd. C 70.03, H 8.08, N 3.40; found C 70.00, H 8.06, N 3.34.

(*R*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-methylpyridine (52): $Pd(OAc)_2$ (74 mg, 0.33 mmol), 1,3-bis(diphenylphosphanyl)-propane (134 mg, 0.33 mmol), NEt_3 (1.3 mL, 9.3 mmol) and formic acid (0.26 mL, 6.9 mmol) were added to a solution of the pyrid-4-yl nonaflate **45** (1.26 g, 2.06 mmol) in DMF (8 mL). The resulting mixture was heated to 65 °C under argon for 16 h. After complete consumption of the starting material (as indicated by TLC), all volatile components were removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 90:10) to provide **52** (630 mg, 98%) as a colourless oil. $[\alpha]_D^{22}$ = –298 (*c* = 0.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = –0.03, 0.00, 0.92 (3 s, 3 H, 3 H, 9 H, OTBS), 2.50 (s, 3 H, Me), 5.85 (s, 1 H, C*H*Ph), 6.95 (d, *J* = 7.7 Hz, 1 H, 3-H/5-H), 7.17–7.20, 7.25–7.29 (2 m, 1 H, 2 H, Ph), 7.35 (d, *J* = 7.7 Hz, 1 H, 3-H/5-H), 7.47–7.53 (m, 3 H, 4-H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.9, 18.2 (q, s, OTBS), 24.4 (q, Me), 25.8 (q, OTBS), 78.0 (d, *C*HPh), 117.1, 121.5 (2 d, C-3/5), 126.1, 126.9, 128.0 (3 d, Ph), 136.8 (d, C-4), 144.1 (s, Ph), 156.9, 163.8 (2 s, C-2/C-6) ppm. IR (film): $\tilde{\nu}$ = 3010–2855 (=C–H, C–H), 1735–1545 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{19}H_{27}NOSi$ 314.1940 $[M + H]^+$; found 314.1940. $C_{19}H_{27}NOSi$ (313.5): calcd. C 72.27, H 8.68, N 4.47; found C 72.70, H 8.51, N 4.39.

(*S*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-ethyl-3-methyl-4-[(triisopropylsilyl)ethynyl]pyridine (54): $PdCl_2(PPh_3)_2$ (3 mg, 0.004 mmol), CuI (1 mg, 0.005 mmol) and (triisopropylsilyl)acetylene (22 mg, 0.12 mmol) were added to a solution of the pyrid-4-yl nonaflate **46** (50 mg, 0.08 mmol) in NEt_3 (1 mL). The resulting mixture was heated to 60 °C under argon for 16 h. After complete consumption of the starting materials, all volatile components were removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 9:1) to afford **54** (40 mg, 99%) as a colourless oil. $[\alpha]_D^{22}$ = –63.8 (*c* = 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = –0.13, 0.10, 0.94 (3 s, 3 H, 3 H, 9 H, OTBS), 1.10 (m_c, 21 H, TIPS), 1.31 (t, X part of an ABX_3 system, $J_{AX} = J_{BX}$ = 7.6 Hz, 3 H, Me), 2.21 (s, 3 H, 5-Me), 2.76, 2.81 (AB part of an ABX_3 system, J_{AB} = 1.9 Hz, 1 H each, CH_2), 6.09 (s, 1 H, C*H*Ph), 7.15–7.38 (m, 6 H, 5-H, Ph) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = –4.81, –4.80 (2 q, OTBS), 11.3 (d, TIPS), 11.4 (q, Me), 14.2 (q, 6-Me), 15.4 (s, OTBS), 18.6 (q, TIPS), 25.9 (q, OTBS), 30.8 (t, CH_2), 80.0 (d, *C*HPh), 98.9, 104.0 (2 s, ≡C), 123.4 (s, C-3), 125.5 (d, Ph), 126.5 (d, C-5), 127.8, 131.1, 142.9 (2 d, s, Ph), 133.6, 158.7, 160.1 (3 s, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3005–2850 (=C–H, C–H), 2200 (C≡C), 1645–1380 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{32}H_{51}NOSi_2$: 522.3587 $[M + H]^+$; found 522.3621.

