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Ligand creation via linking—a rapid and convenient method for construction of novel supported PyOX-ligands

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Abstract—A novel supported amino alcohol linker was synthesized and utilized for attachment of picolinic acid derivatives onto different supports. When the resin bound molecule was further activated, the PyOX-moiety could be constructed reliably in enantiopure form. Furthermore, an efficient Pd-catalyzed modification of a picolinic acid derivative is presented.

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1. Introduction

For economic and environmental reasons, the trend towards the application of enantiopure compounds is undoubtedly increasing. Asymmetric induction with chiral ligands and their transition metal complexes constitutes one of the most versatile methods for the preparation of chiral compounds in enantiopure form.¹ Covalent immobilization of catalysts on insoluble polymer or other supports has received considerable attention in recent years.² Heterogeneous catalysis has two major advantages over homogenous catalysis: (1) separation of the catalyst from reagents and products is technically easier and facilitates recycling and recovery of the valuable catalyst material; (2) optimization of either the diversity of the ligand or the reaction conditions is facilitated. In particular, polymer supported ligands have been studied extensively.³ Whereas the PyOX-core (Fig. 1) has been widely reported in several applications as soluble ligands, solid-supported PyOX-ligands are still very rarely published,⁴ despite their obvious usefulness in various catalytic asymmetric reactions.⁵ Moreover, the C₂-symmetric PyBOX-core has been attached to a solid support using various methods.⁶

In modification processes of the PyOX-core, the modification has traditionally been carried out by altering the amino alcohols, which are used to form the oxazoline part of the PyOX-core (Fig. 1). Much less attention has been focused on the pyridine part.⁷ In this paper, we will introduce a new method to simultaneously link picolinic acid derivatives to a solid support and form the PyOX-core via cyclization on the solid support. For this purpose, a novel tyrosine-based amino alcohol linker 1 was synthesized. This methodology allows the possibility of systematically optimizing the substituents of the pyridine ring in the PyOX. When the pyridine is adorned with a functional tail, the Py-part can be attached to a support and optimization of the oxazoline part can take place.

2. Results and discussion

The main plan for the formation of a novel linker was to utilize the amino alcohol functionality for both linking carboxylic acids and oxazoline formation via varying the substituents of the pyridine ring. Natural tyrosine provides the necessary orthogonal functionalities for linking and oxazoline formation, and was therefore used as the starting material for the linker. As the support we chose the robust Merrifield resin with no additional linkers. Attachment to the resin can be achieved via an ether bond between the resin and the phenolic group of tyrosine. This linking strategy gives us the possibility to prepare additional linkers in the future, if flexibility is needed.

In solution phase model experiments for linker preparation the solid support was replaced with a benzyl group as a soluble analogue of the Merrifield resin. The model reactions were performed in order to optimize the reaction conditions with respect to reaction rate, conversion and retention of stereochemistry. The protected tyrosine 3 was prepared according to published methods (Scheme 1).⁸ Benzylation of the protected tyrosine posed some critical technical issues: the use of cesium carbonate in benzylation
is reported to lead to racemization. On the other hand, it has been reported that the use of K$_2$CO$_3$ in acetone evades the racemization in liquid-phase experiments. However, acetone cannot be used with the Merrifield resin due to poor swelling. We soon discovered that the optical rotation of 4 remained identical, when the solvent was changed from acetone to DMF.

Reduction of 4 could be carried out using the standard LiAlH$_4$-procedure, but we chose NaBH$_4$/LiI-reduction for milder conditions and more convenient work-up with resins. The procedure used for Boc removal was designed for solid phase use. Standard Boc cleavage (50% TFA/CH$_2$Cl$_2$) caused some cleavage of the phenolic ether in 5, whereas p-TsOH proved mild enough to avoid this side reaction. The

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Figure 1. The PyOX-core and its possibilities for optimization.

