Asymmetric acyl-transfer promoted by readily assembled chiral 4-*N*,*N*-dialkylaminopyridine derivatives†

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The development of a new class of chiral 4-*N*,*N*-dialkylaminopyridine acyl-transfer catalysts capable of exploiting both van der Waals (π) and H-bonding interactions to allow remote chiral information to stereochemically control the kinetic resolution of *sec*-alcohols with moderate to excellent selectivity (s = 6–30). Catalysts derived from (*S*)-α,α-diarylprolinol are considerably superior to analogues devoid of a tertiary hydroxyl moiety and possess high activity and selectivity across a broad range of substrates.

Asymmetric organocatalysis has recently been propelled from relative obscurity to the forefront of contemporary organic chemistry research and is fast-becoming a key strategy in enantioselective synthesis.[1,2]

An important facet of this broad domain is the asymmetric non-enzymatic[3] catalysis of acyl-transfer by chiral organic nucleophiles such as tertiary amines,[4–7] phosphines,[8] *N*-heterocyclic carbenes[9,10] and secondary alcohols.[11] Although it has been over a century since the discovery of pyridine-promoted alcohol acylation,[12] the design of efficient and selective *chiral* pyridine-based catalysts for these reactions is a young field less than 10 years old. The desymmetrisation of the 'hypernucleophilic' achiral catalyst 4-*N*,*N*-dimethylaminopyridine (DMAP)[13,14] *via* one of three general strategies, (the introduction of 'planar chirality' either 2,3-pyrido-fused[15] or installed at the C-3-position of the pyridine ring,[16] the use of axially chiral substituents at C-3[17] or the installation of tetrahedral chirality at either C-4,[18–23] or C-3,[24–27]) has proven a particularly productive approach which has given rise to a number of highly selective chiral catalysts for the kinetic resolution (KR) of *sec*-alcohols and other asymmetric acyl-transfer processes.[15,27,28]

The design of such systems is complicated by an *activity–selectivity conundrum*: *i.e.* to maximise the effectiveness of catalyst stereochemical information it is desirable to install chiral groups as close to the nucleophilic ring nitrogen as possible, however, bulky substituents in the vicinity of the same strongly attenuate catalyst activity.[14,17c,29] A successful (*i.e.* active and selective) catalyst design must necessarily embody a compromise between these opposing constraints.

One appealing solution to this problem (inspired by enzymatic systems) is the design of promoters capable of operating by an 'induced-fit' mechanism, in which the catalyst undergoes a conformational change upon acylation driven by intramolecular interaction between the catalyst's chiral substituents and the pyridinium cation moiety, thereby allowing remote chirality to exercise stereochemical control over the subsequent acylation event.[18,27] In this regard, we were intrigued by a report from Yamada and Morita[30] demonstrating that the 3-substituted pyridine **1** exhibited a π–π stacking interaction on acylation/alkylation which both rigidified the structure and effectively shielded one face of the resultant pyridinium cation, allowing the subsequent diastereoselective attack of a nucleophile at C-4 (**1a**, Fig. 1). We therefore reasoned that a 4-pyrrolidino-analogue of **1** (*i.e.* **2**, Fig. 1) held promise as a tunable and easily constructed acyl-transfer catalyst template capable of operating *via* an induced-fit mechanism.[31]

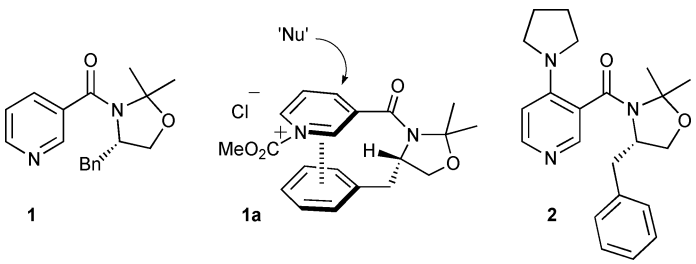

Fig. 1 Yamada's chiral pyridinium ion **1a** and 1st generation chiral acyl-transfer catalyst **2**.

The synthesis of **2** was straightforward: conversion of **3**[32] to its acid-chloride followed by coupling with (*S*)-phenylalaninol-derived **4**[33] gave chloropyridine **5**, which could be converted to **2** *via* a nucleophilic aromatic substitution reaction with excess pyrrolidine (Scheme 1). An immediate cause for concern was the presence of two rotameric species in a *ca.* 1 : 1 ratio in the ^{1}H NMR spectrum of **2**; as only one of these (*i.e.* **2** and not **2′**) could conceivably adopt a conformation conducive to intramolecular π–π-stacking. Interestingly, upon methylation of **2** slow equilibration over 12 h to a single rotamer (**2a**, Scheme 1) which exhibited a ^{1}H NMR spectrum consistent with a π-stacked conformation, as proposed by Yamada,[30] was observed (Scheme 1). It seemed likely therefore, that this equilibration process would be slow enough to allow both rotamers of the intermediate acylated form of **2** to

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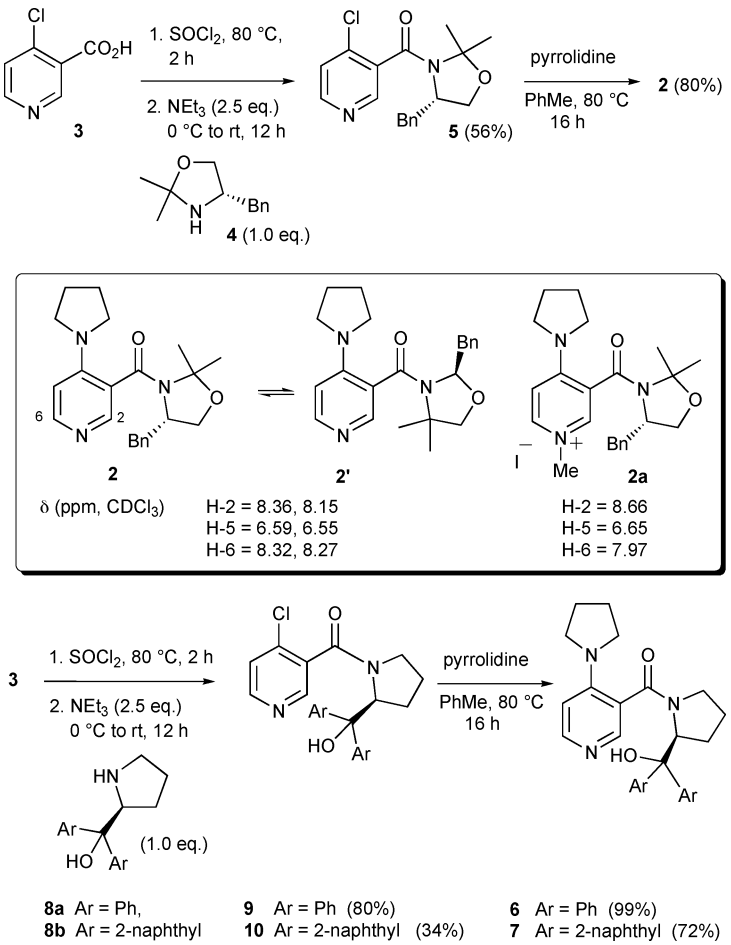
† Electronic supplementary information (ESI) available: General experimental procedures and details, characterisation data for the synthesis of catalysts **14** and **15**, ^{1}H and ^{13}C NMR spectra for **6** and **7** (and their precursors), X-ray crystal structure data for **6-Bn**, atomic coordinates from the DFT calculations and CSP-HPLC data for all resolved alcohols. See DOI: 10.1039/b604632k



Scheme 1 Synthesis of catalysts **2**, **6** and **7**.

possess independent catalytic profiles. In order to a) better control the catalyst's conformational preference and b) augment the potential for π-pyridinium ion interactions we therefore prepared the novel (*S*)-α,α-diphenylprolinol-derived[34] **6** and its 2-naphthyl analogue **7** (Scheme 1), which are characterised by a large steric discrepancy between the substituents α- to the amide nitrogen atom and the presence of an additional pendant aromatic moiety.