(*S*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-6-methyl-4-(piperidin-1-yl)pyridine (55): Piperidine (136 mg, 1.60 mmol) was added to a solution of the pyrid-4-yl nonaflate *ent*-**45** (198 mg, 0.32 mmol) in DMSO (1.6 mL), and the resulting mixture was heated to 60 °C for 90 min. Water (10 mL) and EtOAc (30 mL) were then added, the phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed consecutively with brine/water mixture (1:1) and brine, dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc, 4:1 + 2 vol-% NEt_3) to afford **55** (101 mg, 80%) as a colourless solid, m.p. 71–73 °C. $[\alpha]_D^{22}$ = +34.0 (*c* = 0.5, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.01, 0.02, 0.94 (3 s, 3 H, 3 H, 9 H, OTBS), 1.60 (m_c, 6 H, 3′-H/4′-H/5′-H), 2.40 (s, 3 H, Me), 3.29 (m_c, 4 H, 2′-H/6′-H), 5.77 (s, 1 H, C*H*Ph), 6.37, 6.84 (2 d, *J* = 2.4 Hz, 1 H each, 3-H/5-H), 7.15–7.19, 7.24–7.28, 7.49–7.51 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.9, –4.8, 18.2 (2 q, s, OTBS), 24.4 (q, Me), 24.7 (t, C-4′), 25.1 (t, C-3′/C-5′), 25.8 (q, OTBS), 47.4 (t, C-2′/C-6′), 77.7 (d, *C*HPh), 101.9, 106.2 (2 d, C-3/C-5), 126.1, 126.7, 127.8, 144.4 (3 d, s, Ph), 156.1, 157.3, 164.2 (3 s, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 2950–2810 (C–H), 1590–1450 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{24}H_{36}N_2OSi$ 397.2670 $[M + H]^+$; found 397.2671. $C_{24}H_{36}N_2OSi$ (396.6): calcd. C 72.67, H 9.15, N 7.06; found C 72.57, H 8.94, N 7.03.

(*R*)-2-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-4-methoxy-6-methylpyridine *N*-Oxide (56): *m*-CPBA (2.11 g, 8.78 mmol) was added to a solution of **39** (1.44 g, 4.39 mmol) in CH_2Cl_2 (45 mL). The mixture was stirred at room temp. for 16 h. Water (30 mL) was then added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with satd. aq. $NaHCO_3$ solution (3 × 100 mL), dried with Na_2SO_4 and filtered. Evaporation of the solvent afforded **56** (1.43 g, 91%) as colourless crystals, m.p. 130–132 °C. $[\alpha]_D^{22}$ = –45.1 (*c* = 1.0, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = –0.10, 0.03, 0.88 (3 s, 3 H, 3 H, 9 H, OTBS), 2.44 (s, 3 H, Me), 3.83 (s, 3 H, OMe), 6.36 (s, 1 H, C*H*Ph), 6.68 (d, *J* = 3.5 Hz, 1 H, 3-H or 5-H), 7.19–7.29 (m, 4 H, Ph, 3-H or 5-H), 7.52–7.54 (m, 2 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –5.1, –4.9, 18.1 (2 q, s, OTBS), 18.2 (q, Me), 25.7 (q, OTBS), 55.7 (q, OMe), 64.0 (d, *C*HPh), 106.2, 110.4 (2 d, C-3/C-5), 127.4, 127.5, 128.0, 141.1 (3 d, s, Ph), 149.5, 155.2, 157.0 (3 s, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 2955–2855 (C–H), 1635–1460 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{29}NO_3Si$ 360.1989 $[M + H]^+$; found 360.2005. $C_{20}H_{29}NO_3Si$ (359.5): calcd. C 66.81, H 8.13, N 3.90; found C 65.75, H 7.75, N 3.87.

