Atropisomeric α-methyl substituted analogues of 4-(dimethylamino)pyridine: synthesis and evaluation as acyl transfer catalysts

Alan C. Spivey,*[a] Adrian Maddaford,[a] David P. Leese[a] and Alison J. Redgrave[b]

[a] *Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, UK S3 7HF*
[b] *GlaxoSmithKline Medicines Research Centre, Gunnels Wood Road, Stevenage, Hertfordshire, UK SG1 2NY*

Received (in Cambridge, UK) 17th April 2001, Accepted 13th June 2001
First published as an Advance Article on the web 13th July 2001

The regioselectivity of α-metalation–methylation of *N*-BF_3 adducts of 4-(dimethylamino)pyridines as a function of β-substitution is examined in attempts to prepare configurationally stable atropisomeric derivatives (**I** and **II**) having an α-methyl substituent and a β-biaryl stereogenic axis. The activity of some of these derivatives as catalysts for acyl transfer is examined and the kinetic resolution of 1-(1-naphthyl)ethanol catalysed by α-methyl chiral DMAP (−)-**24** is reported. A rationale for the reduced stereoselectivity of this catalyst relative to its non-α-substituted analogue (−)-**1** is also proposed.

Introduction

Although it has been known since the 1890's that pyridine accelerates the rate of acylation of alcohols with Ac_2O (Einhorn acylation),[1] it was not until the 1950's that this acceleration was shown to be primarily due to nucleophilic catalysis.[2–6] Subsequently, Litvinenko[7] and Steglich[8] independently discovered that 4-(dimethylamino)pyridine (DMAP) was a superior nucleophilic catalyst for acyl transfer reactions and this derivative is now routinely used for this purpose.[9–13] Recently, we[14–17] and others[18–36] have reported chirally modified derivatives of DMAP as catalysts for enantioselective acyl transfer to secondary alcohols in kinetic resolution (KR)[37] and asymmetric desymmetrisation[38] protocols. Our efforts have mainly focused on the development of atropisomeric analogues of DMAP having a stereogenic biaryl axis β to the pyridine nitrogen and this work has led to the identification of chiral DMAP (−)-**1** as an efficient catalyst for the KR of alkylarylcarbinols (Fig. 1).[14–16,39] The configurational stability of this derivative accrues from severe steric hindrance to rotation about the key biaryl axis as the result of di-*ortho* substitution of the non-pyridyl ring.[15] In this paper we describe our attempts to prepare atropisomeric chiral DMAPs **I** and **II** (Fig. 1) having di-*ortho* substitution, relative to the biaryl axis, on the pyridyl ring and evaluate α-methyl chiral DMAP derivative (−)-**24** (see Scheme 5) as a catalyst for asymmetric acyl transfer.

The positioning of the stereogenic axis is central to the design of configurationally stable atropisomeric analogues of DMAP. As a rule-of-thumb, at least three *ortho* substituents are required for rotamers (*i.e.* atropisomers) of a biaryl to be configurationally stable at ambient temperature.[40,41] Cognisant of this, and mindful that several biaryls comprising pyridyl rings display anomalously low barriers to rotation,† we chose to position the axis β to the pyridyl nitrogen so as to allow di-*ortho* substitution on either (or both) of the aryl partners. Di-*ortho* substitution on the pyridyl ring requires a substituent α to the catalytically active pyridyl nitrogen (the other being the 4-amino function). This scenario is attractive as it should allow a mono-*ortho* substituted aryl group as the axial partner, thereby ensuring maximum steric differentiation between the faces of the pyridine ring (which is probably important for enantiodiscrimination). Additionally, a substituent α to the pyridyl nitrogen would be expected to exert a strong influence over the conformation of the carbonyl group in the acylpyridinium intermediate during catalysis of acyl transfer. Such control could enhance enantiodiscrimination[47] and so, although α substitution is known to strongly attenuate the nucleophilicity of pyridines,‡ we anticipated that α-methyl substituted DMAPs might nevertheless be viable templates for asymmetric catalysts. Our initial target structures (**I**, Fig. 1) had α-methyl-*N*-methyl-5-azaindoline **4** as their core catalytic unit as the azaindoline scaffold was anticipated to impart enhanced configurational stability relative to the corresponding DMAP.§

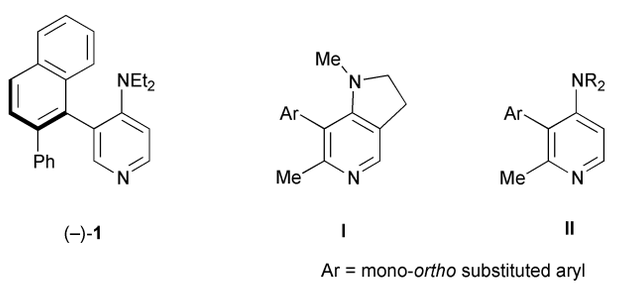


Fig. 1 DMAP-based chiral catalyst and proposed catalyst structures.