Scheme 1. Model experiments with soluble analogues, starting from (L)-tyrosine (2–6) and (D)-tyrosine (7–11). (i) SOCl$_2$, MeOH, –72 °C to reflux, 20 h; (ii) NEt$_3$, Boc$_2$O, MeOH, rt, 17 h, 89% (two steps); (iii) BnBr, K$_2$CO$_3$, KI, acetone, reflux, 4 h, 100%; (iv) NaBH$_4$, LiI, THF, reflux, 3 h, 87%; (v) p-TsOH, CH$_2$Cl$_2$, THF, rt, 20 h, 68% (1 crop).
The synthesis was repeated with D-tyrosine to ascertain that no racemization had occurred during the steps (compounds 7–11). Compounds 4–6 were analyzed by IR and the characteristic signals mapped for comparison with the solid phase analogues.

Enantiomers 5 and 10 were derivatized with the chiral proline derivative 12 to form diastereomers 13 and 14 (Scheme 2). These were shown to be pure by achiral HPLC and NMR.

The optimized reaction conditions from liquid phase experiments (Scheme 1) were applied with the supported 4. Phenol 3 was attached to the Merrifield resin using the benzylation protocol developed above. Reaction monitoring on solid support could easily be performed by FTIR, as the characteristic signals were found by model experiments in solution. The easiest region to follow is the carbonyl region ($\nu = 1750–1600 \text{ cm}^{-1}$) due to the strong signals and characteristic changes. Scheme 3 illustrates the formation of linker 1.

Picolinic acid derivatives were attached to 1 to form the amido alcohol functionality. We focused our attention on acids substituted also at the 5-position, because the corresponding picolinic acids (e.g., 18 and 19, Fig. 2) can be prepared utilizing the differing reactivities of the 2- and 5-positions. The picolinic acid derivatives 18 and 19 were selected so that they have electronically different substituents. Furthermore, these functionalities could be utilized as attachment sites (Fig. 1). Picolinic acid (17) was selected as ‘standard’ with neither electron withdrawing nor donating groups. 5-(Methoxycarbonyl)picolinic acid 18 was prepared using a known procedure through exhaustive esterification and selective hydrolysis (Scheme 6).

Methyl 5-bromopicolinate 22 was prepared according to known procedures by selective lithiation (Scheme 4). Methyl 5-bromopicolinate 22 was prepared according to known procedures by selective lithiation (Scheme 4). Methyl 5-bromopicolinate 22 was prepared according to known procedures by selective lithiation (Scheme 4). Methyl 5-bromopicolinate 22 was prepared according to known procedures by selective lithiation (Scheme 4). We attempted to prepare the acetylenic adduct 19 using standard Sonogashira-conditions in various solvents, but a reproducible protocol was not achieved. Excluding the copper, however, gave excellent results, in contrast to previous literature studies regarding pyridine ring coupling at the 5-position. In that paper, a strict Cu/Pd-ratio was required to achieve acetylenic coupling at the 5-position.

Scheme 2. (i) 12, DIPEA, CH$_2$Cl$_2$, rt, 5 → 13: 18 h; 10 → 14: 20 min.

Scheme 3. (i) Merrifield resin, loading 1.59 mmol/g, K$_2$CO$_3$, KI, DMF, 70 °C, 19 h; (ii) NaBH$_4$, LiI, THF, reflux, 7 h; (iii) $p$-TsOH, CH$_2$Cl$_2$, THF, rt, 1.5 h.

Figure 2. The picolinic acid derivatives used in linking and PyOX formation.
An explanation for this controversial result is probably the methyl ester group at the 2-position in our case (compound 22, Scheme 4). In our hands, coupling of 22 and 23 proceeded, but did not reach complete conversion. Instead, coupling of 22 and 24 gave a total conversion and excellent yield. The ester 25 was then hydrolyzed to give 19 (Scheme 4).

The PyOX core on solid support was constructed by first coupling the picolinic acid and the amine followed by cyclization of the formed amido alcohol using suitable reagents. We optimized the cyclization to suit all PyOX-precursors tested thus far using mesylate activation and DBU assisted cyclization.