(*R*)-{6-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-4-methoxypyridin-2-yl}methyl Acetate (57): The pyridine *N*-oxide **56** (1.87 g, 5.20 mmol) was dissolved in acetic anhydride (100 mL), and the mixture was stirred at 90 °C for 2 h. After complete consumption

of the starting material (as indicated by TLC), all volatile components were removed under reduced pressure to provide **57** (2.05 g, 98%) as a yellow oil. $[\alpha]_D^{22}$ = +37.9 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = –0.01, 0.91 (2 s, 6 H, 9 H, OTBS), 2.11 (s, 3 H, Me), 3.80 (s, 3 H, OMe), 5.11 (s, 2 H, CH_2), 5.83 (s, 1 H, C*H*Ph), 6.68, 7.03 (2 d, *J* = 1.9 Hz, 1 H each, 3-H/5-H), 7.23–7.26, 7.44–7.47 (2 m, 3 H, 2 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.8, 18.4 (q, s, OTBS), 21.1 (q, Me), 25.9 (q, OTBS), 55.2 (q, OMe), 66.8 (t, CH_2), 77.1 (d, *C*HPh), 104.5, 106.8 (2 d, C-3/C-5), 126.2, 127.2, 128.2, 143.7 (3 d, s, Ph), 156.2 (s, C-4), 166.3, 167.2 (2 s, C-2/C-6), 170.7 (s, CO) ppm. IR (ATR): $\tilde{\nu}$ = 2950–2855 (=C–H, C–H), 1745–1575 (C=O, C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{22}H_{31}NO_4Si$ 402.2095 [M + H]$^+$; found 402.2119.

(*R*)-{6-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-4-methoxypyridin-2-yl}methanol (58): The pyridine derivative **57** (1.90 g, 4.71 mmol) was dissolved in MeOH (45 mL) and K_2CO_3 (3.26 g, 23.6 mmol) was added. The resulting mixture was stirred at room temp. for 6 h. The solvent was removed under reduced pressure and the residue was dissolved in EtOAc (30 mL) and water (30 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude material was purified by flash column chromatography (silica gel, hexane/EtOAc, 3:2) to afford **58** (1.07 g, 63%) as a yellow oil. $[\alpha]_D^{22}$ = +11.6 (*c* = 0.43, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02, 0.00, 0.92 (3 s, 3 H, 3 H, 9 H, OTBS), 3.80 (s, 3 H, OMe), 4.58, 4.64 (AB system, J_{AB} = 23.5 Hz, 1 H each, CH_2), 5.79 (s, 1 H, C*H*Ph), 6.51, 7.03 (2 d, *J* = 3.5 Hz, 1 H each, 3-H/5-H), 7.21–7.26, 7.43–7.46 (2 m, 3 H, 2 H Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.1, –4.9, 18.3, 28.2 (2 q, s, q, OTBS), 55.2 (q, OMe), 63.6 (t, CH_2), 77.3 (d, *C*HPh), 104.0, 104.7 (2 d, C-3/C-5), 126.2, 127.2, 128.1, 143.5 (3 d, s, Ph), 159.2, 164.8, 167.1 (3 s, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3235 (OH), 2950–2850 (=C–H, C–H), 1730–1460 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{29}NO_3Si$ 360.1995 [M + H]$^+$; found 360.1998.

(*R*)-6-[(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-4-methoxypicolinaldehyde (59)

(A) By Swern Oxidation: DMSO (44 mg, 0.56 mmol) was added at –60 °C to a solution of oxalyl dichloride (39 mg, 0.31 mmol) in CH_2Cl_2 (1 mL). The resulting mixture was stirred at the same temperature under argon for 5 min, after which **58** (100 mg, 0.28 mmol, dissolved in 1.4 mL of CH_2Cl_2) was added, followed by NEt_3 (196 μL, 1.40 mmol). Stirring at –60 °C was continued for 20 min, after which the mixture was allowed to warm to room temp. over 2.5 h. All volatile components were then removed under reduced pressure to provide **59** (97 mg, 97%) as a yellow oil. No further purification was necessary.