† For example, at ambient temperature 2,2′,6,6′-tetracarboxy-4,4′-diphenyl-3,3′-bipyridyl racemises rapidly whereas biphenyls substituted with *ortho* substituents of comparable size are configurationally stable.[42] However, configurationally stable pyridyl-containing biaryls are known.[43–46]

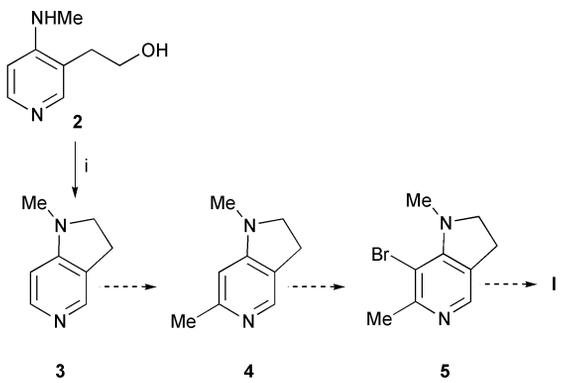
‡ Following pioneering studies by Gold and Butler,[6] Litvinenko and co-workers found that the ratio of rates of catalysis by DMAP, pyridine, 2-methylpyridine, and 2,6-dimethylpyridine relative to the uncatalysed reaction for the benzoylation of benzyl alcohol using BzCl (1 eq.) in benzene are: $3.45 \times 10^8 : 9.29 \times 10^3 : 435 : 115$.[48] More recently, Sammakia and Hurley have shown that the ratio of rates of catalysis by 4-(pyrrolidino)pyridine (PPY), 2-methyl-PPY, and 2-ethyl-PPY (1 mol%) (relative to the uncatalysed reaction) for the acetylation of menthol using Ac_2O–Et_3N (10 eq.) in CH_2Cl_2 is 120 : 4.0 : 1.7 and that 2-isopropyl-PPY and 2-*tert*-butyl-PPY do not show catalytic activity above that of the uncatalysed reaction.[49]

§ This turned out not to be the case.[15] The results of an investigation into the reasons for this are the subject of a forthcoming full paper.

DOI: 10.1039/b103385a

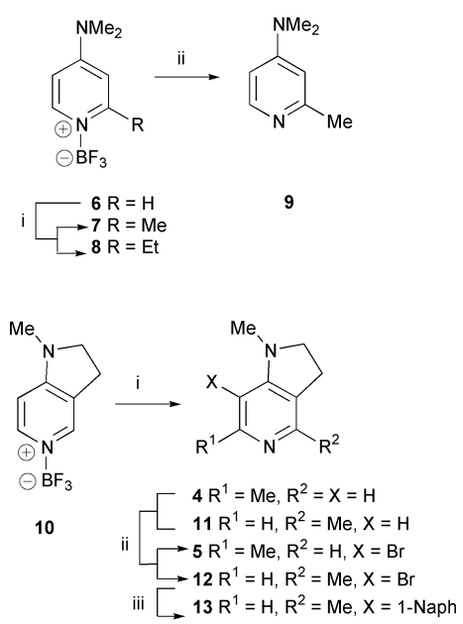
Results and discussion

Our strategy for the preparation of catalyst candidates of type **I** is outlined in Scheme 1. *N*-Methyl-5-azaindoline **3** was



Scheme 1 A strategy for preparation of atropisomeric α-methyl chiral DMAPs **I**. *Reagents*: i, *p*-NsCl, Et_3N [98%].