Model experiments were performed to examine the signals on FTIR and define characteristic signals for a facile monitoring of the reaction progress on solid support. The most informative signal turned out to be the amide signal: the signal of amido alcohol 26 was present, as the coupling of 6 and 18 was made. Mesylation of 26 shifted the amide signal to a higher wave number, as expected. The mesyl signal was in the fingerprint region and thus very hard to detect and define, especially in the case of the resins. The slowest reaction step, that is, cyclization to 28 (Scheme 5), could also be monitored using FTIR, because of the apparent signal shift towards a lower wavenumber. A summary of changes in the IR shift is shown in Table 1.

To our knowledge, this is the first time a solid-supported PyOX-ligand has been prepared by simultaneous linking and cyclization. In the rare reported cases, the solid-supported PyOX-ligands have been prepared by forming the PyOX-core and then attaching the compound to a solid support. We reasoned that formation of the PyOX on the solid support allows to use efficient reactions and monitor the reactions reliably. The picolinic acid derivatives 18–19 were all attached using a peptide coupling protocol, viz.

Scheme 4. (i) MeOH, H2SO4, reflux, 22 h; (ii) NaOH, MeOH, reflux, 2 h, 62% (from 20); (iii) n-BuLi, PhMe, –77 °C, 3 h; (iv) CO2; (v) SOCl2, reflux, 4 h; (vi) MeOH, NEt3, rt, 46% (over four steps); (vii) TBSCI, NEt3, DMAP, CH2Cl2, rt, 20 h, 85%; (viii) 24, Pd(PPh3)2Cl2, NEt3, THF, reflux, 24 h, 92%; (ix) NaOH, aqueous MeOH, reflux, 6 h, 64%.

Scheme 5. Model compounds for FTIR analysis. (i) (a) 18, SOCl2, reflux, 2.5 h, (b) 6, NEt3, CH2Cl2, rt, 15 min, 62% (from 18); (ii) MsCl, NEt3, DMAP, CH2Cl2, rt, 1 min, 81%; (iii) DBU, THF, 40 °C, 24 h, 43%.

An explanation for this controversial result is probably the methyl ester group at the 2-position in our case (compound 22, Scheme 4). In our hands, coupling of 22 and 23 proceeded, but did not reach complete conversion. Instead, coupling of 22 and 24 gave a total conversion and excellent yield. The ester 25 was then hydrolyzed to give 19 (Scheme 4).

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Acid chloride formation turned out to be too vigorous, since the use of acid chlorides also gave rise to double coupling, that is, also the corresponding amido ester was formed. In the case of picolinic acid attachment, however, this was not the case and the acid chloride protocol could be used. Activation of the amido alcohols was achieved with the usual mesylation protocol and cyclization was efficiently performed with DBU to form the PyOX-ligands (Scheme 6). In none of the cases could the cyclization be brought to completion using the one-step cyclization by Meyers, involving either the tosylate or the mesylate activation. The general reaction path is shown in Scheme 6.

### Table 1. The IR signals of either the amide or the C=N-group of oxazoline

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Amido alcohol</th>
<th>Mesylate</th>
<th>PyOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>CO₂Me</td>
<td>1651</td>
<td>1666</td>
<td>1637</td>
</tr>
<tr>
<td>H</td>
<td>CO₂Me</td>
<td>1662</td>
<td>1669</td>
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<tr>
<td></td>
<td>OTBS</td>
<td>1656</td>
<td>1671</td>
<td>1636</td>
</tr>
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</table>

HOBT/DIC-activation. Acid chloride formation turned out to be too vigorous, since the use of acid chlorides also gave rise to double coupling, that is, also the corresponding amido ester was formed. In the case of picolinic acid attachment, however, this was not the case and the acid chloride protocol could be used. Activation of the amido alcohols was achieved with the usual mesylation protocol and cyclization was efficiently performed with DBU to form the PyOX-ligands (Scheme 6). In none of the cases could the cyclization be brought to completion using the one-step cyclization by Meyers, involving either the tosylate or the mesylate activation. The general reaction path is shown in Scheme 6.

