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A simple and effective synthetic approach to chiral 4-pyridinyl proline derivatives

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Abstract—A rapid approach has been developed to provide a novel series of 4-pyridinyl proline derivatives as potential stereoselective catalysts. Nucleophilic displacement at the 4-pyridinyl position proved straightforward using proline but required microwave heating to proceed when using the more bulky α-methyl proline. Total control of enantioselectivity was obtained for the synthesis of proline derivatives.

4-Dimethylaminopyridine (DMAP) and 4-pyrrolidinopyridine (PPY) (Fig. 1) have been extensively used as potent nucleophilic catalysts in acylation reactions and related transformations.[1–7] Recently, chiral PPY derivatives have been described as powerful catalysts in kinetic resolution of racemic alcohols.[8–11] Such compounds require the presence of a stereogenic centre in order to induce stereoselectivity during the catalytic process. However, preparation of these new catalysts tends to involve complex routes of synthesis and does not generally allow facile structural modifications.

Our approach is based on the design of a 'library-friendly' route to chiral PPY derivatives, which we believe will allow rapid optimisation and may lead to novel catalysts for the reactions mentioned above. Such an approach is ideally suited for rapid iterations aimed at increasing enantioselectivity for a given substrate. Furthermore, this approach allows new families of privileged structures to become available for screening in the reaction of interest. The general structure for this new family of *N*-4-pyridinylproline derivatives **1** is represented in Fig. 1. This paper describes routes developed for the preparation of **2** and **3**, the first examples of novel PPY analogues **1**.

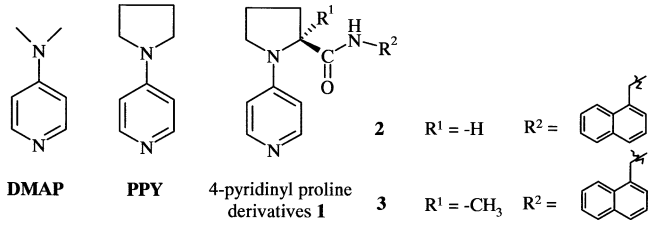

Figure 1.

The synthesis of compound **4** (Scheme 1a), the precursor of **2**, has already been described in the literature.[12,13] Compound **4** was prepared by nucleophilic substitution of 4-chloropyridine with L-proline. A carboxylate anion is pre-formed by an excess of cesium carbonate, hence avoiding racemisation of the chiral centre (ee **4** = 100%).[14]

Our first attempt to form an amide with 1-naphthylmethylamine using HATU (*O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate) as the coupling reagent gave 70% yield of a racemic mixture of enantiomers **2** and **5** after an overnight reaction (Scheme 1b, entry 1).[14] Reducing the time of experiment to 1 hour and running the reaction under the same conditions (where the starting amine and *N*,*N*-diisopropylethylamine (DIPEA) were added 15 minutes after the pre-activation of **4** by HATU), led to partial racemisation (Scheme 1b, entry 2). Finally, changing the order of addition of the starting materials

Keywords: 4-pyridinyl proline; DMAP; PPY; chiral catalysts.

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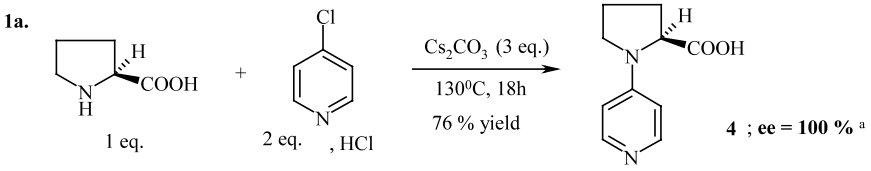
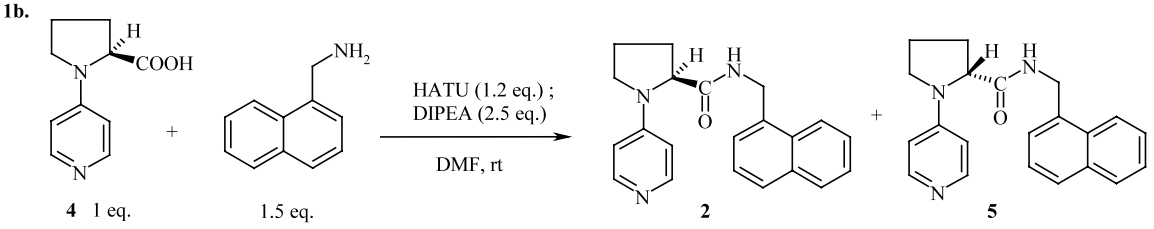