Catalysts **2**, **6** and **7** were evaluated in the acylative KR of *cis*-1,2-cyclohexane diol derivatives **11**–**13** (Table 1) using isobutyric anhydride. Prototype promoter **2** displayed excellent activity, however enantioselectivity (quantified by *s*; the ratio of the second order acylation rate constants for the fast and slow reacting alcohol enantiomers respectively[35]) was unsatisfactory (entry 1). Gratifyingly, bis-aryl catalysts **6** and **7** exhibited more promising selectivity approaching that regarded as synthetically useful ($s = 10$) at low temperature (entry 3).

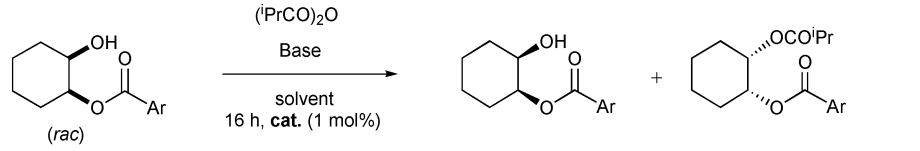
Optimisation of the reaction conditions identified CH_2Cl_2 and NEt_3 as the optimum solvent and general-base additive respectively. It is notable that selectivity diminished in polar solvents and that poor enantio-discrimination was also observed in the aromatic (yet relatively non-polar) solvent (entry 10). Bis-naphthyl catalyst **7** was found to be a marginally more selective catalyst than bis-phenyl variant **6** (entries 2 and 5), and relatively electron-rich benzoates **11** and **12** were superior substrates to the unsubstituted analogue **13**.

We speculated that the latter observation could be due to either the involvement of a hydrogen bonding or a π-pyridinium ion interaction between the substrate and the acylated catalyst in the enantioselection process.[36] To determine the contribution of the catalyst hydroxy group to enantioselectivity, we prepared reduced analogues of **6** and **7** (**14** and **15** respectively),[37] and evaluated their performance as catalysts in the KR of *sec*-alcohol **16** (Table 2).

The results of these experiments were instructive; while removal of the hydroxy moiety from **6** and **7** had little effect on catalyst activity, reduced catalysts **14** and **15** promoted the formation of the opposite antipode of **17** to that observed using either **6** or **7**, with reduced enantioselectivity. It was therefore clear that the catalyst tertiary alcohol moiety plays a pivotal role in determining which enantiomer of the racemic substrate is preferentially acylated by both **6** and **7**. It is also noteworthy that in line with the trend observed using hydroxy substituted catalysts, bis-naphthyl derivative **15** proved more selective (albeit not significantly) than the less hindered analogue **14**.

In order to garner further insight into the mode of action of **6**–**7**, attention turned to the question of substrate scope. A range of substrates (**18**–**25**) chosen to systematically probe the catalyst's sensitivity to substrate steric, electronic and hydrogen-bond donating/accepting characteristics were acylated by isobutyric anhydride in the presence of **6** at low temperature. The results of these studies are presented in Table 3; in the case of benzyl

Table 1 Evaluation of **2**, **6** and **7** in the KR of **11–13**



11 Ar = 4-$NMe_2C_6H_4$
12 Ar = 4-$OMeC_6H_4$
13 Ar = C_6H_5

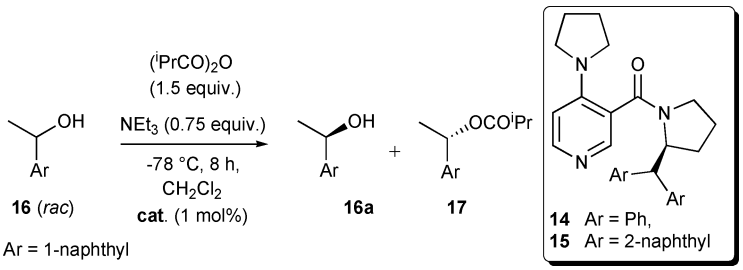
11a Ar = 4-$NMe_2C_6H_4$
12a Ar = 4-$OMeC_6H_4$
13a Ar = C_6H_5

11b Ar = 4-$NMe_2C_6H_4$
12b Ar = 4-$OMeC_6H_4$
13b Ar = C_6H_5

Entry	Catalyst	Substrate	Solvent	Base	Conversion (%)[d]	Ee (%)[e]	s[f]	Abs. config.[g]
1[a]	**2**	**11**	CH_2Cl_2	NEt_3	55	13	1.4	(1*S*,2*R*)
2[a]	**6**	**11**	CH_2Cl_2	NEt_3	78	93	4.9	(1*S*,2*R*)
3[b]	**6**	**11**	CH_2Cl_2	NEt_3	69	97	9.4	(1*S*,2*R*)
4[a]	**6**	**12**	CH_2Cl_2	NEt_3	68	74	4.3	(1*S*,2*R*)[h]
5[a]	**7**	**11**	CH_2Cl_2	NEt_3	73.5	90	5.4	(1*S*,2*R*)
6[a]	**7**	**12**	CH_2Cl_2	NEt_3	71	80	4.4	(1*S*,2*R*)[h]
7[a]	**7**	**13**	CH_2Cl_2	NEt_3	88	95	3.5	(1*S*,2*R*)[h]
8[c]	**6**	**11**	CH_2Cl_2	NEt_3	64	70	4.6	(1*S*,2*R*)
9[c]	**6**	**11**	$CDCl_3$	NEt_3	69	77	4.4	(1*S*,2*R*)
10[c]	**6**	**11**	PhMe	NEt_3	67	67	3.7	(1*S*,2*R*)
11[c]	**6**	**11**	THF	NEt_3	63	55	3.1	(1*S*,2*R*)
12[c]	**6**	**11**	Et_2O	NEt_3	64	26	1.7	(1*S*,2*R*)
13[c]	**6**	**11**	DMSO	NEt_3	66	20	1.5	(1*S*,2*R*)
14[c]	**6**	**11**	CH_2Cl_2	$^iPr_2NEt$	64	70	4.6	(1*S*,2*R*)
15[c]	**6**	**11**	CH_2Cl_2	DABCO[i]	61	63	4.4	(1*S*,2*R*)
16[c]	**6**	**11**	CH_2Cl_2	Imidazole	19	6	1.9	(1*S*,2*R*)
17[c]	**6**	**11**	CH_2Cl_2	DBU[j]	38.5	28	3.4	(1*S*,2*R*)
18[c]	**6**	**11**	CH_2Cl_2	Na_2CO_3	61	58	3.7	(1*S*,2*R*)

[a] Conditions: $(^iPrO)_2O$ (0.80 equiv.), NEt_3 (0.80 equiv.), rt. [b] Reaction at −78 °C for 8 h using 1.5 equiv. $(^iPrCO)_2O$. [c] Conditions: $(^iPrO)_2O$ (0.70 equiv.), base (0.70 equiv.), rt. [d] Conversion could be determined (with excellent agreement) either by ^1H NMR spectroscopy or using chiral HPLC, where conversion = 100 × $ee_{alcohol}/(ee_{alcohol} + ee_{ester})$. [e] Ee of **11a–13a** determined by chiral HPLC using a Chiralcel OD-H column (4.6 × 250 mm) [f] s = enantioselectivity (k_{fast}/k_{slow}, see ref. 35). [g] Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times (ref. 7). [h] Tentative assignment based on the elution order of the *p*-dimethylamino-benzoate. [i] 1,4-Diazabicyclo[2.2.2]octane. [j] 1,8-Diazabicyclo[5.4.0]undec-7-ene.

