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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 phosphine[2] and amine[3–5] 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),[6] has been demonstrated to be a particularly useful target for desymmetrisation by Vedejs,[7] Fu,[8] Spivey,[9] and (*inter alia*[10]) Fuji.[11]

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_{cat} : k_{uncat} ratio) in these systems are remarkably sensitive to substitution adjacent to the nucleophilic ring-heteroatom.[3a] An interesting approach to addressing this issue is embodied by **1** (Fig. 1), which operates *via* an '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.[11a]

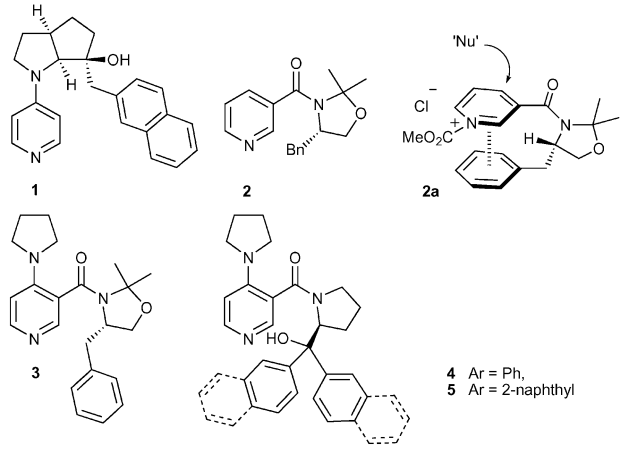
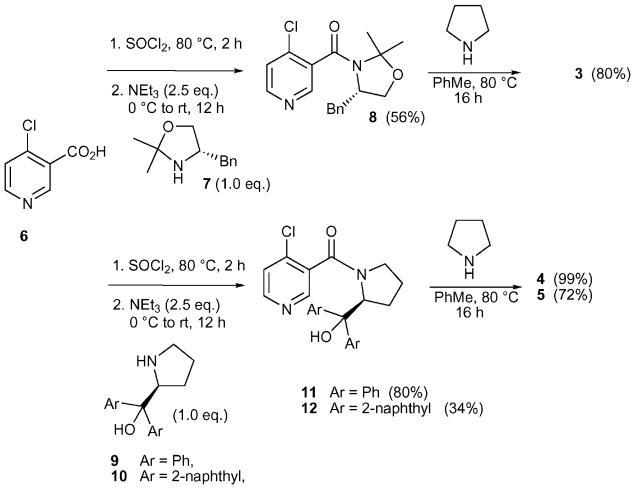


Fig. 1 Chiral 4-(pyrrolidino)-pyridine analogues.

In this context, we were intrigued by a report demonstrating that the 3-substituted pyridine **2** exhibited a similar π–π stacking interaction on acylation/alkylation,[12] allowing the subsequent attack of a nucleophile at C-4 (**2a**, Fig. 1) to proceed in a face-selective manner.[12,13] We therefore reasoned that a 4-pyrrolidino-analogue of **2** (*i.e.*, **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 **4** and **5** also seemed worthy of investigation.

The synthesis of **3** was carried out as outlined in Scheme 1. Treatment of 3-carboxy-4-chloropyridine (**6**)[14] with thionyl chloride furnished the corresponding acid chloride hydrochloride, which was then coupled with amine **7**[15] to afford amide **8** in reasonable yield. Subsequent substitution of the 4-chloro-substituent with excess pyrrolidine afforded catalyst **3**. In a similar fashion, **4**† and **5** were prepared from **6** using commercially available enantiopure (*S*)-α,α-diphenylprolinol (**9**) and its readily accessible 2-naphthyl analogue **10**[16] (Scheme 1).



Scheme 1 Synthesis of catalysts **3**,**4** and **5**.

Catalysts **3**–**5** were evaluated in the kinetic resolution of mono-protected diols **13**–**15** in the presence of isobutryic anhydride (Table 1). As expected, **3**–**5** promoted the smooth acylation of **13**–**15** at low catalyst loadings. While the prototype catalyst **3** exhibited disappointing selectivity (entry 1),[17] acylation promoted by the (*S*)-prolinol-derived **4** and **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 **4** for 2-napthyl moieties (catalyst **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 **4** and **5** (**19** and **20**, respectively), were prepared using an identical strategy to that outlined in Scheme 1.[20] Catalysts **4**, **5**, **19** and **20** were then compared in the kinetic resolution of alcohol **21** (Table 2).