### 3. Conclusions

A new and general method to form PyOX-ligands on solid support is presented. It involves a simple path to link picolinic acids and functionalize them as the PyOX-core in three steps. Functionalization at the 5-position of the pyridine ring has also been carried out. The aim of functionalizing the 5-position was to build further functional groups for various needs. It is also surprisingly easy to differentiate between the 2-position and the 5-position of the pyridine ring due to the reactivity gap between these positions. This gives nearly unlimited resources, when variation around the PyOX-core is needed. Our strategy gives also the opportunity to link the PyOX-core from either the oxazoline or the pyridine ring. New support materials will also be used in the formation of supported PyOX-ligands. We are currently exploring one application, the use of the mercapto ester derived PyOX in nanotechnology, which will be reported in due course.

### 4. Experimental

#### 4.1. General methods

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. Non-aqueous reagents were transferred under argon via syringe and dried prior to use. Toluene was distilled from Na, THF was distilled from Na/benzophenone. CH₂Cl₂ was distilled from CaH₂. Other solvents and reagents were used as

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**Scheme 6.** Formation of the PyOX-ligands. (i) 5-R-picolinic acid, HOBT, DIC, CH₂Cl₂, DMF, rt; (ii) MsCl, NEt₃, DMAP, CH₂Cl₂, rt; (iii) DBU, THF, 50 °C.
obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light or by staining upon heating with KMnO4-solution (1.0 g KMnO4, 6.7 g K2CO3, 1.7 ml 5% aqueous NaOH-solution, 100 ml H2O) or ninhydrin solution (1.0 g ninhydrin, 0.2 ml glacial AcOH, 100 ml EtOH). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted. The 1H and 13C NMR spectra were recorded in either CDCl3 or d6-DMSO on a Bruker Avance 400 (1H 399.98 MHz; 13C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to CDCl3 (δ 7.26) or d6-DMSO (δ 2.50) as an internal standard. For the 13C NMR spectra, the residual CDCl3 (δ 77.0) or d6-DMSO (δ 39.5) were used as the internal standard. The optical purity of products 13 and 14 was determined by HPLC in comparison to the corresponding racemic samples using Waters 501 pump and Waters 486 detector. ThermoHypersil column and i-PrOH/hexanes as eluent. IR spectra were recorded on a Perkin-Elmer Spectrum One spectrometer using KBr-disc. Optical rotations were obtained with a Perkin-Elmer 343 polarimeter. High-resolution mass spectrometric data were obtained at the University of Oulu on Micromass LCT spectrometer. The elemental analyses were performed at the Analytical Services of the Department of Chemical Technology, Laboratory of Organic Chemistry.

4.1.1. Phenylsulfonylproline O-benzyl-tert-butyloxycarbonyltyrosinyl esters 13 and 14. Compound 12 was prepared according to a literature procedure4 by dissolving (S)-phenylsulfonyl proline (1.27 g, 5.0 mmol) in 10 ml CH2Cl2. Oxalyl chloride (1.0 ml, 11.5 mmol, 230 mol%) was added, followed by two drops of DMF. This caused a violent heat evolution, which settled after 5 min. The oxalyl chloride (1.0 ml, 11.5 mmol, 230 mol%) and KI (430 mg, 2.59 mmol, 40 mol%) was added. After heating on a 70°C oil bath for 19 h. The resin was filtered and washed subsequently with DMF, methanol and CH2Cl2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1717.

4.1.2. N-tert-butyloxycarbonyl tyrosine methyl ester resin 15. Merrifield resin (4.61 g, 7.33 mmol based on reported loading, 100 mol%) and K2CO3 (1.78 g, 12.5 mmol, 200 mol%) were suspended in 20 ml DMF. In another flask, 3 (4.10 g, 13.9 mmol, 190 mol%) was dissolved in 40 ml DMF and K2CO3 (3.55 g, 25.7 mmol, 350 mol%) was added. After 15 min, the suspension of 3/K2CO3 was added to the resin and the mixture was heated on a 70°C oil bath for 19 h. The resin was filtered and washed subsequently with DMF, DMF/H2O 1:1, DMF, methanol and CH2Cl2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1685.