Table 2 Determination of the influence of the catalyst hydroxy substituent on selectivity

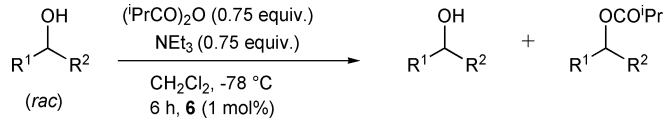


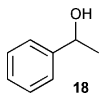
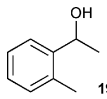
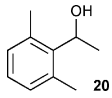
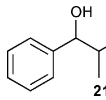
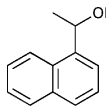
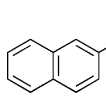
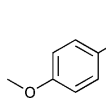
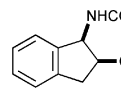
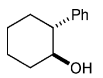
Entry	Catalyst	C (%)[a]	$Ee_{alcohol}$ (%)[b]	Ee_{ester} (%)[b]	s[c]	Abs. config.[d]
1	**6**	72	93	29	6.3	(*R*)
2	**7**	43[e]	51	63	8.7	(*R*)
3	**14**	36	22	36	2.8	(*S*)
4	**15**	43	30	38	3.0	(*S*)

[a] Refers to conversion, which could be determined (with excellent agreement) either by ^1H NMR spectroscopy or using chiral HPLC, where C = 100 × $ee_{alcohol}/(ee_{alcohol} + ee_{ester})$. [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. 35). [d] Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times (ref. 17*f*). [e] 0.8 eq. $(^iPrCO)_2O$, 8 h.

alcohols **18–22**, as expected selectivity increased with aliphatic substituent bulk (entries 1 and 4), while an enlargement of the steric requirement of the aromatic substituent was poorly tolerated by the catalyst (entries 1–3 and 5–6). The latter observation was somewhat surprising, as examples of the beneficial effects of augmenting alkyl and aromatic substituent bulk on enantioselectivity being additive (in a qualitative sense) are known in the literature,[15d,17f] which strongly implies that the nature of the aromatic substituent is critical for the efficient KR of benzyl alcohols promoted by **6**. This thesis was supported by the clear

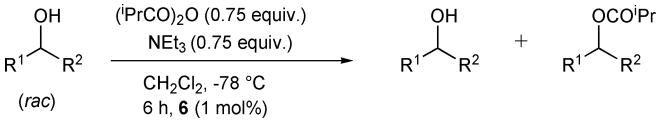
Table 3 Substrate scope

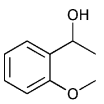
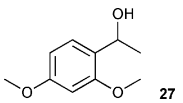
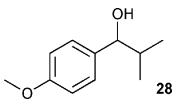
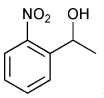
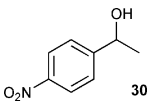


Entry	Substrate	*C* (%)[a]	Ee (%)[b]	*s*[c]	Abs. config.[d]
1	 **18**	27.5	25	6.3	*R*
2	 **19**	17	14	6.0	*R*
3	 **20**	14.6	1	1.1	*R*
4	 **21**	19	19	13.5	*R*
5	 **16**	22.5	20	6.6	*R*
6	 **22**	37	40	7.6	*R*
7	 **23**	20	19	9.1	*R*
8	 **24** Ar = 4-$NMe_2C_6H_4$	23	11	2.3	*R*
9	 **25**	19	22	30.0	1*R*,2*S*

[a] 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* = enantioselectivity (k_{fast}/k_{slow}, see ref. 35). [d] Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data (see supplementary information†).

Table 4 Contribution of substrate aromatic group to enantioselectivity



Entry	Substrate	*C* (%)[a]	Ee (%)[b]	*s*[c]	Abs. config.[d]
1	 **26**	18	18	11.4	*R*
2	 **27**	40	40	6.2	*R*
3	 **28**	15	14	9.5	*R*
4	 **29**	28	6	1.5	*R*
5	 **30**	27	6	1.4	*R*

[a] 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* = enantioselectivity (k_{fast}/k_{slow}, see ref. 35). [d] Absolute configuration of the recovered alcohol (major enantiomer) as determined by comparison with literature retention times or optical rotation data (see supplementary information†).

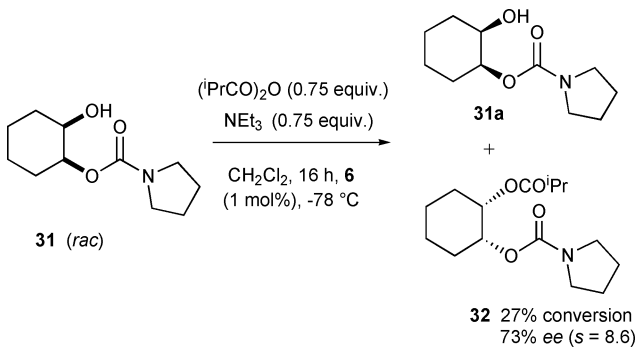
superiority of 4-methoxy substituted substrate **23** over the unsubstituted parent alcohol **18** (entries 1 and 7).

In this context, it is interesting to note that **24**, which may have been expected to prove a suitable KR substrate (considering the obvious compatibility of **11** with **6**, Table 1) underwent acylation with poor selectivity.[38] In contrast, the KR of *trans*-2-phenylcyclohexanol (**25**) using **6** proceeded with excellent enantioselectivity (entry 9).

It was clear at this juncture that both the steric and electronic makeup of the substrate aromatic substituents influence the efficacy of enantio-discrimination using catalyst **6**. In an attempt to clarify this role, *o*- and *p*-substituted aromatic *sec*-alcohols **26–30** were evaluated (Table 4) under identical conditions to those used in the KR of **18–23**. Substrates incorporating relatively electron deficient aromatic substituents performed poorly in comparison with more electron rich analogues (entries 1 and 4; compare also entry 7, Table 3 with entry 5, Table 4). The presence of a substrate *o*-methoxy group clearly facilitates enantio-discrimination (entry 1), however the effects of increased electron density at the aromatic ring and augmented aliphatic substituent steric bulk on enantioselectivity are not additive (entries 1–3), even though **6** promotes the preferential acylation of the same (*R*)-antipode of **26**, **27** and **28**.

In view of the considerable sensitivity of the catalyst to the nature of the substrate aromatic group, aliphatic carbamate **31** was acylated in the presence of **6** under standard conditions (Scheme 2). The resolution of this substrate with relatively good selectivity ($s = 8.6$) demonstrates the broad scope of catalyst **6** and indicates that an aromatic substituent is not an absolute requirement for selectivity in this system.