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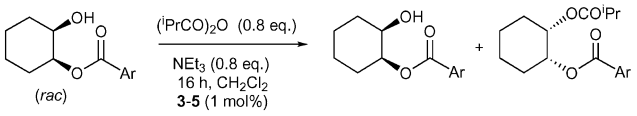
Table 1 Evaluation of **3**–**5** in the kinetic resolution of *sec*-alcohols **13**–**15**



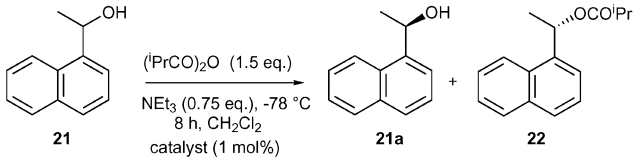
13 Ar = 4-$NMe_2C_4H_6$
14 Ar = 4-$OMeC_4H_6$
15 Ar = C_6H_5

13a Ar = 4-$NMe_2C_4H_6$ **16** Ar = 4-$NMe_2C_4H_6$
14a Ar = 4-$OMeC_4H_6$ **17** Ar = 4-$OMeC_4H_6$
15a Ar = C_6H_5 **18** Ar = C_6H_5

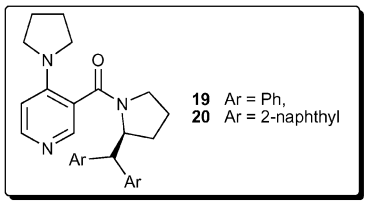
Entry	Catalyst	ROH	T/°C	*C* (%)[a]	Ee (%)[b]	*S*[c]	Absolute configuration[d]
1	**3**	**13**	25	55	13	1.4	(1*S*, 2*R*)
2	**4**	**13**	25	78	93	4.9	(1*S*, 2*R*)
3	**4**	**13**	−78	69[e]	97	9.4	(1*S*, 2*R*)
4	**4**	**14**	25	68	74	4.3	(1*S*, 2*R*)[f]
5	**5**	**13**	25	73.5	90	5.4	(1*S*, 2*R*)
6	**5**	**14**	25	71	80	4.4	(1*S*, 2*R*)[f]
7	**5**	**15**	25	88	95	3.5	(1*S*, 2*R*)[f]

[a] Refers to conversion, which could be determined (with excellent agreement) either by ^{1}H NMR spectroscopy or using chiral HPLC, where $C = 100 \times ee_{alcohol}/(ee_{alcohol} + ee_{ester})$. [b] Ee of **13a**–**15a** determined by chiral HPLC using a Chiralcel OD-H column (4.6 × 250 mm). [c] *S* = selectivity index (k_{fast}/k_{slow}, see ref. 18). [d] Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times (ref. 10*d*). [e] 1.5 eq. $(^iPrCO)_2O$, 8 h. [f] 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



21 **21a** **22**



19 Ar = Ph,
20 Ar = 2-naphthyl

Entry	Catalyst	*C* (%)[a]	$Ee_{alcohol}$ (%)[b]	Ee_{ester} (%)[b]	*S*[c]	Absolute configuration[d]
1	**4**	72	93	29	6.3	(*R*)
2	**5**	43[e]	51	63	8.7	(*R*)
3	**19**	36	22	36	2.8	(*S*)
4	**20**	43	30	38	3.0	(*S*)

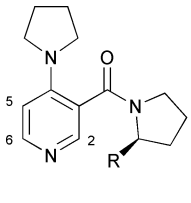
[a] Refers to conversion, which could be determined (with excellent agreement) either by ^{1}H NMR spectroscopy or using chiral HPLC, where $C = 100 \times ee_{alcohol}/(ee_{alcohol} + ee_{ester})$. [b] Determined by chiral HPLC using a Chiralcel OD-H column (4.6 × 250 mm). [c] *S* = selectivity index (k_{fast}/k_{slow}, see ref. 18). [d] Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times (ref. 9*h*). [e] 0.8 eq. $(^iPrCO)_2O$, 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]

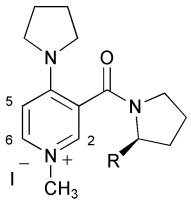
In an attempt to detect possible aryl-pyridinium ion π-stacking interactions, the ^{1}H NMR spectra of catalysts **4**, **5**, **19**, **20** and control material **23** (prepared from **6** and pyrrolidine) was compared to that of their corresponding products on methylation with iodomethane (Table 3).[12] These experiments were instructive; while little evidence was found to support a 'face–face' π–π stacking interaction (Fig. 1),[11,12] 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 **5a** and **20a**, where even the pyridinium methyl protons are significantly shielded relative to the corresponding **23a** methyl group. It is also noteworthy that δ 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 the 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

Table 3 Selected ^{1}H NMR chemical shifts for **4**, **5**, **19**, **20** and **23** and their methylated analogues



4 R = $COHPh_2$
5 R = $COH(2\text{-naphthyl})_2$
19 R = $CHPh_2$
20 R = $CH(2\text{-naphthyl})_2$
23 R = H



4a R = $COHPh_2$
5a R = $COH(2\text{-naphthyl})_2$
19a R = $CHPh_2$
20a R = $CH(2\text{-naphthyl})_2$
23a R = H