prepared from 4-aminopyridine (4 steps, 72% overall yield) by a modification of our previous method[15] now employing cyclisation of intermediate alcohol **2** using *p*-nitrobenzenesulfonyl chloride (NsCl)–Et_3N in CH_2Cl_2 (99%). We envisaged that α-metalation–methylation of an *N*-BF_3 pyridine adduct[50,51] would effect efficient introduction of the α-methyl group¶ (*i.e.* **3** → **4**, Scheme 1). Thus, metalation of DMAP–BF_3 **6**[53] with lithium 2,2,6,6-tetramethylpiperidine (LTMP) in a modification of a procedure described by Vedejs and Chen,‖[18] followed by alkylation with MeI afforded α-methyl and α-ethyl products **7** and **8** in 60 and 17% respectively (Scheme 2). α-Ethyl-DMAP–BF_3 **8** presumably results from *in situ* lateral deprotonation of α-methyl-DMAP–BF_3 **7**.** This side reaction



Scheme 2 *Reagents*: i, (a) LTMP, (b) MeI {**6** → **7** [60%] + **8** [17%]; **10** → **4** + **11** [~1 : 3, 73%]}, or (a) BuLi, ^{t}BuOK, (b) MeI {**6** → **7** [87%]}; ii, MeOH {**7** → **9** [99%]; **4** + **11** → **5** [17%] + **12** [53%]}; iii, Na_2CO_3, $Pd(PPh_3)_4$ (cat.), 1-naphthylboronic acid [98%].

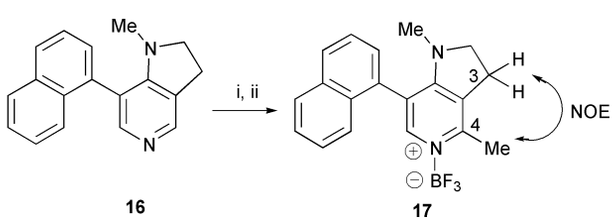
¶ An alternative approach for the introduction of an α-methyl substituent into pyridine *N*-oxides using the Tebbe reagent has recently been reported by Nicolaou *et al.*[52]

‖ Vedejs has prepared DMAP–BF_3 **6** *in situ* and quenched with pivaldehyde.[18] For methylation, we obtained better results by isolation of *N*-BF_3 adduct **6** which is stable to flash chromatography on SiO_2.[53]

** Analogous ethylation when quenching α-metalated pyridine with Me_2SO_4 has recently been reported by Fort and co-workers.[54]

could be eliminated by employing BuLi as base to give exclusively α-methyl-DMAP–BF_3 **7** in 87% yield in a protocol similar to one recently developed by Sammakia and Hurley.[49] Heating at reflux in MeOH effected quantitative decomplexation of the BF_3 to give α-methyl-DMAP **9**. With an efficient procedure for α-methylation established, we turned our attention to the α-methylation of *N*-methyl-5-azaindoline **3**. Methylation of BF_3 adduct **10** afforded a 1 : 3 mixture of regioisomers†† (**4** and **11**, 73% combined yield, for assignment see later) favouring the more hindered (and undesired) 4-methyl isomer **11**. These were inseparable by flash chromatography both before and after BF_3 decomplexation but bromination with NBS[15] afforded a separable mixture of regioisomeric bromides **5** (17%) and **12** (53%) (Scheme 2). Although the desired bromide **5** was the minor isomer we were able to prepare ample quantities to explore subsequent Suzuki type cross-coupling of both isomers with 1-naphthylboronic acid. Unfortunately, under conditions which we had previously optimised for analogous couplings in the non α-methyl series,[15] bromide **12** coupled to give biaryl **13** in 98% yield but bromide **5** underwent hydrodebromination to regenerate 5-azaindoline **4** in 95% yield. Despite extensive experimentation, we were unable to effect coupling of bromide **5** [or 3-bromo-2-methyl-4-(dimethylamino)pyridine (**14**)]‡‡ with 1-naphthylboronic acid or other comparably hindered boronic acids.

We reasoned that cross-coupling prior to α-methylation might circumvent this impasse and furnish the desired isomer as the major product, providing that α-methylation once again occurred at the (presumably) more hindered 6-position *ortho* to the biaryl axis. In the event, methylation of the BF_3 adduct of biaryl **16**[15] gave the undesired 4-methyl product **17** exclusively (71%) (Scheme 3). A strong NOE to the C-3 methylene protons