On analysis of the data in Tables 1–4, a picture emerges in which a confluence of contributions from the catalyst hydroxy



Scheme 2 Kinetic resolution of aliphatic carbamate **31**.

group/aromatic substituents (Tables 1 and 2) and substrate aliphatic/aromatic components (Tables 3 and 4) seem responsible for selectivity in KR processes using catalyst **6**. In an attempt to detect possible aryl–pyridinium ion π-stacking interactions, the ^{1}H NMR spectra of catalysts **6**, **7**, **14**, **15** and control material **33** (prepared from **3** and pyrrolidine) were compared to those of their corresponding products on methylation with iodomethane (Table 5).[30] These experiments were informative; while little evidence was found to support a 'face–face' π–π stacking interaction (Fig. 1),[18,30] a strong *upfield* shift associated with H-2 upon methylation of **6**, **7**, **14** and **15** (which is absent on methylation of **33**) 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.[22,39]

While **6a** proved difficult to crystallise, an X-ray structure of the corresponding benzylated catalyst **6-Bn** was obtained (Fig. 2).[40] The amide moiety is in an s-*cis* conformation with the diaryl tertiary alcohol substituent oriented towards H-2 and the nucleophilic ring-nitrogen: consistent with the proposed π-interactions and observed catalytic importance of the hydroxy group.

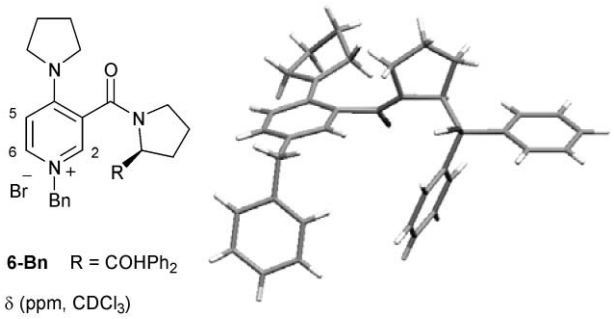
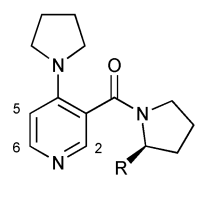


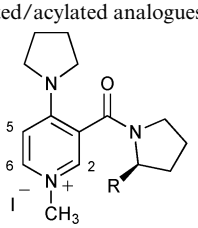
Fig. 2 Crystal structure of benzylated catalyst **6-Bn** (counterion has been omitted for clarity).‡

‡ Crystal data for **6-Bn**: $C_{34}H_{36}N_3O_2$2(CH_2Cl_2)Br, $M = 768.45$, orthorhombic, $a = 9.7318(13)$, $b = 18.078(2)$, $c = 20.751(3)$ Å, $\alpha = \beta = \gamma = 90°$, $U = 3650.8(8)$ Å^3, $T = 123$ K, space group $P2_12_12_1$, $Z = 4$, μ(Mo-Kα) = 0.650 mm^{-1}, 28680 reflections collected, 12852 unique ($R_{int} = 0.0676$). $R = 0.0777$, w$R2$ [$I > 2\sigma(I)$] = 0.1786. CCDC reference numbers 293598. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b604632k.

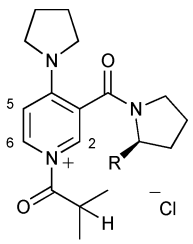
Table 5 Selected ^{1}H NMR data for **6**, **7**, **14**, **15**, **33** and methylated/acylated analogues



6 R = $COHPh_2$
7 R = $COH(2\text{-naphthyl})_2$
14 R = $CHPh_2$
15 R = $CH(2\text{-naphthyl})_2$
33 R = H



6a R = $COHPh_2$
7a R = $COH(2\text{-naphthyl})_2$
14a R = $CHPh_2$
15a R = $CH(2\text{-naphthyl})_2$
33a R = H



6b R = $COHPh_2$
33b R = H

Entry	Cat.	δ H-2[a,b,c]	δ H-5[a,b,c]	δ H-6[a,b,c]	δ CH_3/$HCMe_2$
1	**6**	7.33	6.45	8.09	—
2	**6a**	6.52 (−0.81)	6.80 (0.45)	8.04 (−0.05)	3.88
3	**6b**	8.06 (0.73)	7.15 (0.70)	9.10 (1.01)	4.14
4	**7**	7.51	6.45	8.09	—
5	**7a**	5.99 (−1.52)	6.70 (0.25)	7.88 (−0.21)	3.33
6	**14**	7.73	6.42	8.12	—
8	**14a**	6.68 (−1.05)	6.79 (0.37)	8.10 (−0.02)	4.02
9	**15**	7.93	6.42	8.11	—
10	**15a**	6.39 (−1.54)	6.66 (0.24)	7.88 (−0.23)	3.49
11	**33**	8.19	6.47	8.16	—
12	**33a**	8.17 (−0.02)	6.90 (0.43)	8.21 (0.05)	4.21
13	**33b**	8.72 (0.53)	7.32 (0.85)	9.32 (1.16)	4.11

[a] δ quoted in ppm in $CDCl_3$ as solvent. [b] Value in parentheses represents $\Delta\delta$: the change in chemical shift of the proton indicated on methylation or acylation (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).

Similar, yet less dramatic effects were observed upon acylation of both **6** and **33** with isobutyric acid chloride. While no upfield shift of the H-2 resonance was observed upon acylation of **6**, this is perhaps unsurprising in view of the powerful (anisotropic) electron withdrawing ability of the carbonyl moiety. However, it is noteworthy that H-2 of acylated catalyst **6b** resonates at considerably higher field (*ca.* 0.5 ppm) than that of **33b** and that there is a greater difference between δ H-2 and δ H-6 in pyridinium ion **6b** (1.04 ppm) than in the case of **33b** (0.50 ppm). These results indicate that in the case of both **6b** and **33b** (contrary to what might be expected from first principles but in agreement with reports from Spivey[17c] and Yamada[27]) the bulky isopropyl moiety is located on the same side of the *N*–*N* axis as the catalyst amide substituent[41] (*i.e.* as depicted above Table 5).

The results in Tables 1–5 indicate that the ability of **6** and **7** to serve as active and enantioselective acyl-transfer catalysts is due to a unique combination of several factors including aryl–pyridinium ion π–π (or π–H), and substrate–catalyst H-bonding and possibly also π–π interactions. To better understand the origins of enantiodiscrimination using **6** and **7** we have examined the conformational preferences of **6a** and **6c** (the *N*-acetyl analogue of **6b**) using B3LYP hybrid density functional theory (Gaussian 03, 6-31G* basis set[42]). Postulating that two conformational features would have particularly strong influence on catalyst performance: 1) isomerism of the C-3 amide linkage (*i.e.* s-*cis vs.* s-*trans*) and crucially, the preferred conformation of the acyl-moiety in **6b**, we calculated the gas-phase energetics of methylated and acetylated analogues of **6** (**I–IV**, Fig. 3 and Table 6) with respect to these parameters. The results of these calculations are presented in Table 6. Examination of the relative energies for the s-*cis vs.* s-*trans* chiral amide conformation reveal a strong preference for the s-*cis* rotamer (entries 1–2, Table 6), consistent with the X-ray crystal structure obtained for **6-Bn** (Table 6 entries 1–2).

