Kinetic resolution of sec-alcohols using a new class of readily assembled (S)-proline-derived 4-(pyrrolidino)-pyridine analogues

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We report the development of a new class of readily prepared chiral 4-(pyrrolidino)-pyridine catalysts capable of exploiting both van der Waals (π) and H-bonding interactions, thus allowing remote chiral information to stereochemically control the kinetic resolution of sec-alcohols.

The development of small chiral organic molecules capable of mimicking enzymatic action (in an asymmetric catalysis context) is a challenge that is receiving considerable attention in contemporary organic chemistry.1 Significant advances have been made recently in the design of chiral catalysts based on the tertiary phosphine2 and amine3,4 structural motifs for enantioselective acyl-transfer reactions and a range of other processes susceptible to the influence of nucleophilic catalysis.3 The reactive and robust catalyst N,N-dimethylaminopyridine (DMAP),5 has been demonstrated to be a particularly useful target for desymmetrisation by Vedejs,6 Fu,7 Spivel,8 and (inter alia)9 Fuji.10

The most successful designs for pyridine-based catalytic systems represent a practical compromise between the opposing considerations of reactivity and selectivity; i.e. to maximise selectivity it is desirable to install chiral information as close to the site of acylation as possible, however reaction rates (and therefore the $k_{\text{cat}}:k_{\text{sec}}$ ratio) in these systems are remarkably sensitive to substitution adjacent to the nucleophilic ring-heteroatom.11 An interesting approach to addressing this issue is embodied by 1 (Fig. 1), which operates vis a ‘induced-fit’ mechanism whereby, in the absence of an acylating agent, the catalyst adopts an ‘open’ unhindered (and therefore reactive) form, but which on acylation adopts a ‘closed’ conformation due to an attractive π–π interaction between the pyridinium ring and the naphthyl moiety, resulting in the stereoselective shielding of one face of the acylated catalyst.12

![Fig. 1 Chiral 4-(pyrrolidino)-pyridine analogues.](Image)

In this context, we were intrigued by a report demonstrating that the 3-substituted pyridine $\text{2}$ exhibited a similar π–π stacking interaction on acylation/alkylation,12 allowing the subsequent attack of a nucleophile at C-4 ($\text{2a}$, Fig. 1) to proceed in a face-selective manner.12,13 We therefore reasoned that a 4-pyrrolidino-analogue of $\text{2}$ (i.e. $\text{3}$ [Fig. 1]) held promise as a tuneable and easily-constructed acyl-transfer catalyst template capable of operating via an induced-fit mechanism. With a view toward maximising both catalyst rigidity and potential for π–π interaction, novel (S)-proline-derived structures $\text{4}$ and $\text{5}$ also seemed worthy of investigation.

The synthesis of $\text{3}$ was carried out as outlined in Scheme 1. Treatment of 3-carboxy-4-chloropyridine ($\text{6}$)14 with thionyl chloride furnished the corresponding acid chloride hydrochloride, which was then coupled with amine $\text{7}$ to afford amide $\text{8}$ in reasonable yield. Subsequent substitution of the 4-chloro-substituent with excess pyrrolidine afforded catalyst $\text{3}$. In a similar fashion, $\text{4}$ and $\text{5}$ were prepared from $\text{6}$ using commercially available enantiopure (S)-α,α-diphenylprolinol ($\text{9}$) and its readily accessible 2-naphthyl analogue $\text{10}$ (Scheme 1).

![Scheme 1. Synthesis of catalysts $\text{3, 4}$ and $\text{5}$.](Image)

Catalysts $\text{3–5}$ were evaluated in the kinetic resolution of mono-protected diols $\text{13–15}$ in the presence of isobutyric anhydride (Table 1). As expected, $\text{3–5}$ promoted the smooth acylation of $\text{13–15}$ at low catalyst loadings. While the prototype catalyst $\text{3}$ exhibited disappointing selectivity (entry 1),17 acylation promoted by the (S)-prolinol-derived $\text{4}$ and $\text{5}$ was considerably more enantioselective (entries 2–7), with synthetically useful selectivity possible at low temperature (entry 3). It is noteworthy that the exchange of the phenyl substituents of catalyst $\text{4}$ for 2-naphthyl moieties (catalyst $\text{5}$) resulted in a marginal improvement in performance (entries 4 and 6), and that a decrease in the substrate carbonyl Lewis-basicity led to an attenuation of enantioselectivity (entries 5–7), indicating that catalyst-substrate H-bonding may contribute to selectivity in these systems.19