4.1.3. N-tert-butyloxycarbonyl tyrosinol resin 16. Functionalised resin 15 (2.10 g, 3.34 mmol, 100 mol%) was suspended in 50 ml THF. LiI (4.47 g, 33.4 mmol, 1000 mol%) was added, followed by NaBH4 (1.26 g, 33.3 mmol, 1000 mol%). The mixture was set for reflux for 7 h and filtered. It was washed subsequently with THF/H2O 1:1, THF, methanol and CH2Cl2. The resin was dried at the aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1685.

4.1.4. Tyrosinol resin 1. To 16 (2.00 g, 3.18 mmol, 100 mol%) was added a stock solution3 of p-TsOH.
100 mol%), 18 ml dry THF, NEt₃ (0.58 ml, 4.16 mmol, 2.50 mmol, 92%) as an almost colourless oil. 19 picolinate 25.

and the mixture was set for reflux for 6 h. The solution was ground NaOH (82 mg, 2.05 mmol, 110 mol%) was added and the mixture was heated to reflux for 24 h and diluted with CH₂Cl₂. It was quenched with saturated aqueous NaHCO₃ and extracted three times with CH₂Cl₂. The organics were washed with brine and dried over Na₂SO₄ to give 1.56 g of a dark brown oil. It was purified by FC (EtOAc/hexane 1:4) to give 25 (800 mg, 2.50 mmol, 92%) as an almost colourless oil. Rᵣ = 0.29 (EtOAc/hexane 1:1, UV). ¹H NMR (400 MHz, CDCl₃) δ 8.70 (dd, J = 0.8, 2.0 Hz, 1H, 6-Py-CH), 8.04 (dd, J = 0.8, 8.0 Hz, 1H, 3-Py-CH), 3.93 (s, 3H, –CO₂Me), 3.81 (t, J = 6.8 Hz, 2H, –CH₂CH₂OSi(R₃)), 2.65 (t, J = 6.8 Hz, 2H, –CH₂CH₂OSi(R₃)), 0.89 (s, 9H, –(CH₃)₃), 0.07 (s, 6H, –Si(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ 165.2 (–CO₂CH₃), 152.2 (6-Py-CH), 145.7 (2-Py-C–CO₂Me), 139.2 (4-Py-C), 124.4 (3-Py-C), 124.3 (5-Py-C-R), 94.6 (Ar-C≡C–CH₂R), 77.9 (Ar-C≡C–CH₂R), 61.4 (–CH₂CH₂OSi(R₃)), 52.8 (–CO₂CH₃), 25.8 (–SiR(C(CH₃)₃)₂), 24.0 (–C≡C–CH₂–R), 18.3 (–SiR₂(CH₂C(OH)₃)), –5.3 (–Si(CH₃)₂CH₂CH₂O); HRMS (ESI) calc for C₁₅H₂₅NO₃Si 320.1682, found 320.1690 (M+1).

4.1.8. 5-Methoxy carbonylpicolinyl-(1′-(S)-(p-benzyloxyphenyl)-2′-mesoxy)ethylamide 27. Amide 26 (50 mg, 0.12 mmol, 100 mol%) was dissolved in 3 ml CH₂Cl₂, Et₃N (0.10 ml, 0.72 mmol, 600 mol%) and DMAP (3 mg, 0.03 mmol, 20 mol%) were added, followed by MsCl (30 µl, 0.39 mmol, 320 mol%). This caused a spontaneous heating of the mixture. TLC monitoring showed total conversion after 3 min. The reaction was quenched with water 10 min later. The mixture was extracted three times with CH₂Cl₂. The combined organics were washed with brine and dried over Na₂SO₄. The solvents were evaporated and the crude mixture filtered through a short pad of silica and recrystallized from EtOAc/hexane to yield 48 mg (0.10 mmol, 81%) of 27 as a white solid. Rᵣ = 0.15 (EtOAc/hexane 1:1, KMnO₄); [α]D²⁵ + 21.0 (c 0.07, CHCl₃); mp 115–117.5 °C; IR (KBr, cm⁻¹) 2229, 1703; ¹H NMR (400 MHz, d₆-DMSO) δ 8.62 (s, 1H, 6-Py-CH), 7.97 (d, J = 7.9 Hz, 1H, 4-Py-CH), 7.90 (d, J = 8.0 Hz, 1H, 3-Py-CH), 3.80 (t, J = 6.4 Hz, 2H, –CH₂CH₂–OSi(R₃)), 2.68 (t, J = 6.4 Hz, 2H, –CH₂CH₂OSi(R₃)), 2.08 (s, 1H, –CO₂H), 0.89 (s, 9H, –(CH₃)₃), 0.08 (s, 6H, –Si(CH₃)₂); ¹³C NMR (100 MHz, d₆-DMSO) δ 165.8 (–CO₂CH₃), 151.1 (6-Py-C), 147.9 (2-Py-C–CO₂H), 139.3 (4-Py-C), 124.1 (3-Py-C), 122.7 (5-Py-C-R), 94.5 (Ar-C≡C–CH₂R), 77.9 (Ar-C≡C–CH₂R), 61.0 (–CH₂CH₂OSi(R₃)), 25.7 (–SiR₂(CH₂C(OH)₃)), 23.3 (–C≡C–CH₂–R), 17.9 (–SiR(C(CH₃)₃)), –5.3 (–Si(CH₃)₂CH₂CH₂O); HRMS (ESI) calc for C₁₇H₂₃NO₅SiNa 328.1345, found 328.1342 (M + Na).