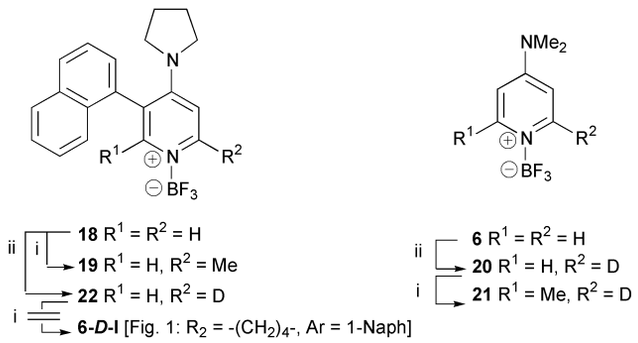
Scheme 3 *Reagents*: i, BF_3·Et_2O; ii, (a) BuLi, (b) MeI [71% overall].

in BF_3 adduct **17** confirmed the position of the methyl group. The decomplexed product was identical to the previously obtained biaryl **13**, thereby confirming our previous assignments. To probe further the factors influencing the regioselectivity of metalation, and also in the hope of obtaining a configurationally stable biaryl derivative for KR studies, we next studied methylation of the BF_3 adduct **18** of 3-(1-naphthyl)-4-(pyrrolidino)pyridine.[15] Disappointingly, this derivative also gave the undesired 6-methyl regioisomer **19** exclusively (68%) (Scheme 4), indicating that the regioselectivity observed with biaryl **16** was a result of additive preferences for metalation distal to the biaryl axis (strong) and proximal to the ring junction (weak).

Since the biaryl axis clearly directed metalation to the distal α-position, our next strategy was to introduce a removable

†† Our observations with *N*-BF_3 complex **10** contrast sharply with those of Abramovitch and co-workers who have noted that *N*-oxides of 3-alkyl substituted pyridines tend to metalate at the less hindered 6-position[55,56] and undergo nucleophilic addition at the more hindered 2-position.[57]

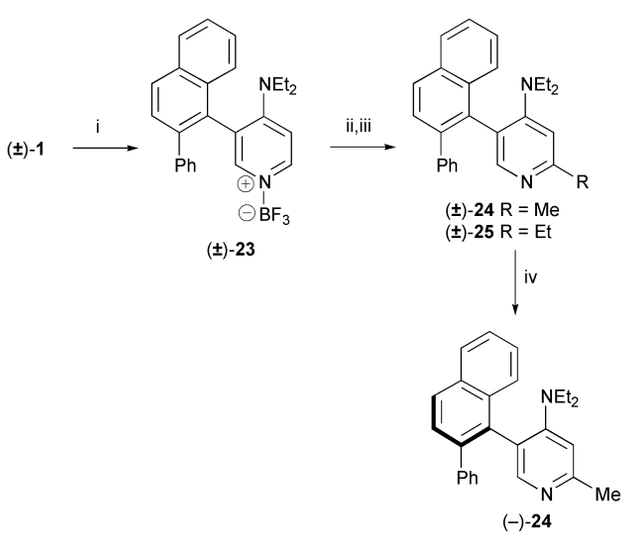
‡‡ Pyridine **14** and its regioisomer, 3-bromo-6-methyl-4-(dimethylamino)pyridine (**15**) were obtained by bromination of α-methyl-DMAP **9**. Isomer **14**, the product of bromination at the more hindered position, predominates under our NBS-based conditions whereas it has been reported that 2-methyl-4-(piperidino)pyridine brominates predominantly at the less hindered position using Br_2–K_2CO_3.[58]



Scheme 4 *Reagents*: i, (a) BuLi, (b) MeI {**18** → **19** [68%]; **20** → **21** [72%]}; ii, (a) BuLi, (b) D_2O {**6** → **20** [97%]; **18** → **22** [61%]}.

blocking group at this position. We were attracted to the possibility of using deuterium for this purpose as metalation processes are known to be subject to significant primary deuterium isotope effects ($k_H/k_D > 30$).[59] Moreover, deuterium should be readily washed out of the α-position in DMAP-like systems using dilute alkali.[60] Preliminary investigations into the feasibility of this approach involved the preparation of 2-deuterio-DMAP–BF_3 **20** (97%) by quenching lithiated **6** with D_2O. Pleasingly, lithiation of this adduct and alkylation with MeI as before afforded the desired 2-methyl-6-deuterio-DMAP–BF_3 **21** exclusively (72%) (Scheme 4). To test if this isotope effect was sufficient to overcome the bias exerted by the biaryl axis, 6-deuteriobiaryl **22** was prepared in 61% yield by quenching the lithiated **18** with D_2O (Scheme 4). However, this molecule resisted metalation–methylation (or deuteriation) under the optimised conditions and starting material was recovered almost quantitatively on each occasion.