To determine the influence of the hydroxyl group on catalyst selectivity, reduced analogues of $\text{4}$ and $\text{5}$ ($\text{19}$ and $\text{20}$, respectively), were prepared using an identical strategy to that outlined in Scheme 1.20 Catalysts $\text{4, 5, 19}$ and $\text{20}$ were then compared in the kinetic resolution of alcohol $\text{21}$ (Table 2).
Table 1  Evaluation of 3–5 in the kinetic resolution of sec-alcohols 13–15

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>ROH</th>
<th>T/°C</th>
<th>C (%)(^{a})</th>
<th>Ee (%)(^{b})</th>
<th>S(^{c})</th>
<th>Absolute configuration(^{d})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>13</td>
<td>25</td>
<td>55</td>
<td>13</td>
<td>1.4</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>13</td>
<td>25</td>
<td>78</td>
<td>93</td>
<td>4.9</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>13</td>
<td>-78</td>
<td>69(^{p})</td>
<td>97</td>
<td>9.4</td>
<td>(1S, 2R(^{p}))</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>13</td>
<td>25</td>
<td>68</td>
<td>74</td>
<td>4.3</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>13</td>
<td>25</td>
<td>73.5</td>
<td>90</td>
<td>5.4</td>
<td>(1S, 2R)</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>14</td>
<td>25</td>
<td>71</td>
<td>80</td>
<td>4.4</td>
<td>(1S, 2R(^{f}))</td>
</tr>
<tr>
<td>7</td>
<td>5</td>
<td>15</td>
<td>25</td>
<td>88</td>
<td>95</td>
<td>3.5</td>
<td>(1S, 2R(^{f}))</td>
</tr>
</tbody>
</table>

\(^{a}\) Refers to conversion, which could be determined (with excellent agreement) either by \(^{1}\)H NMR spectroscopy or using chiral HPLC, where \(C = 100 \times \epsilon_{\text{elution}} / (\epsilon_{\text{elution}} + \epsilon_{\text{eqalcohol}})\). \(^{b}\) Ee of 13\(^{a}\)–15\(^{a}\) determined by chiral HPLC using a Chiralcel OJ-H column (4.6 × 250 mm). \(^{c}\) S = selectivity index \((k_{\text{fast}} / k_{\text{slow}})\), see ref. 18. \(^{d}\) Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times (ref. 19). \(^{e}\) Tentative assignment assuming that the elution order is identical to that of the p-dimethylamino-benzoate.

Table 2  Determination of the H-bonding contribution to selectivity

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>C (%)(^{a})</th>
<th>Ee(_{\text{alcohol}}) (%)(^{b})</th>
<th>Ee(_{\text{ester}}) (%)(^{b})</th>
<th>S(^{c})</th>
<th>Absolute configuration(^{d})</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>72</td>
<td>93</td>
<td>29</td>
<td>6.3</td>
<td>(R)</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>43(^{r})</td>
<td>51</td>
<td>63</td>
<td>8.7</td>
<td>(R)</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>36</td>
<td>22</td>
<td>36</td>
<td>2.8</td>
<td>(S)</td>
</tr>
<tr>
<td>4</td>
<td>20</td>
<td>43</td>
<td>30</td>
<td>38</td>
<td>3.0</td>
<td>(S)</td>
</tr>
</tbody>
</table>

\(^{a}\) Refers to conversion, which could be determined (with excellent agreement) either by \(^{1}\)H NMR spectroscopy or using chiral HPLC, where \(C = 100 \times \epsilon_{\text{elution}} / (\epsilon_{\text{elution}} + \epsilon_{\text{eqalcohol}})\). \(^{b}\) Determined by chiral HPLC using a Chiralcel OD-H column (4.6 × 250 mm). \(^{c}\) S = selectivity index \((k_{\text{fast}} / k_{\text{slow}})\), see ref. 18. \(^{d}\) Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times (ref. 19). \(^{e}\) 0.8 eq. (PrCO)\(_{2}\)O, 8 h.