4.1.7. 5-Methoxy carbonylpicolinyl-(1′-(S)-(p-benzyloxyphenyl)-2′-hydroxy)ethylamide 26. Acid 18 (70 mg, 0.39 mmol, 100 mol%) was refluxed in 3 ml SOCl₂ for 2.5 h. The mixture was evaporated to dryness. Amino alcohol 6 (100 mg, 0.39 mmol, 100 mol%) was dissolved in 4 ml CH₂Cl₂ and 0.30 ml NEt₃. The residue of 18 was dissolved in 2 ml CH₂Cl₂ and this solution was added to the solution of 6. After 15 min, ice water was added to the mixture and it was extracted three times with CH₂Cl₂. The combined organics were washed with brine and dried over Na₂SO₄. The solvents were evaporated and the crude product recrystallized from EtOAc/hexane to yield 100 mg (0.24 mmol, 62%) of 26 as a white solid. Rᵣ = 0.15 (EtOAc/hexane 1:1, KMnO₄); [α]D²⁵ − 25.5 (c 0.07, CHCl₃); mp 165–165.5 °C; IR (KBr, cm⁻¹) 1717, 1651; ¹H NMR (400 MHz, CDCl₃) δ 6.912 (dd, J = 0.9, 2.0 Hz, 1H, 6-Py-CH), 8.44 (dd, J = 2.0, 8.0 Hz, 1H, 4-Py-CH), 8.30 (d, J = 8.2 Hz, 1H, –NHCO₂Ar), 8.25 (dd, J = 0.8, 8.0 Hz, 1H, 3-Py-CH), 7.43–7.30 (m, 5H, Ar-H), 7.19 (d, J = 8.6 Hz, 2H, Ar-H), 6.92 (d, J = 8.6 Hz, 2H, Ar-H), 5.04 (s, 2H, PhCH₂OAr), 4.32 (m, 1H, –CH₂CH₂(NHCOAr(CH₂OH)), 3.99 (s, 3H, –CO₂CH₃), 3.81 (m, 1H, –RC(O)CH₂ArOH-A), 3.73 (m, 1H, –RC(O)CH₂ArOH-B), 2.96 (m, 2H, Ar-CH₂–CH₂R), 2.47 (t, J = 5.4 Hz, 1H, –CH₂OH); ¹³C NMR (100 MHz, CDCl₃) δ 165.0 (Ar-C=CH₂), 163.7 (–NHCO₂Ar), 157.6 (C₆H₅–OR), 152.6 (2-Py-C–CONH), 149.4 (6-Py-C), 138.5 (C₆H₅–CH₂OAr), 137.0 (4-Py-C), 130.2 (Ar), 129.7 (Ar), 128.5 (Ar), 128.1 (Ar), 127.9 (Ar), 127.4 (Ar), 121.8 (Ar), 115.0 (Ar), 70.0 (PhCH₂OAr), 64.3 (–R₂CH₂OH), 53.5 (–R₂CH₂CH₂OH), 52.6 (–CO₂CH₃), 36.3 (ArCH₂CHR); HRMS (ESI) calc for C₂₂H₃₅N₂O₅Na 443.1583, found 443.1576 (M + Na).
4.1.9. 5-Methoxycarbonyl-2-(4′-(5)-p-benzyloxybenzyl-2′-oxazolino)-pyridine 28. Mesylate 27 (26 mg, 52 μmol, 100 mol%) was dissolved in 4 ml THF. DBU (35 μl, 230 μmol, 450 mol%) was added and the mixture was stirred for 20 h at 40 °C oil bath for 24 h. The reaction was quenched with water and brine and dried over Na2SO4. The crude product was purified by FC (EtOAc/hexane 2:1) to yield 9 mg (22 μmol, 43%) of 28 as a white solid. Rf = 0.45 (EtOAc/hexane 2:1, UV); [α]D 22 +18.0 (c 0.07; CH2Cl2); mp 165–170 °C (dec); IR (KBr, cm−1) 1716, 1637; 1H NMR (400 MHz, CDCl3) δ 8.28 (dd, J = 0.5, 2.0 Hz, 1H, 6-Py-C), 8.38 (dd, J = 2.1, 8.2 Hz, 1H, 4-Py-CH), 8.13 (dd, J = 0.5, 8.2 Hz, 1H, 3-Py-CH), 7.44–7.30 (m, 5H, Ar-H), 7.17 (d, J = 8.6 Hz, 2H, Ar-H), 6.92 (d, J = 8.6 Hz, 2H, Ar-H), 5.05 (s, 2H, PhCH2OAr), 4.65 (app dq, J = 5.3, 8.7 Hz, 1H, 4-oxazoline-CH), 4.48 (app t, J = 8.7 Hz, 1H, 5-oxazoline-CH2-A), 4.25 (app t, J = 8.7 Hz, 1H, 5-oxazoline-CH2-B), 3.98 (s, 3H, –CO2CH3), 3.22 (dd, J = 5.3, 13.9 Hz, 1H, Ar-CH2-oxazoline-A), 2.74 (dd, J = 8.7, 13.9 Hz, 1H, Ar-CH2-oxazoline-B); 13CN M R δ 157.7 (Ar-CO), 155.0 (4-OAr), 153.7 (5-oxazoline-C), 70.1 (PrCH2OAr), 68.4 (4-oxazoline-C), 52.6 (CO2CH3), 40.6 (Ar-CH2-oxazoline); HRMS (ESI) calcd for C24H22N2O4 403.1658, found 403.1653 (M + 1).