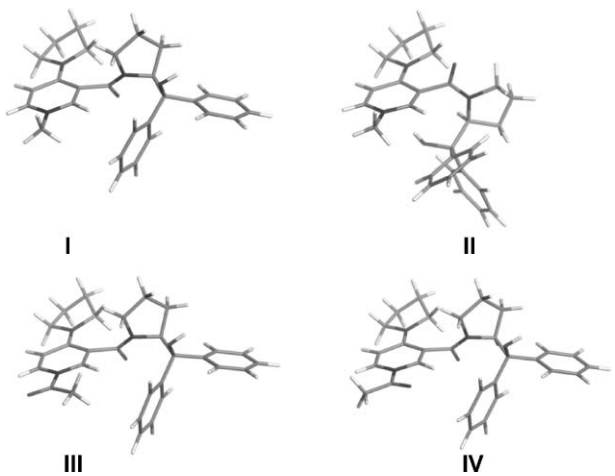
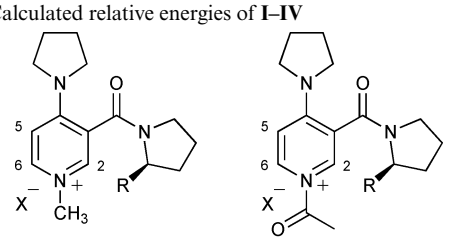


Fig. 3 Calculated optimum conformers of **6a** (**I–II**) and **6c** (**III–IV**).

Interestingly, these studies also indicate (somewhat counter-intuitively but nonetheless consistent with the findings of the NMR-studies, see Table 5) that the conformer of **6c** (s-*cis* C-3 amide) in which the methyl group resides on the more hindered catalyst hemisphere (**III**) is more stable than the corresponding conformer where the smaller carbonyl group is directed towards the chiral amide substituent (**IV** entries 3–4, Table 6). Since this phenomenon does not seem to be sterically driven, it may, by analogy with a suggestion made by Spivey,[17c] be related to partial conjugation with the C-3 substituent. In this regard it is interesting that a C_2-symmetric analogue of **6** (**34**, Fig. 4) designed to circumvent potential problems associated with *N*-acyl isomerism proved a completely inactive acylation catalyst.

Table 6 Calculated relative energies of **I–IV**



6a R = $COHPh_2$ **6c** R = $COHPh_2$

Entry	Cat.	Conformation	Amide rotamer	*N*-Acetyl rotamer	Relative energy/ kJ mol^{-1} [a,b]
1	**6a**	**I**	s-*cis*	—	0
2	**6a**	**II**	s-*trans*	—	44.9
3	**6c**	**III**	s-*cis*	s-*trans*	0
4	**6c**	**IV**	s-*cis*	s-*cis*	4.2

[a] Calculated relative energies. [b] Does not account for the influence of the counter ion.

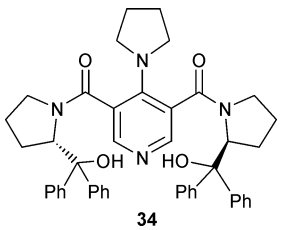


Fig. 4 C_2-symmetric catalyst **34**.

Conclusions

In summary, we have developed a new class of active, chiral 4-(pyrrolidino)-pyridine derivatives (**6** and **7**) for the kinetic resolution of an exceptionally wide range (both aromatic and aliphatic) of *sec*-alcohols with synthetically useful selectivity. These proline-derived promoters are readily prepared from simple, readily available starting materials[34] without the need for resolution steps. A combination of optimisation (Table 1), substrate screening (Tables 1, 3 and 4), catalyst modification (Table 2), spectroscopic (Table 5) and computational (Table 6) studies have clearly identified both hydrogen bonding and (intra as well as possibly also intermolecular) π-pyridinium-ion interactions as playing a role in enantiodiscrimination, and have provided insight into the conformational preferences of the key acylated catalytic intermediates in these reactions. To our knowledge **6** and **7** 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, and while the levels of enantiodiscrimination possible are lower than that associated with the benchmark literature catalyst, nonetheless synthetically useful

($s > 10$) KR processes promoted by **6** have been demonstrated (up to a maximum of $s = 30$). Furthermore, the ready accessibility of these materials combined with the demonstrable influence of three independent, tunable catalyst properties (hydrogen bond accepting/donating ability, aromatic substituent steric and electronic characteristics) on enantioselectivity provides considerable scope for future catalyst development.

Experimental

General

Proton nuclear magnetic resonance spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ referenced relative to residual $CHCl_3$ ($\delta = 7.26$ ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. All melting points are uncorrected. Infrared spectra were obtained on a Perkin Elmer spectrophotometer. Flash chromatography was carried out using silica gel, particle size 0.04–0.063 mm. TLC analysis was performed on precoated $60F_{254}$ slides, and visualised by either UV irradiation or $KMnO_4$ staining. Optical rotation measurements were made on a Rudolph Research Analytical Autopol IV instrument, and are quoted in units of 10^{-1} deg cm^2 g^{-1}. Toluene, ether and THF were distilled from sodium. Methylene chloride and triethylamine were distilled from calcium hydride. Analytical CSP-HPLC was preformed using Daicel CHIRALCEL OD-H (4.6 mm × 25 cm) and CHIRALCEL AS-H (4.6 mm × 25 cm) columns. Unless otherwise stated, all chemicals were obtained from commercial sources and used as received. Alcohols **20**, **21**, **24**, **28**, **26**, **29**, and **30** were synthesised according to literature procedures. Alcohol **27** was prepared by the reduction of 2,4-dimethoxyacetophenone with $NaBH_4$ and was purified by flash chromatography prior to use. Unless otherwise specified, all reactions were carried out in oven-dried glassware with magnetic stirrers under an atmosphere of argon.

Chloropyridine 9. A 10 cm^3 round bottom flask charged with 4-chloronicotinic acid (**3**) (315 mg, 2.00 mmol) and $SOCl_2$ (2.00 cm^3) was fitted with a reflux condenser and heated at 90 °C for 1 hour. Removal of $SOCl_2$ by distillation gave 4-chloronicotinic acid chloride hydrochloride as a yellow solid, which was placed under an atmosphere of Ar, cooled to 0 °C and suspended in THF (5 cm^3) added *via* syringe. Subsequently a solution of (*S*)-α,α-diphenylprolinol (**8a**) (506 mg, 2.00 mmol) and NEt_3 (550 μL, 3.96 mmol) in THF (4 cm^3), was added *via* syringe. The yellow solution was left to stir overnight. CH_2Cl_2 (100 cm^3) was then added and resulting solution washed with $NaHCO_3$ (2 × 40 cm^3), and brine (2 × 40 cm^3). The organic extracts were separated, dried ($MgSO_4$) and the solvent removed *in vacuo.* Purification by column chromatography (9 : 1 $CHCl_2$–EtOAc, R_f 0.2) gave **9** (627 mg, 80%) as a white solid, mp 64–66 °C; $[\alpha]_D^{20} = -95$ (*c* 0.11 in $CHCl_3$); δ_H ($CDCl_3$) 1.74 (2H, m), 2.05 (1H, m), 2.22 (1H, m), 2.90 (1H, m,), 3.10 (1H, m), 5.30 (1H, dd, *J* 7.0 and 8.0), 6.48 (1H, s), 7.22–7.60 (12H, m), 8.52 (1H, d, *J* 5.6); δ_C ($CDCl_3$) 23.9, 30.1, 50.5, 68.2, 81.8, 124.5, 127.5, 127.55, 127.6, 127.7, 127.8, 128.0, 132.7, 140.0, 142.7, 145.2, 148.1, 150.9, 167.2; ν_{max} (KBr)/cm^{-1} 3281, 1615, 1431, 1155, 699; *m/z* (ES) 415.1200 (M^+ + Na. $C_{23}H_{21}N_2O_2ClNa$ requires 415.1189).