We decided to terminate this line of enquiry and to assess the impact of α-methyl substitution on both catalytic activity and KR selectivity by preparing the derivative of chiral catalyst (−)-**1**[16] having an α-methyl group distal to its biaryl axis using the BF_3 adduct metalation–methylation methodology. Accordingly, this compound was prepared in racemic form (Scheme 5) and



Scheme 5 *Reagents*: i, $BF_3{\cdot}Et_2O$ [62%]; ii, (a) BuLi, (b) MeI; iii, MeOH {**23** → **24** [25%] + **25** [11%]}; iv, CSP HPLC (for **24** only).

resolved by semipreparative chiral stationary phase (CSP) HPLC to give enantiomerically pure α-methylpyridine (−)-**24**.

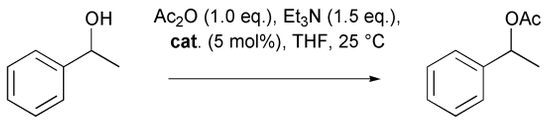
α-Methylpyridines **4**, **9**, and **13** were shown to catalyse the acetylation of 1-phenylethanol with Ac_2O under standard conditions at 25 °C (Table 1). Although the catalytic activity of these catalysts is, as expected, reduced relative to the parent heterocycles (*e.g.* DMAP, entry 3, Table 1) they all catalyse the transformation significantly.

To compare the selectivity (*s*) achieved using α-methylpyridine (−)-**24** with that using non-α-methylpyridine (−)-**1**, parallel KR experiments were performed under identical conditions employing 1-(1-naphthyl)ethanol and $(^iPrCO)_2O$ at 0 °C in toluene (Table 2). It can be seen that both catalysts have the same sense of stereoinduction but that catalyst (−)-**24** is significantly less selective (*s* = 2.0, entry 4, Table 2) than catalyst (−)-**1** (*s* = 5.2, entry 3). Although this decrease in selectivity was disappointing, we had expected that KR selectivity would be strongly influenced by the presence of an α-methyl group. We had reasoned that an α-methyl group would impose a significant bias on the conformation of the acyl C=O function in the key acylpyridinium salt intermediate in the catalytic cycle favouring the planar conformation in which the acyl oxygen is positioned closest to the α-methyl group to minimise $A^{1,3}$ strain §§ (*i.e.* such that the C=O bond is aligned parallel to the biaryl axis for catalyst **24**). As a consequence of this, the incoming alcohol nucleophile would have fewer Burgi–Dunitz trajectories available to it (relative to in the corresponding non-α-methyl substituted salt for which both planar conformations would be significantly populated) and this would result in a change in stereoselectivity.

In order to further understand the effect of α-methyl substitution on acylpyridinium carbonyl conformation and corroborate this hypothesis we performed a series of ^1H NMR experiments at 400 MHz on solutions (~30 mg cm^{-3}) of (±)-**1**, (±)-**24**, DMAP (**30**), and α-methyl-DMAP **9** in acid free $CDCl_3$ at ambient temperature. For each catalyst, AcCl (1 equiv.) was added and ^1H NMR spectra acquired at $t = 2$ min and regular time intervals thereafter. Each experiment was performed in duplicate and gave good reproducibility between runs. Catalysts **1**, **30**, and **9** were converted to acetylpyridinium chlorides **26**, **31**, and **32**, respectively, within 2 min (see Table 3 for diagnostic ^1H NMR data) although the half-lives of these salts with respect to subsequent decomposition to their respective hydrochlorides **28**, **33**, and **34**, respectively, varied dramatically [**26**: $t_{\frac{1}{2}} \approx 12$ h; **31**: $t_{\frac{1}{2}} \approx 36$ h; **32**: $t_{\frac{1}{2}} \approx 2.5$ h]. With catalyst **24** we were unable to observe acetylpyridinium chloride **27** as quantitative conversion to hydrochloride **29** was complete within 2 min [*i.e.* presumably **27** has $t_{\frac{1}{2}} < 1$ min]. Analysis of the spectra for acetylpyridinium chlorides **26**, **31**, and **32** reveals a number of interesting features. The α protons and the β protons in DMAP-derived salt **31** appear as two sets of doublets (H^a/H^b at δ 9.06 ppm, and H^c/H^d at δ 7.19 ppm). Therefore rotation about the N–Ac bond is rapid on the NMR timescale at this temperature. Consequently, these chemical shifts are average values for the individual signals dependent on the N–Ac bond-rotation. This interpretation is confirmed by comparison with the ^1H NMR spectrum acquired at −115 °C (at which temperature N–Ac rotation is 'frozen-out')[61] on the acetylpyridinium acetate of 4-(pyrrolidino)pyridine (PPY), which reveals that protons corresponding to H^a and H^b resonate at δ 8.7 and 10.1 ppm, and H^c and H^d at δ 6.9 and 7.2 ppm, respectively.[9] It follows that at ambient temperature rotation about the N–Ac bond will not be resolved in the spectrum of acetylpyridinium chloride **26** either. However, the fact that the signal for H^a (which is unambiguously assigned on the basis of its multiplicity) resonates at δ 8.30 ppm [*i.e.* $\Delta\delta = +0.12$ ppm *cf.* **1**] and the signal for H^b resonates at δ 9.91 ppm [*i.e.* $\Delta\delta = +1.69$ ppm *cf.* **1**] in the spectrum of acetylpyridinium chloride **26** strongly suggests that *even in the absence of an α-methyl* group the conformation in which the acetyl C=O bond