4.1.10. Picolanyl amido alcohol resin 29. Resin 1 (203 mg, 0.32 mmol based on the reported Merrifield resin loading 1.59 mmol/g, 100 mol%) was suspended in 3 ml CH2Cl2 and 0.2 ml NEt3. To the solution was added 46 mg (0.32 mmol, 100 mol%) of picolanyl chloride (prepared from 17). The solution turned dark blue in a matter of minutes. The resin was filtered 3 h later and washed subsequently with DMF/H2O 3:1, DMF, methanol and CH2Cl2. Resin 29 was dried, first at the aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1662.

4.1.11. (5-Methoxycarbonyl)picolinyl amido alcohol resin 30. Acid 18 (46 mg, 0.25 mmol, 110 mol%) was dissolved in 3 ml CH2Cl2 and 1 ml DMF. HOBT (35 mg, 0.26 mmol, 110 mol%) was added and allowed to stir for 60 min. The mixture was added to the suspension of resin 1 (150 mg, 0.24 mmol, 100 mol%) in 5 ml CH2Cl2, followed by DCC (40 μl, 0.26 mmol, 110 mol%). The solution turned orange after 30 min. After 24 h stirring, the resin was filtered and washed subsequently with CH2Cl2, DMF/H2O 3:1, DMF, methanol and CH2Cl2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1733, 1664.