Chloropyridine 10. Prepared as per the synthesis of **9** using **3** (329 mg, 2.09 mmol), $SOCl_2$ (2.0 cm^3), THF (5 + 4 cm^3), **8b**[43] (740 mg, 2.10 mmol) and triethylamine (870 μL, 6.28 mmol). Purification by column chromatography (9 : 1 $CHCl_2$–EtOAc, R_f 0.3) gave **10** (350 mg, 34%) as a white solid, mp 140–142 °C; $[\alpha]_D^{20} = -84$ (*c* 0.1 in $CHCl_3$); δ_H ($CDCl_3$) 1.61–1.94 (2H, m), 2.18–2.42 (2H, m,), 2.92 (1H, m), 3.11 (1H, m), 5.61 (1H, dd, *J* 7.0 and 7.5), 6.62 (1H, s) 7.30–7.91 (15H, m), 8.20 (1H, s), 8.47 (1H, d, *J* 5.6); δ_C ($CDCl_3$) 23.5, 29.6, 49.9, 67.5, 81.7, 125.3, 125.5, 125.7, 125.8, 125.9, 126.2, 126.7, 126.9, 127.1, 127.7, 127.9, 128.0, 132.2, 132.3, 132.4, 132.5, 139.7, 142.2, 147.7, 150.5, 165.9; ν_{max} (KBr)/cm^{-1} 3371, 1612, 1377, 1155, 721; *m/z* (ES) 493.1681 (M^+ + H. $C_{31}H_{26}N_2O_2Cl$ requires 493.1683).

Catalyst 6. A 10 cm^3 round bottom flask was charged with **9** (160 mg, 0.41 mmol) and toluene (4 cm^3) with stirring. To this was added pyrrolidine (2.00 cm^3, 28.2 mmol) *via* syringe. The flask was fitted with a reflux condenser and heated at 85 °C for 16 h. CH_2Cl_2 (20 cm^3) was then added and the solution washed with $NaHCO_3$ (2 × 30 cm^3) and brine (2 × 30 cm^3). The organic extracts were separated, dried ($MgSO_4$) and the solvent removed *in vacuo.* Purification by column chromatography (80 : 20 EtOAc–$CHCl_2$, R_f 0.3), gave **6** (171 mg, 98%) as a white solid, mp 144–146 °C; $[\alpha]_D^{20} = -98$ (*c* 0.96 in $CHCl_3$); δ_H ($CDCl_3$) 1.48–1.72 (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 and 8.5), 6.45 (1H, d, *J* 6.0), 7.25–7.38 (6H, m), 7.41–7.53 (4H, m), 7.60 (2H, d, *J* 6.0), 8.09 (1H, d, *J* 6.0); δ_C ($CDCl_3$) 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; ν_{max} (KBr)/cm^{-1} 3179, 2854, 1590, 1304, 971; *m/z* (ES) 428.2328 (M^+ + H. $C_{27}H_{30}N_3O_2$ requires 428.2338).

Catalyst 7. Prepared as per the synthesis of **6** using **10** (71.5 mg, 0.145 mmol), toluene (4 cm^3) and pyrrolidine (2.00 cm^3, 28.2 mmol). Purification of the resulting product by column chromatography (99 : 1 EtOAc–NEt_3, R_f 0.2) gave **7** (55 mg, 72%) as a white solid, mp 146–148 °C; $[\alpha]_D^{20} = -65$ (*c* 0.11 in $CHCl_3$); δ_H ($CDCl_3$) 1.34–1.62 (2H, m), 1.88–2.27 (6H, m), 2.92–3.15 (3H, m,), 3.35–3.53 (3H, m,), 5.43 (1H, app. t, *J* 8.0), 6.45 (1H, d, *J* 6.0), 7.41–7.56 (5H, m), 7.64–7.94 (10H, m), 8.09 (1H, d, *J* 6.0), 8.16 (1H, s); δ_D ($CDCl_3$) 23.6, 25.4, 30.2, 48.8, 51.7, 67.6, 82.0, 108.3, 116.4, 125.7, 125.9, 126.0, 126.1, 126.5, 126.9, 127.3, 127.4, 127.8, 128.2, 128.3, 132.5, 132.6, 132.7, 140.1, 142.6, 148.2, 148.3, 149.4, 171.7; ν_{max} (KBr)/cm^{-1} 3369, 1588, 1539, 1505, 1123, 721; *m/z* (ES) 528.2673 (M^+ + H. $C_{35}H_{34}N_3O_2$ requires 528.2651).

Kinetic resolution experiments: general procedure

A 1 cm^3 reaction vessel charged with catalyst (2.34 μmol) and a small magnetic stirring bar was placed under an atmosphere of Ar. To this was added a solution of alcohol (0.234 mmol) and triethylamine (23 μL, 0.164 mol) in $CHCl_2$ (500 μL). The resulting solution was cooled to −78 °C and left to stir for 30 minutes. Isobutyric anhydride (0.183 mmol) was subsequently added *via* syringe. After 8 h at − 78 °C the reaction was quenched by the addition of MeOH (200 μL) and allowed to warm to ambient temperature. Solvents were removed *in vacuo.* The alcohol and its ester were separated from the catalyst by passing a concentrated solution of the crude (CH_2Cl_2) through a pad of silica gel. The

selectivity of the kinetic resolution was then established by CSP-HPLC.

NMR analysis of pyridinium salts (Table 5): general procedures

Methyl pyridinium salts. To a solution of the pyridine (0.07 mmol) in CH_2Cl_2 (0.5 cm^3) in a 5 cm^3 round bottomed flask was added iodomethane (0.7 mmol) *via* syringe and the resulting solution stirred at room temperature. After TLC analysis indicated complete conversion of the starting material the resulting solution was concentrated *in vacuo*, taken up in $CDCl_3$ (0.4 cm^3) and analysed by ^1H NMR spectroscopy.

Isobutyryl pyridinium salts. (**Note:** These intermediates are relatively unstable and decompose rapidly in the presence of adventitious water. Under anhydrous conditions these materials are stable enough to be analysed by ^1H NMR spectroscopy over a period of several hours.) A solution of the pyridine (0.07 mmol) in $CDCl_3$ (0.4 cm^3, freshly distilled and stored for short periods under Ar over 4 Å mol. sieves) was added to a screw-cap-NMR tube under an atmosphere of Ar. To this was added isobutryic acid chloride (0.07 mmol) *via* syringe. The NMR tube was shaken for 10 s and the resulting mixture analysed by ^1H NMR spectroscopy.

References

1 For selected early examples of asymmetric organocatalysis see: (*a*) G. Bredig and K. Fajans, *Ber. Dtsch. Chem. Ges.*, 1908, **41**, 752; (*b*) G. Bredig and P. S. Fiske, *Biochem. Z.*, 1912, **46**, 7; (*c*) R. Wegler, *Ann.*, 1932, **498**, 62; (*d*) V. Prelog and H. Wilhelm, *Helv. Chim. Acta*, 1954, **37**, 1634; (*e*) H. Pracejus, *Justus Liebigs Ann. Chem.*, 1960, **634**, 9; (*f*) D. Borrmann and R. Wegler, *Chem. Ber.*, 1967, **100**, 1575; (*g*) H. Wynberg and R. Helder, *Tetrahedron Lett.*, 1975, **16**, 4057.