§§ The carbonyl oxygen is smaller than the acyl substituent.[47] Fu and co-workers have obtained an X-ray crystal structure of an acetylpyridinium salt of one of their ferrocenyl DMAPs showing an approximately planar conformation in which steric interactions with the fused five-membered ring are minimised.[29]

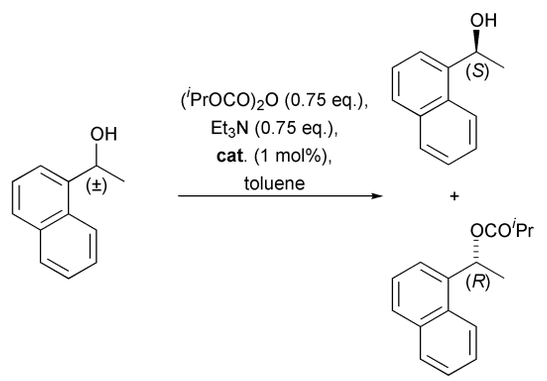
Table 1 Catalysis of acylation of 1-phenylethanol with Ac_2O–Et_3N



		Alcohol : acetate ratios[a]			
Entry	Catalyst	After 5 min	After 15 min	After 4 h	After 24 h
1	No catalyst[b]	—[c]	—[c]	—[c]	94 : 6
2	No catalyst	>99 : 1	>99 : 1	98 : 2	91 : 9
3	DMAP	83 : 17	<1 : 99	<1 : 99	<1 : 99
4	**9**	97 : 3	92 : 8	45 : 55	15 : 85
5	**4**	99 : 1	97 : 3	67 : 33	16 : 84
6	**13**	99 : 1	96 : 4	61 : 39	14 : 86

[a] Determined by HPLC on a Chiralcel OD column. [b] No Et_3N. [c] Not determined.

Table 2 KR of 1-phenylethanol using C_2-symmetric PPYs



Entry	Catalyst	*T*/°C	*t*/h	C (%)[a]	(*R*)-Alcohol ee_A (%)[b]	(*S*)-Ester ee_E (%)[b]	*s*
1	No catalyst	0	24.0	3	—	—	—
2	(−)-**1**	−78	9.0	45.1	69.2	84.1	24
3	(−)-**1**	0	0.08	40.8	39.1	56.6	5.2
4	(−)-**24**	0	24.0	15.3	5.6	30.9	2.0

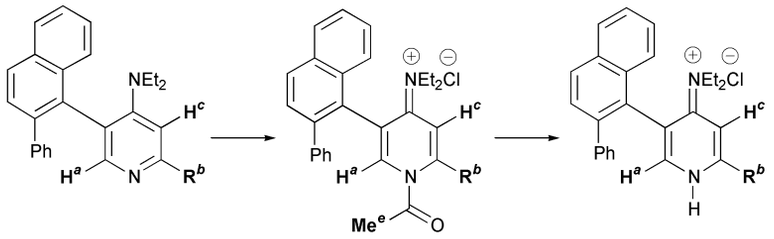
[a] Conversion by (HPLC) mass balance. [b] By HPLC using a Chiralcel OD column.