4.1.12. (5′-(1′-Butyldimethylsilyloxy)-4′-butynyl)picolanyl amido alcohol resin 31. Acid 19 (97 mg, 0.32 mmol, 100 mol%) was dissolved in 4 ml CH2Cl2 and 1 ml DMF. HOBut (43 mg, 0.32 mmol, 100 mol%) was added and allowed to stir for 60 min. The mixture was added to the suspension of resin 1 (200 mg, 0.32 mmol, 100 mol%) in 6 ml CH2Cl2, followed by DCC (50 μl, 0.32 mmol, 100 mol%). The solution turned orange after a few hours. After 23 h stirring, the resin was filtered and washed subsequently with DMF, DMF/H2O 2:1, DMF, methanol and CH2Cl2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 2238, 1656.

4.1.13. Picolanyl amido mesylate resin 32. Amide resin 29 (50 mg, 80 μmol, 100 mol%) was suspended in 6 ml CH2Cl2 and 0.2 ml NEt3. DMAP (3 mg, 25 μmol, 30 mol%) was added, followed by MsCl (30 μl, 0.39 mmol, 490 mol%). The reaction mixture turned bright yellow with slight heating. After 17.5 h, the resin was filtered and washed subsequently with CH2Cl2, DMF and CH2Cl2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1669.

4.1.14. (5-Methoxycarbonyl)pyridyl amido mesylate resin 33. Resin 30 (70 mg, 110 μmol, 100 mol%) was suspended in 6 ml CH2Cl2 and 0.2 ml NEt3. DMAP (5 mg, 40 μmol, 40 mol%) was added, followed by MsCl (50 μl, 0.64 mmol, 580 mol%). The reaction mixture turned orange with slight heating. After 17.5 h, the resin was filtered and washed subsequently with CH2Cl2, DMF and CH2Cl2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1727, 1668.

4.1.15. (5′-(1′-Butyldimethoxysilyloxy)-4′-butynyl)pyridyl amido mesylate resin 34. Resin 31 (190 mg, 0.30 mmol, 100 mol%) was suspended in 5 ml CH2Cl2 and 0.3 ml NEt3. DMAP (10 mg, 82 μmol, 30 mol%) was added, followed by MsCl (70 μl, 0.90 mmol, 300 mol%). The reaction mixture turned orange with slight reflux. After 25 min, the resin was filtered and washed subsequently with CH2Cl2, DMF and CH2Cl2 and dried at aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 2238, 1671.

4.1.16. Pyridine 2-(2′-oxazolinyl)resin 35. Resin 32 (40 mg, 60 μmol, 100 mol%) was suspended in 3 ml THF. DBU (0.24 ml, 1.60 mmol, 2500 mol%) was added and the mixture was heated in a 50 °C oil bath for 48 h and filtered. The resin was washed subsequently with THF, DMF/10% aqueous citric acid 2:1, THF, methanol and CH2Cl2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1641.

4.1.17. (5-Methoxycarbonyl)pyridine 2-(2′-oxazolinyl)resin 36. Resin 33 (65 mg, 100 μmol, 100 mol%) was suspended in 4 ml THF. DBU (0.12 ml, 0.80 mmol, 800 mol%) was added and the mixture was heated on a 45 °C oil bath for 20 h and filtered. The resin was washed subsequently with THF, DMF/10% aqueous citric acid 2:1, DMF, methanol and CH2Cl2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 1728, 1635.

4.1.18. (5′-(1′-Butyldimethoxysilyloxy)-4′-butynyl)pyridine 2-(2′-oxazolinyl)resin 37. Resin 34 (175 mg, 280 μmol, 100 mol%) was suspended in 5 ml THF. DBU (0.23 ml, 1.54 mmol, 550 mol%) was added and the mixture was heated in a 50 °C oil bath for 22 h and filtered. The resin was washed successively with THF, THF/H2O 2:1, THF, methanol and CH2Cl2. The resin was dried at aspirator pressures and finally under high vacuum. IR (KBr, cm−1) 2237, 1636.
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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.08.073.

References and notes

15. Copies of all spectra of new compounds can be found in the Supporting information of this article.