2 Recent general reviews: (*a*) S. Jayasree and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719; (*b*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*c*) K. N. Houk and B. List, *Acc. Chem. Res.*, 2004, **37**, Issue 8; (*d*) A. Berkessel and H. Gröger, *Asymmetric Organocatalysis*, Wiley Interscience, Weinheim, 2005.

3 For selected reviews of enzymatic acyl-transfer catalysis see: (*a*) F. Theil, *Chem. Rev.*, 1995, **95**, 2203; (*b*) C.-S. Chen and C. Sih, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 695; (*c*) C.-H. Wong and G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*, Elsevier Science, Oxford, 1994.

4 Recent reviews: (*a*) S. J. Connon, *Lett. Org. Chem.*, 2006, **3**, 333; (*b*) E. R. Jarvo and S. J. Miller, in *Comprehensive Asymmetric Catalysis*, 2004, Supplement 1, ed. E. N. Jacobsen, A. Pfaltz and H Yamamoto, Springer-Verlag, Berlin, Heidelberg, ch. 43, (Asymmetric Acylation); (*c*) S. J. Miller, *Acc. Chem. Res.*, 2004, **37**, 601; (*d*) S.-K. Tian, Y. Chen, J. Hang, L. Tang, P. McDaid and L. Deng, *Acc. Chem. Res.*, 2004, **37**, 621; (*e*) G. C. Fu, *Acc. Chem. Res.*, 2004, **37**, 542; (*f*) S. France, D. J. Guerin, S. J. Miller and T. Lectka, *Chem. Rev.*, 2003, **103**, 2985; (*g*) E. R. Jarvo and S. J. Miller, *Tetrahedron*, 2002, **58**, 248; (*h*) G. C. Fu, *Acc. Chem. Res.*, 2000, **33**, 412; (*i*) A. C. Spivey, A. Maddaford and A. Redgrave, *Org. Prep. Proced. Int.*, 2000, **32**, 331.

5 Aliphatic diamine catalysts: (*a*) D. Terakado, H. Koutaka and T. Oriyama, *Tetrahedron: Asymmetry*, 2005, **16**, 1157; (*b*) T. Oriyama, K. Imai, T. Hosoya and T. Sano, *Tetrahedron Lett.*, 1998, **39**, 397; (*c*) T. Oriyama, K. Imai, T. Sano and T. Hosoya, *Tetrahedron Lett.*, 1998, **39**, 3529; (*d*) T. Sano, K. Imai, K. Ohashi and T. Oriyama, *Chem. Lett.*, 1999, 265.

6 For reports of highly enantioselective synthetic peptide-based catalysts see: (*a*) S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann and E. M. Ruel, *J. Am. Chem. Soc.*, 1998, **120**, 1629; (*b*) G. T. Copeland and S. J. Miller, *J. Am. Chem. Soc.*, 2001, **123**, 6496; (*c*) E. R. Jarvo, C. A. Evans, G. T. Copeland and S. J. Miller, *J. Org. Chem.*, 2001, **66**, 5522; (*d*) M. M. Vasbinder, E. R. Jarvo and S. J. Miller, *Angew. Chem., Int. Ed.*, 2001, **40**, 2824; (*e*) B. R. Sculibrene and S. J. Miller, *J. Am. Chem. Soc.*, 2001, **123**, 10125; (*f*) B. R. Sculibrene, A. J. Morgan and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 11653; (*g*) J. E. Imbriglio, M. M. Vasbinder and S. J. Miller, *Org. Lett.*, 2003, **5**, 3741; (*h*) M. B. Fierman, D. J. O'Leary, W. E. Steinmetz and S. J. Miller, *J. Am. Chem. Soc.*, 2004, **126**, 6967; (*i*) F. Formaggio, A. Barazza, A. Bertocco, C. Toniolo, Q. B. Broxterman, B. Kaptein, E. Brasola, P. Pengo, L. Pasquato and P. Scrimin, *J. Org. Chem.*, 2004, **69**, 3849.

7 For the development of a highly selective histidine-derived catalyst for the kinetic resolution of *sec*-alcohols see: K. Ishihara, Y. Kosugi and M. Akahura, *J. Am. Chem. Soc.*, 2004, **126**, 12212.

8 (*a*) E. Vedejs, O. Daugulis and S. T. Diver, *J. Org. Chem.*, 1996, **61**, 430; (*b*) E. Vedejs and O. Daugulis, *J. Am. Chem. Soc.*, 1999, **121**, 5813; (*c*) E. Vedejs and J. A. MacKay, *Org. Lett.*, 2001, **3**, 535; (*d*) E. Vedejs and E. Rozners, *J. Am. Chem. Soc.*, 2001, **123**, 2428; (*e*) E. Vedejs, O. Daugulis, L. A. Harper, J. A. MacKay and D. R. Powell, *J. Org. Chem.*, 2003, **68**, 5020; (*f*) E. Vedejs and O. Daugulis, *J. Am. Chem. Soc.*, 2003, **125**, 4166.

9 Y. Suzuki, K. Yamauchi, K. Muramatsu and M. Sato, *Chem. Commun.*, 2004, 2770.

10 T. Kano, K. Sasaki and K. Maruoka, *Org. Lett.*, 2005, **7**, 1347.

11 G. T. Notte, T. Sammakia and P. J. Steel, *J. Am. Chem. Soc.*, 2005, **127**, 13502.

12 A. Einhorn and F. Hollandt, F., *Ann.*, 1898, **301**, 95.

13 (*a*) L. M. Litvinenko and A. I. Kirichenko, *Dokl. Chem.*, 1967, 763; (*b*) W. Steglich and G. Höfle, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 981.

14 For reviews see: (*a*) A. C. Spivey and S. Arseniyadis, *Angew. Chem., Int. Ed.*, 2004, **43**, 5436; (*b*) R. Murugan and E. F. V. Scriven, *Aldrichimica Acta*, 2003, **103**, 3401; (*c*) U. Ragnarsson and L. Grehn, *Acc. Chem. Res.*, 1998, **31**, 494; (*d*) A. Hassner, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, New York, 1995, vol. 3, pp. 2002; (*e*) E. F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129; (*f*) G. Höfle, W. Steglich and H. Vorbruggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569.

15 (*a*) J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1996, **61**, 7230; (*b*) J. C. Ruble, H. A. Lantham and G. C. Fu, *J. Am. Chem. Soc.*, 1997, **119**, 1492; (*c*) B. Tao, J. C. Ruble, D. A. Hoic and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 5091; (*d*) J. C. Ruble, J. Tweddell and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 2794; (*e*) S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling and G. C. Fu, *Chem. Commun.*, 2000, 1009; (*f*) M. Harmata, M. Kahraman and G. C. Fu, *J. Org. Chem.*, 1999, **64**, 4949; (*g*) Y. Ie and G. C. Fu, *Chem. Commun.*, 2000, 119; (*h*) S. Arai, S. Bellemin-Laponnaz and G. C. Fu, *Angew. Chem., Int. Ed.*, 2001, **40**, 234; (*i*) B. L. Hodous and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 1578; (*j*) J. E. Wilson and G. C. Fu, *Angew. Chem., Int. Ed.*, 2004, **43**, 6358; (*k*) B. L. Hodous, J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 2637; (*l*) S. L. Wiskur and G. C. Fu, *J. Am. Chem. Soc.*, 2005, **127**, 6176; (*m*) B. L. Hodous and G. C. Fu, *J. Am. Chem. Soc.*, 2002, **124**, 10006; (*n*) J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154; (*o*) A. H. Mermerian and G. C. Fu, *J. Am. Chem. Soc.*, 2003, **125**, 4050; (*p*) A. H. Mermerian and G. C. Fu, *Angew. Chem., Int. Ed.*, 2005, **44**, 949; (*q*) J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 11532; (*r*) I. D. Hills and G. C. Fu, *Angew. Chem., Int. Ed.*, 2003, **42**, 3921; (*s*) C. Schaefer and G. C. Fu, *Angew. Chem., Int. Ed.*, 2005, **44**, 4606.