(B) By IBX Oxidation: IBX (398 mg, 1.42 mmol) was added to a solution of **58** (446 mg, 1.29 mmol) in CH_2Cl_2 (10 mL) and DMSO (1.4 mL) and the resulting mixture was stirred at room temp. for 16 h. Aq. $Na_2S_2O_3$ solution (1 M, 5 mL) and EtOAc (20 mL) were then added, and the mixture was stirred until it became homogeneous (15 min). The phases were separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and all volatile components were removed under reduced pressure to leave pure **59** (453 mg, 98%) as a colourless oil. $[\alpha]_D^{22}$ = +13.5 (*c* = 0.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.00, 0.01, 0.93 (3 s, 3 H, 3 H, 9 H, OTBS), 3.86 (s, 3 H, OMe), 5.91 (s, 1 H, C*H*Ph), 7.27–7.33 (m, 5 H, Ph, 3-H/5-H), 7.48–7.50 (m, 2 H, Ph), 9.95 (s, 1 H, CHO) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.9, –4.8, 18.2, 25.8 (2 q, s, q, OTBS), 55.5 (q, OMe), 77.2 (d, *C*HPh), 105.6, 110.3 (2 d, C-3/C-5), 126.1, 127.4, 128.1, 143.2 (3 d, s, Ph), 153.6, 166.9, 167.2 (3 s, C-2/C-4/C-6), 193.6 (d, CHO) ppm. IR (ATR): $\tilde{\nu}$ = 3060–2860 (=C–H, C–H), 1715 (C=O), 1595–1470 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{27}NO_3$: 358.1833 [M + H]$^+$; found 358.1820.

(*R*)-2-(Bromomethyl)-6-[(*tert*-butyldimethylsiloxy)(phenyl)methyl]-4-methoxypyridine (60): CBr_4 (98 mg, 0.29 mmol) and PPh_3 (77 mg, 0.29 mmol) were added to a solution of **58** (88 mg, 0.25 mmol) in CH_2Cl_2 (3 mL), and the resulting mixture was stirred at room temp. for 5 h. All volatile components were removed under reduced pressure, and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc, 9:1) to afford **60** (51 mg, 49%) as a colourless oil. $[\alpha]_D^{22}$ = +51.1 (*c* = 2.5, $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$): δ = 0.01, 0.02, 0.94 (3 s, 3 H, 3 H, 9 H, OTBS), 3.81 (s, 3 H, OMe), 4.44, 4.46 (AB system, J_{AB} = 11.0 Hz, 1 H each, CH_2Br), 5.84 (s, 1 H, C*H*Ph), 6.79, 7.01 (2 d, *J* = 2.4 Hz, 1 H each, 3-H/5-H), 7.19–7.22, 7.25–7.30, 7.47–7.49 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (176 MHz, $CDCl_3$): δ = –4.9, 18.2, 25.8 (q, s, q, OTBS), 34.1 (t, CH_2Br), 55.2 (q, OMe), 77.3 (d, *C*HPh), 104.5, 108.3 (2 d, C-3/C-5), 126.0, 127.1, 128.1, 143.5 (3 d, s, Ph), 157.0, 166.2, 167.1 (3 s, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3090–2855 (=C–H, C–H), 1595–1460 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{28}BrNO_2Si$ 422.1145 [M + H]$^+$; found 424.1099.