Catalyst	δ H-2[a,b,c]	δ H-5[a,b,c]	δ H-6[a,b,c]	δ CH_3
4	7.33	6.45	8.09	—
4a	6.52 (−0.81)	6.80 (0.45)	8.04 (−0.05)	3.88
5	7.51	6.45	8.09	—
5a	5.99 (−1.52)	6.70 (0.25)	7.88 (−0.21)	3.33
19	7.73	6.42	8.12	—
19a	6.68 (−1.05)	6.79 (0.37)	8.10 (−0.02)	4.02
20	7.93	6.42	8.11	—
20a	6.39 (−1.54)	6.66 (0.24)	7.88 (−0.23)	3.49
23	8.19	6.47	8.16	—
23a	8.17 (−0.02)	6.90 (0.43)	8.21 (0.05)	4.21

[a] Values for δ are quoted in ppm with $CDCl_3$ as solvent. [b] Value in parenthesis represents $\Delta\delta$: the change in chemical shift of the proton indicated on methylation (in ppm); a negative value for $\Delta\delta$ indicates an upfield shift. [c] All pyridine ring proton resonances were unambiguously assigned by NMR spectroscopy (^{1}H–^{1}H COSY, ^{1}H–^{13}C COSY, NOE and 1-D TOCSY experiments).

trajectory of **21** by H-bonding and (assuming that the naphthyl moiety avoids the acylated catalyst) the (***R***)-**21** antipode reacts relatively slowly due to catalyst-methyl group repulsion as the substrate approaches (Fig. 2).

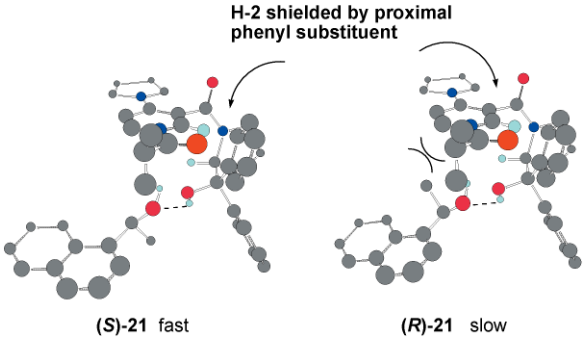


Fig. 2 Possible pre-TS-assemblies for the acylation of **21** by $(^iPrCO)_2O$ catalysed by **4**.

In summary, we have developed a new class of active, chiral 4-(pyrrolidino)-pyridine derivatives (**4** and **5**) for the kinetic resolution of *sec*-alcohols such as **15** and **21** with selectivity approaching synthetically useful levels. These proline-derived promoters are readily prepared from simple starting materials without the need for resolution steps.[24] To our knowledge **4** and **5** represent the first chiral 4-*N*,*N*-dialkylaminopyridine catalysts to (synergistically) employ both van der Waals (π) interactions and hydrogen bonding to allow remote chirality to exert stereochemical influence on an acylation reaction. Experiments are underway to further explore both the mode-of-action and potential utility of these catalysts (and modified analogues) in a range of enantioselective acyl-transfer reactions. The results of these studies will be reported in due course.

We would like to thank Dr John O'Brien for NMR spectra. Financial support from the Irish Research Council for Science Engineering and Technology (IRCSET) and Trinity College Dublin is also gratefully acknowledged.

Notes and references

† Characterisation data for **4**: mp 144–146 °C, $[\alpha]_D^{20}$ −98 (*c* 0.96, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 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); δ_C (100 MHz, $CDCl_3$) 23.3, 25.1, 30.2, 48.8, 51.6, 68.3, 81.5, 108.1, 116.2, 127.0, 127.1, 127.2, 127.3, 127.4, 127.6, 142.1, 144.6, 146.6, 147.6, 148.5, 170.4; HRMS calcd. for $C_{27}H_{30}N_3O_2$ (M + 1) 428.2328, found 428.2338.

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17 It is noteworthy that two distinct rotameric forms of **3** (in a *ca.* 1 : 1 ratio) are identifiable by ^{1}H 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.

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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.

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21 Screening studies identified CH_2Cl_2 as an ideal solvent, use of protic, polar aprotic and aromatic solvents (*e.g.* toluene) resulted in lower selectivity.

22 (*a*) For general references concerning cation–π and intermolecular pyridinium cation–π interactions see: J. C. Ma and D. A. Dougherty, *Chem. Rev.*, 1997, **97**, 1303; (*b*) G. T. Hwang and B. H. Kim, *Tetrahedron Lett.*, 2000, **41**, 5917; (*c*) K. Araki and H. Hayashida, *Tetrahedron Lett.*, 2000, **41**, 1209; (*d*) S. M. Ngola and D. A. Dougherty, *J. Org. Chem.*, 1998, **63**, 4566.

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 ^{1}H NMR chemical shift data outlined in Table 3.

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