16 J. G. Setizberg, C. Dissing, I. Søtofte, P.-A. Norrby and M. Johannsen, *J. Org. Chem.*, 2005, **70**, 8332.

17 (*a*) A. C. Spivey, T. Fekner and H. Adams, *Tetrahedron Lett.*, 1998, **39**, 8919; (*b*) A. C. Spivey, T. Fekner, S. E. Spey and H. Adams, *J. Org. Chem.*, 2000, **65**, 3154; (*c*) A. C. Spivey, A. Maddaford, D. P. Leese and A. J. Redgrave, *J. Chem. Soc., Perkin Trans. 1*, 2001, 1785; (*d*) A. C. Spivey, P. Charbonneau, T. Feckner, D. H. Hochmuth, A. Maddaford, C. Malardier-Jugroot, A. J. Redgrave and M. A. Whitehead, *J. Org. Chem.*, 2001, **66**, 7394; (*e*) A. C. Spivey, F. Zhu, M. B. Mitchell, S. G. Davey and R. L. Jarvest, *J. Org. Chem.*, 2003, **68**, 7379; (*f*) A. C. Spivey, D. P. Leese, F. Zhu, S. G. Davey and R. L. Jarvest, *Tetrahedron*, 2004, **60**, 4513.

18 (*a*) T. Kawabata, M. Nagato, K. Takasu and K. Fuji, *J. Am. Chem. Soc.*, 1997, **119**, 3169; (*b*) T. Kawabata, Y. Yamamoto, H. Yoshida, Y. Nagaoka and K. Fuji, *Chem. Commun.*, 2001, 2700.

19 T. Sano, H. Miyata and T. Oriyama, *Enantiomer*, 2000, **5**, 135.

20 A. C. Spivey, A. Maddaford, T. Fekner, A. J. Redgrave and C. S. Frampton, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3460.

21 (*a*) G. Priem, M. S. Anson, S. J. F. Macdonald, B. Pelotier and I. B. Campbell, *Tetrahedron Lett.*, 2002, **43**, 6001; (*b*) B. Pelotier, G. Priem,

I. B. Campbell, S. J. F. Macdonald and M. S. Anson, *Synlett*, 2003, 679; (*c*) G. Priem, B. Pelotier, S. J. F. Macdonald, M. S. Anson and I. B. Campbell, *J. Org. Chem.*, 2003, **68**, 3844.
22 (*a*) T. Kawabata, R. Stragies, T. Fukaya and K. Fuji, *Chirality*, 2003, **15**, 71; (*b*) T. Kawabata, R. Stragies, T. Fukaya, Y. Nagaoaka, H. Schedel and K. Fuji, *Tetrahedron Lett.*, 2003, **44**, 1545.
23 D. Díez, M. J. Gil, R. F. Moro, N. M. Garrido, I. S. Marcos, P. Basabe, S. Sanz, H. B. Broughton and J. G. Urones, *Tetrahedron: Asymmetry*, 2005, **16**, 2980.
24 K.-S. Jeong, S.-H. Kim, H.-J. Park, K.-J. Chang and S. K. Kim, *Chem. Lett.*, 2002, 1114.
25 S. A. Shaw, P. Aleman and E. Vedejs, *J. Am. Chem. Soc.*, 2003, **125**, 13368.
26 T. Poisson, M. Penhoat, C. Papamicaël, G. Dupas, V. Dalla and F. Marsais, *Synlett*, 2005, 2285.
27 S. Yamada, T. Misono and Y. Iwai, *Tetrahedron Lett.*, 2005, **46**, 2239.
28 Recently it has been shown that chiral 1,2-dihydroimidazo[1,2-*a*]pyridine and quinoline systems can serve as highly effective chiral nucleophilic catalysts for the KR of secondary alcohols, see: (*a*) V. B. Birman, E. W. Uffman, H. Jiang, X. Li and C. J. Kilbane, *J. Am. Chem. Soc.*, 2004, **126**, 12227; (*b*) V. B. Birman and H. Jiang, *Org. Lett.*, 2005, **7**, 2445.
29 E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 1809.
30 S. Yamada and S. Morita, *J. Am. Chem. Soc.*, 2002, **124**, 8184.
31 Preliminary communication: C. Ó Dálaigh, S. J. Hynes, D. J. Maher and S. J. Connon, *Org. Biomol. Chem.*, 2005, **3**, 981.
32 F. Guiller, F. Nivoliers, A. Godard, F. Marsais, G. Quéguiner, M. A. Siddiqui and V. Snieckus, *J. Org. Chem.*, 1995, **60**, 292.
33 S. Kanemasa and K. Onimura, *Tetrahedron*, 1992, **48**, 8631.
34 Both antipodes of α,α-diphenylprolinol are commercially available.
35 H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249.
36 It has also been shown alcohols can participate as both nucleophiles and general base catalysts in the acylation of primary alcohols by aroyl and α-chloro acid chlorides, and as such an intriguing general-base role for the catalyst tertiary hydroxy group cannot be ruled out: (*a*) T. W. Bentley, H. C. Harris, Z. H. Ryu, G. T. Lim, D. D. Sung and S. R. Szajda, *J. Org. Chem.*, 2005, **70**, 8963; (*b*) T. W. Bentley, R. O. Jones and I. S. Koo, *J. Chem. Soc., Perkin Trans. 2*, 1994, 753; (*c*) T. W. Bentley and R. O. Jones, *J. Chem. Soc., Perkin Trans. 2*, 1993, 2351; (*d*) T. W. Bentley and H. C. Harris, *J. Org. Chem.*, 1988, **53**, 724.
37 See supplementary information for synthetic details†.
38 While it is tempting to point toward the presence of two substrate aromatic moieties here, other factors such as the conformational preferences of the amide (relative to the ester functionality of substrate **11**), the relative planarity of the benzo-fused five membered ring and the presence of a second potentially hydrogen bond donating group (amide N-H) may also contribute to making **24** a poor substrate for KR using **6**.
39 (*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.
40 This structure has been deposited at the Cambridge Crystallographic Data Center, deposit No. CCDC 293598. The solvent molecules and bromide counter-ion have been removed for clarity.
41 Several attempts to support this hypothesis (which is based on δ H-2 and δ H-6) through the detection of an NOE between the isopropyl proton and either H-2 or H-6 of **6b** proved inconclusive.
42 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03, Revision C.03*, Gaussian, Inc., Wallingford CT, 2004.
43 D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R. A. Reamer, J. J. Mohan, E. T. Turner-Jones, K. Hoogsteen, M. W. Baum and E. J. Grabowski, *J. Org. Chem.*, 1991, **56**, 751.