[(*S*)-1-({6-[(*R*)-(*tert*-Butyldimethylsiloxy)(phenyl)methyl]-4-methoxypyridin-2-yl}methyl)pyrrolidin-2-yl]diphenylmethanol (62): K_2CO_3 (33 mg, 0.24 mmol) and (*S*)-diphenylprolinol (**61**, 30 mg, 0.12 mmol) were added to a solution of **60** (50 mg, 0.12 mmol) in EtOH (1 mL). The resulting mixture was stirred at room temp. for 3 d. The solvent was then removed under reduced pressure, the residue was dissolved in EtOAc (10 mL), and water (10 mL) was added. The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc, 9:1) to afford **62** (53 mg, 74%) as a colourless oil. $[\alpha]_D^{22}$ = +56.8 (*c* = 2.5, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00, 0.02, 0.94 (3 s, 3 H, 3 H, 9 H, OTBS), 1.54–1.61, 1.63–1.75, 1.85–1.97 (3 m, 2 H, 1 H, 1 H, 3′-H/4′-H), 2.64 (dd, *J* = 7.9, 17.2 Hz, 1 H, 2′-H), 2.98 (m_c, 1 H, 5′-H), 4.13 (br. dd, *J* = 4.9, 9.0 Hz, 1 H, 5′-H), 3.26, 3.32 (AB system, J_{AB} = 14.1 Hz, 1 H each, 2-CH_2), 3.78 (s, 3 H, OMe), 5.08 (br. s, 1 H, OH), 5.79 (s, 1 H, C*H*Ph), 6.33, 6.92 (2 d, *J* = 2.4 Hz, 1 H each, 3-H/5-H), 7.02–7.06, 7.13–7.30, 7.43–7.45, 7.52–7.54, 7.62–7.64 (5 m, 1 H, 8 H, 2 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.8, 18.4, 26.0 (q, s, q, OTBS), 24.6, 29.9 (2 t, C-3′/C-4′), 55.1 (q, OMe), 55.5 (t, C-5′), 61.1 (t, CH_2), 70.2 (d, C-2′), 77.5 (d, *C*HPyr), 78.0 (s, *C*Ph_2), 104.2, 107.1 (2 d, C-3/C-5), 125.8, 126.2, 126.3, 126.8, 127.7, 128.1, 144.0, 146.6, 148.0 (6 d, 3 s, Ph), 160.3, 165.4, 166.7 (3 s, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3220 (br., OH), 3085–2850 (=C–H, C–H), 1655–1445 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{37}H_{47}N_2O_3Si$ 595.3351 [M + H]$^+$; found 595.3392.

(*R*)-2-[(*tert*-Butyldimethylsilyloxy)(phenyl)methyl]-6-ethynyl-4-methoxypyridine (64): Dimethyl (1-diazo-2-oxopropyl)phosphonate (**63**, 101 mg, 0.53 mmol) and K_2CO_3 (121 mg, 0.88 mmol) were added to a solution of **58** (150 mg, 0.42 mmol) in MeOH (7 mL). The resulting mixture was stirred at room temp. for 90 min. After consumption of the starting material, satd. aq. $NaHCO_3$ solution (10 mL) and Et_2O (20 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 30 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude material was purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1) to provide **64** (95 mg, 64%) as a colourless

solid, m.p. 102 °C. $[\alpha]_D^{22}$ = +109.6 (*c* = 0.52, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = –0.01, 0.10, 0.93 (3 s, 3 H, 3 H, 9 H, OTBS), 3.08 (s, 1 H, ≡CH), 3.80 (s, 3 H, OMe), 5.86 (s, 1 H, C*H*Ph), 6.85, 7.10 (2 d, *J* = 2.5 Hz, 1 H each, 3-H/5-H), 7.18–7.21, 7.26–7.29, 7.48–7.50 (3 m, 1 H, 2 H, 2 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = –4.9, 18.2, 25.8 (q, s, q, OTBS), 55.2 (q, OMe), 76.4, 84.0 (s, d, ≡C), 77.3 (d, *C*HPh), 105.9, 112.6 (2 d, C-3/C-5), 125.9, 127.1, 128.1, 143.3 (3 d, s Ph), 141.9, 166.3, 166.9 (3 s, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3315 (≡C–H), 3005–2855 (=C–H), 1585–1430 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{21}H_{27}NO_2Si$ 354.1884 $[M + H]^+$; found 354.1884. $C_{21}H_{27}NO_2Si$ (353.5): calcd. C 71.34, H 7.70, N 3.96; found C 71.36, H 7.54, N 4.03.