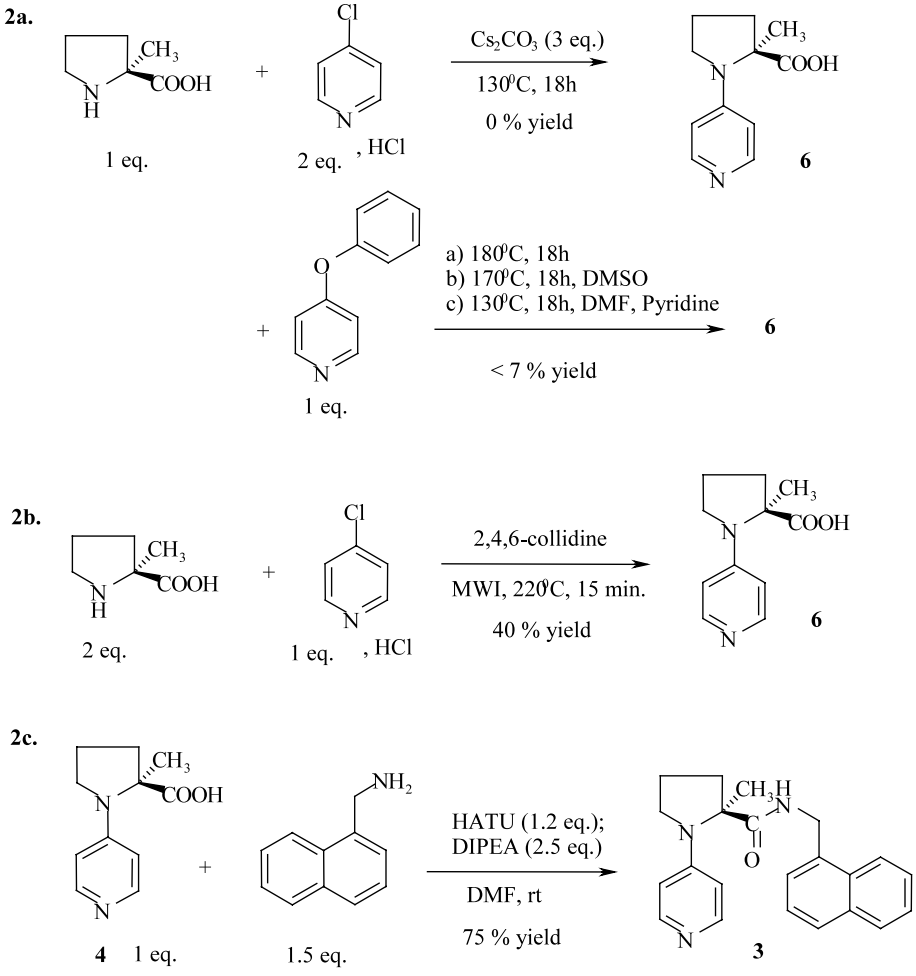
[a] enantioselectivity was determined by chiral HPLC analysis (see ref. 14)



Entries	time (h)	yield (%)	% ee[c]
1	18[a]	70	0
2	1[a]	30	50
3	1[b]	35	**100**

[a] HATU + **4** stirred together before addition of the amine and DIPEA.
[b] HATU was added last.
[c] enantioselectivity was determined by chiral HPLC analysis (see ref. 14) from the isolated fraction of **2** and **5**.

Scheme 1.



Scheme 2.

(HATU was added last) gave enantiomer **2** with lower yield (35%) but enantiomerically pure after 1 hour (Scheme 1b, entry 3).[16]

As we had concerns regarding maintaining the chiral integrity of potential catalysts containing a readily racemisable centre, we sought to prepare compound **3** (Fig. 1), containing a methyl group in the *alpha* position of the carbonyl functionality. However, the increased steric demand of this group inhibits the formation of the precursor **6**. Heating α-methyl-L-proline and 4-chloropyridine or 4-phenoxypyridine up to 180°C for prolonged periods, in the presence or absence of a base,[12,13] gave no more than a 7% yield (Scheme 2a). Given the recent use of microwave heating as a fast and powerful method for activating chemical reactions,[15] we applied this approach to the synthesis of **6**. This gave the desired compound in a greatly increased yield of 40% (Scheme 2b). Subsequent HATU coupling gave the final compound **3** in 75% yield (Scheme 2c).[16]

In conclusion, we have developed synthetic routes for the preparation of a novel family of chiral *N*-4-pyridinyl proline derivatives **1**. For the synthesis of compound **2**, we were able to overcome problems of racemisation linked to the presence of a highly acidic hydrogen in the molecule. We have also developed a new synthetic approach for the synthesis of compound **3** via a microwave reaction. These two compounds are closely related to DMAP but contain a stereogenic centre. We will report an investigation of the catalytic properties of these interesting molecules in due course.