While the hydroxy-substituted catalysts 4 and 5 promoted acylation with a useful level of selectivity (entries 1 and 2), 19 and 20 furnished recovered alcohol 21a with relatively poor enantioselectivity and with the opposite sense of stereoinduction to that observed using 4 and 5 (entries 3 and 4). These findings strongly indicate that the hydroxyl moiety plays a critical role in determining the preference of the acylated catalyst for one antipode of the sec-alcohol racemate in these reactions.\(^{21}\)

In an attempt to detect possible aryl-pyridinium ion π-stacking interactions, the \(^{1}\)H NMR spectra of catalysts 4, 5, 19, 20 and control material 23 (prepared from 6 and pyrrolidine) was compared to that of their corresponding products on methylation with iodomethane (Table 3).\(^{12}\) These experiments were instructive; while little evidence was found to support a ‘face–face’ π–π stacking interaction (Fig. 1).\(^{12}\) \(^{12}\) A strong upfield shift associated with H-2 upon methylation of 4, 5, 19 and 20 (which is absent on methylation of 23) was observed, the magnitude and localisation of which indicates that an interaction between the substituted edge of the pyridinium cation (or H-2 itself) and one of the pendant aryl moieties takes place.\(^{22}\) This effect is more dramatic in the case of naphthyl-substituted 25a and 26a, where even the pyridinium methyl protons are significantly shielded relative to the corresponding 25a methyl group. It is also noteworthy that H-2 is observed at considerably higher field in the cases of 4 and 5 than for 23, which we propose demonstrates that the aforementioned interaction is also a feature of the solution-state structure of these materials.\(^{23}\)

The results in Tables 1–3 indicate that the ability of 4 and 5 to serve as active and enantioselective acyl-transfer catalysts is due to a unique combination of both aryl-pyridinium ion π–π (or π–H) and substrate–catalyst H-bonding interactions. Based on this data, a rationale for the selectivity observed in the acylation of 21 catalysed by 4 is shown in Fig. 2. H-2 is located in the vicinity of the π-cloud of one of the phenyl substituents (the proximity of which to the ring nitrogen forces the isopropyl group to occupy the distal side of the N–N pyridine-axis), with the second phenyl moiety orientated into the solvent. In this conformation the hydroxyl group can control the Bürgi–Dunitz...
Engineering and Technology (IRCSET) and Trinity College Dublin is also gratefully acknowledged.

Notes and references

1 Characterisation data for 4: mp 144–146 °C; [α]D0 = −98 (c 0.96, CHCl3); δH (400 MHz, CDCl3), 0.95–1.18 (2H m), 1.80−2.20 (6H m), 2.90–3.15 (3H m), 3.40–3.55 (3H m), 5.20 (1H dd, J = 9.0, 8.5 Hz), 6.45 (1H, d, J = 6.0 Hz), 7.25–7.38 (5H m), 7.41–7.53 (4H m), 7.60 (2H, d, J = 6.0 Hz), 8.09 (1H d, J = 6.0 Hz); δC (100 MHz, CDCl3), 23.3, 25.1, 30.2, 48.8, 51.6, 63.8, 81.1, 108.1, 116.2, 127.0, 127.1, 127.2, 127.3, 127.4, 127.6, 142.1, 144.6, 146.6, 147.6, 148.8, 170.4; HRMS caledd for C31H39NO3: (M + 1) 428.2328, found 428.2338.


17 It is noteworthy that two distinct rotameric forms of 3 (in a ca. 1:1 ratio) are identifiable by $^1H$ NMR spectroscopy and that the opposite rotamer to that shown in Fig. 1 would be unable to adopt a conformation conducive to π–π stacking.


19 Fuji et al. have suggested that the greater selectivity observed using 13 is due to an additional π-stacking interaction with the acylated catalyst.


21 Screening studies identified CH2Cl2 as an ideal solvent, use of protic, polar aprotic and aromatic solvents (e.g. toluene) resulted in lower selectivity.


23 Preliminary crystal structure data indicates that the solid-state conformation of 4 is dominated by an intramolecular hydrogen bond between the hydroxy group and the amide carbonyl oxygen, which could explain neither the observed selectivity nor the $^1H$ NMR chemical shift data outlined in Table 3.

24 Both antipodes of α,α-diphenylprolinol are commercially available.