Typical Procedure for the Desilylation of TBS-Protected Hydroxymethyl-Substituted Pyridine Derivatives. (*R*)-(4-Methoxy-6-methylpyridin-2-yl)(phenyl)methanol (40): TBAF (1 M in THF, 0.37 mL, 0.37 mmol) was added to a solution of **39** (106 mg, 0.31 mmol) in THF (3 mL), and the resulting mixture was stirred at room temp. for 2 h, after which water (10 mL) and EtOAc (20 mL) were added. The phases were separated, and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layers were dried with Na_2SO_4 and filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (silica gel, hexane/EtOAc, 7:3) to afford **40** (71 mg, 99%) as colourless crystals, m.p. 107–108 °C. $[\alpha]_D^{22}$ = –104.0 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.52 (s, 3 H, Me), 3.72 (s, 3 H, OMe), 4.80 (br. s, 1 H, OH), 5.63 (s, 1 H, *C*HPh), 6.41, 6.56 (2 s, 1 H each, 3-H/5-H), 7.23–7.38 (m, 5 H, Ph) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 24.3 (q, Me), 55.0 (q, OMe), 74.6 (d, CHOH), 104.2, 108.0 (2 d, C-3/C-5), 127.0, 127.6, 128.4, 143.4 (3 d, s, Ph), 158.1, 161.8, 166.7 (3 s, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3140 (OH), 2920–2850 (=C–H), 1600–1580 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{14}H_{15}NO_2$: 230.1176 $[M + H]^+$; found 230.1189. $C_{14}H_{15}NO_2$ (229.1): calcd. C 73.34, H 6.59, N 6.11; found C 73.00, H 6.39, N 6.04.

(*S*)-1-(4-Methoxy-6-methylpyridin-2-yl)-2-methylpropan-1-ol (42): Compound **41** (88 mg, 0.28 mmol) was treated with TBAF (1 M in THF, 0.31 mL, 0.31 mmol) according to the typical procedure to provide **42** [33 mg, 59%, starting material (20 mg) was reisolated, yield based on recovered starting material 77%] as colourless crystals after flash column chromatography (silica gel, hexane/EtOAc, 7:3), m.p. 96–97 °C. $[\alpha]_D^{22}$ = +30.0 (*c* = 0.12, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.76, 1.00 (2 d, *J* = 6.8 Hz, 3 H each, *i*Pr), 1.97 (dsept, *J* = 4.1, 6.8 Hz, 1 H, *i*Pr), 2.47 (s, 3 H, Me), 3.81 (s, 3 H, OMe), 4.42 (d, *J* = 4.1 Hz, 1 H, C*H*OH), 6.52, 6.55 (2 d, *J* = 2.2 Hz, 1 H each, 3-H/5-H) ppm; the OH signal was not detected. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 15.9, 19.6 (2 q, *i*Pr), 24.4 (q, Me), 35.0 (d, *i*Pr), 55.0 (q, OMe), 76.8 (d, CHOH), 103.6, 107.7 (2 d, C-3/C-5), 158.1 (s, C-4), 162.2, 166.4 (2 s, C-2/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3165 (OH), 2970–2845 (=C–H, C–H), 1595–1465 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{11}H_{17}NO_2$: 196.1338 $[M + H]^+$; found 196.1389. $C_{11}H_{17}NO_2$ (195.3): calcd. C 67.66, H 8.78, N 7.17; found 67.69, H 8.58, N 6.99.

(*R*)-(6-Methyl-4-phenylpyridin-2-yl)(phenyl)methanol (48): Compound **47** (183 mg, 0.47 mmol) was treated with TBAF (1 M in THF, 0.52 mL, 0.52 mmol) according to the typical procedure to provide **48** (124 mg, 96%) as colourless crystals after flash column chromatography (silica gel, hexane/EtOAc, 7:3), m.p. 126–128 °C. $[\alpha]_D^{22}$ = –10.3 (*c* = 0.50, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.65 (s, 3 H, Me), 5.60 (br. s, 1 H, OH), 5.78 (s, 1 H, C*H*OH), 7.13 (s, 1 H, 3-H), 7.23–7.29 (m, 2 H, Ph, 5-H), 7.33–7.45, 7.52–7.53 (2 m, 7 H, 2 H, Ph) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.3 (q, Me), 74.8 (d, CHOH), 116.4, 120.1 (2 d, C-3/C-5), 127.0, 127.1, 127.7, 128.5, 128.9 (5 d, Ph),* 138.2, 143.4, 149.7 (3 s, Ph, C-4), 157.1, 160.6 (2 s, C-2/C-6) ppm; * the signal of one carbon atom could not be detected. IR (ATR): $\tilde{\nu}$ = 3310 (OH), 3060–2850 (=C–H, C–H), 1605–1555 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{19}H_{17}NO$ 276.1388 $[M + H]^+$; found 276.1392. $C_{19}H_{17}NO$ (275.2): C 82.88, H 6.22, N 5.09; found C 82.53, H 5.95, N 5.23.