Acknowledgements

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14. The enantiomeric excess (ee) was determined by HPLC analysis (conditions: 25 cm Chiralpak AD-H column, eluents: ethanol/heptane/TFA (3/7/0.01); flow: 1 ml/min.; 215 nm). Retention times for compounds **2**, **4** and **5** are, respectively, 16.17, 6.26 and 20.45 min.
15. For a general review on microwave reactions in organic synthesis, see Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225–9283 and 10229.
16. Compound **2**: To a solution of compound **4** (0.4 mmol) in DMF at 0°C was added consecutively 1-naphthyl-methylamine (1.5 equiv.), and DIPEA (2.5 equiv.). The mixture was stirred 15 min before addition of HATU (1.2 equiv.). After 1 h stirring, the DMF was removed and the residue was washed with a 5% $NaHCO_3$ solution, a 10% citric acid solution, water and brine. Compound **2** was purified by column chromatography (eluents: toluene/MeOH/Et_3N: 9/1/0.5); 35% yield; pale yellow solid, mp 73–75°C; ^1H NMR (CD_3OD) δ 8.00–7.65 (m, 5H, Ar*H*), 7.50–7.25 (m, 4H, Ar*H*), 6.30 (d, 2H, Ar*H*, $J=6$ Hz), 4.72 (s, 2H, -CH_2-NH-), 4.05 (dd, 1H, -C*H*-, $J=8$ Hz, $J=2$ Hz), 3.55 (m, 1H, -CH_2-N-), 3.20 (m, 1H, -CH_2-N-), 2.20–1.88 (m, 4H, -CH_2-CH_2-CH-); ^{13}C NMR (CD_3OD) δ 162.00 (*C*O), 128.44, 128.03, 127.79, 126.19, 125.98, 125.53, 124.96, 123.23, 123.03, 107.76 (*C*Ar), 62.04 (*C*H), 47.93 (*C*H_2), 41.03 (*C*H_2), 31.15 (*C*H_2), 23.35 (*C*H_2); m/z (ES)=332 (M+H^+).
Compound **6**: α-methyl-L-proline (2 equiv.) and 4-chloropyridine hydrochloride (0.4 mmol) were introduced into a 2 ml vial, with 1 ml of 2,4,6-collidine. The reaction was heated in a Smith Creator™ microwave machine (220°C, 15 min). Collidine was removed under reduced pressure and the crude residue was purified by column chromatography (eluents: DCM/MeOH/Et_3N: 8/2/0.5); 40% yield; yellow foam; ^1H NMR (CD_3OD) δ 8.02 (m, 2H, Ar*H*), 6.75 (m, 2H, Ar*H*), 3.72 (m, 2H, -CH_2-N-), 2.42–2.15 (m, 4H, -CH_2-CH_2-CH$_2$-N-), 1.57 (s, 3H, -CH_3); ^{13}C NMR (CD_3OD) δ 140.00, 116.55, 108.65 (*C*Ar), 62.19 (*C*H), 50.63 (*C*H_2), 40.83 (*C*H_2), 22.44 (*C*H_2), 20.05 (*C*H_3); m/z (ES)=207 (M+H^+).
Compound **3**: Compound **6** (0.1 mmol) was stirred in the presence of HATU (1.2 equiv.) and Et_3N (2.5 equiv.) for 1 h at 0°C before addition of 1-naphthylmethylamine (1.5 equiv.). The reaction was stirred overnight at room temperature. The DMF was removed and the residue was washed with a 5% $NaHCO_3$ solution, a 10% citric acid solution, water and brine. Compound **3** was purified by column chromatography (eluents: toluene/MeOH/Et_3N: 9/1/0.5); 75% yield; white powder, mp 95–97°C; ^1H NMR (CD_3OD) δ 7.85–7.55 (m, 5H, Ar*H*), 7.40–7.10 (m, 4H, Ar*H*), 6.10 (d, 2H, Ar*H*, $J=6$ Hz), 4.08 (s, 2H, -CH_2-NH-), 3.20 (m, 2H, -CH_2-N-), 2.10–1.80 (m, 4H, -CH_2-CH_2-C(CH$_3$)-), 1.32 (s, 3H, -CH_3); ^{13}C NMR (CD_3OD) δ 150.00 (*C*O), 134.00, 133.33, 131.00, 128.00, 127.33, 126.00, 125.33, 124.80, 124.33, 122.66, 108.66 (*C*Ar), 66.66 (*C*H), 48.53 (*C*H_2), 41.33 (*C*H_2), 40.66 (*C*H_2), 21.86 (*C*H_2); m/z (ES)=346 (M+H^+).