(*R*)-4-{2-[Hydroxy(phenyl)methyl]-6-methylpyridin-4-yl}benzonitrile (50): Compound **49** (609 mg, 1.47 mmol) was treated with TBAF (1 M in THF, 1.62 mL, 1.62 mmol) according to the typical procedure to provide **50** (397 mg, 90%) as colourless crystals after flash column chromatography (silica gel, hexane/EtOAc, 4:6), m.p. 156–158 °C. $[\alpha]_D^{22}$ = –13.8 (*c* = 0.50, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.70 (s, 3 H, Me), 5.42 (br. s, 1 H, OH), 5.81 (s, 1 H, C*H*OH), 7.14, 7.27 (2 s, 1 H each, 3-H/5-H), 7.29–7.33, (m, 1 H, Ph), 7.36–7.39, 7.44–7.45, 7.63–7.65, 7.73–7-75 (4 m, 2 H each, Ph, Ar) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.3 (q, Me), 74.5 (d, CHOH), 112.6 (s, Ar), 116.3 (d, C-3 or C-5), 118.3 (s, CN), 120.1 (d, C-3 or C-5), 127.1, 127.8, 127.8, 128.6, 132.7 (5 d, Ph, Ar), 142.8, 143.0, 147.7, 157.7, 161.2 (5 s, Ph, Ar, C-2/C-4/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3495 (OH), 2950–2800 (=C–H, C–H), 2230 (CN), 1600–1390 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{20}H_{16}N_2O$ 301.1341 $[M + H]^+$; found 301.1337. $C_{20}H_{16}N_2O$ (300.4): calcd. C 79.98, H 5.37, N 9.33; found C 78.65, H 5.47, N 9.46.

(*R*)-(6-Methylpyridin-2-yl)(phenyl)methanol (53): Compound **52** (623 mg, 1.99 mmol) was treated with TBAF (1 M in THF, 2.19 mL, 2.19 mmol) according to the typical procedure to provide **53** (366 mg, 92%) as colourless crystals after flash column chromatography (silica gel, hexane/EtOAc, 1:1), m.p. 103–104 °C. $[\alpha]_D^{22}$ = –181 (*c* = 0.60, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.59 (s, 3 H, Me), 5.69 (s, 1 H, C*H*OH), 6.88, 7.03 (2 d, *J* = 7.7 Hz, 1 H each, 3-H/5-H), 7.24–7.28, 7.30–7.39 (2 m, 1 H, 4 H, Ph), 7.48 (t, *J* = 7.7 Hz, 1 H, 4-H) ppm; the OH signal was not detected. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 24.2 (q, Me), 74.5 (d, CHOH), 118.3, 121.8 (2 d, C-3/C-5), 127.1, 127.7, 128.5 (3 d, Ph), 137.1 (d, C-4), 143.4 (s, Ph), 156.6, 159.8 (2 s, C-2/C-6) ppm. IR (ATR): $\tilde{\nu}$ = 3200 (OH), 2950–2840 (=C–H, C–H), 1685–1575 (C=C) cm^{-1}. HRMS (ESI-TOF): calcd. for $C_{13}H_{13}NO$ 200.1075 $[M + H]^+$; found 200.1082. $C_{13}H_{13}NO$ (199.2): calcd. for C 78.36, H 6.58, N 7.03; found C 78.33, H 6.53, N 6.95.

Supporting Information (see footnote on the first page of this article): Detailed description of Mosher ester formation and determination of the enantiomeric excess.

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