is aligned parallel to the biaryl axis [*i.e.* as drawn in the Table 3 graphic)] is significantly favoured.¶¶ We currently have no convincing explanation for this preference, although it may reflect a stereoelectronic stabilisation dependent on partial conjugation across the biaryl bond. Our inability to observe acetylpyridinium chloride **27** derived from α-methyl catalyst **24** does not allow us to corroborate our prediction that an α-methyl group imposes an additional bias towards this same conformer. Indeed, the fact that the signal for H^a in the spectrum of α-methylacetylpyridinium chloride **32** resonates at δ 8.57 ppm [*i.e.* $\Delta\delta = +0.63$ ppm *cf.* **9**] and the signal for the α-methyl $CH_3{}^b$ resonates at δ 2.69 ppm [*i.e.* $\Delta\delta = +0.18$ ppm *cf.* **9**] does not appear to support this hypothesis. By analogy with the data for compounds **1**, **26**, **30** and **31** the signal for H^a would not be expected to shift and the signal for $CH_3{}^b$ would be expected to shift to lower field if the planar conformation drawn were to be significantly populated for pyridinium chloride **32**. This suggests that the effect of an α-methyl group may be to force the acetyl group and pyridine ring to adopt a non-planar conformation in solution. Such an orientation could explain the shorter half-lives of the α-methylacetylpyridinium chlorides **27** and **32** relative to their non-α-methyl counterparts **26** and **31**. The conversion of an acetylpyridinium chloride to give a hydrochloride presumably involves elimination of ketene.[62] For a non-planar acetylpyridinium salt in which conjugation between the C=O function and the aromatic ring is compromised this elimination should be particularly facile. The generation of ketene under KR conditions could also account for the reduced selectivity of α-methyl substituted catalyst (−)-**24** relative to catalyst (−)-**1**, since ketene itself is an achiral acylating agent. Although we saw no ketene (or diketene) in our NMR spectra, it is volatile and we did observe the formation of acetic acid which could, among other pathways, be produced by reaction of ketene with adventitious water.

In summary, the α-methylation of DMAP derivatives by metalation–methylation of *N*-BF_3 adducts has been explored and the regioselectivity of this process has been shown to be strongly dependent on the substitution pattern at the β-positions. α-Methyl-DMAPs, as expected, display significantly reduced catalytic activity in the acylation of secondary alcohols by Ac_2O as the result of decreased nucleophilicity. Moreover, enantiomerically pure DMAP (−)-**24**, which contains an α-methyl group distal to its biaryl axis, displays moderate selectivity in the KR of 1-(1-naphthyl)ethanol compared to its

¶¶ The complexity of the *N*-ethyl resonances of acetylpyridinium chloride **26** reveals that there is restricted rotation about the C_{Ar}–N bond at ambient temperature. This bond rotation is not resolved for the parent catalyst **1** and confirms the expected increase in conjugation across the C_{Ar}–N bond as the result of *N*-acetylation. The magnitudes of energy barriers to rotation about the three rotatable bonds in catalyst **1** are therefore in the order: biaryl ⩾ C_{Ar}–N > N–Ac.

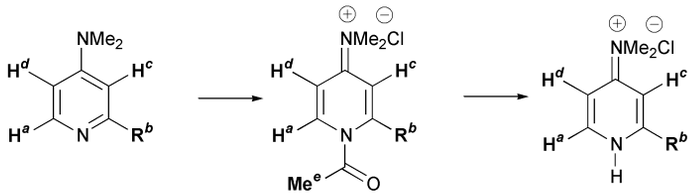
Table 3 Comparison of selected ^{1}H NMR signals for free, acylated, and protonated forms of (±)-**24**,**29** (DMAP), and **9** following treatment with AcCl in $CDCl_3$ at rt



(±)-**1** R = H
(±)-**24** R = Me

(±)-**26** R = H
(±)-**27** R = Me

(±)-**28** R = H
(±)-**29** R = Me



30 R = H
9 R = Me

31 R = H
32 R = Me

33 R = H
34 R = Me

Cat	H^a	R^b	H^c	H^d	Me^e
(+)-**1**	8.18 (s)	8.22 (d, 6.0 Hz)	6.50 (d, 6.0 Hz)	—	—
(+)-**26**	8.30 (d, 2.0 Hz)	9.91 (d, 8.0, 2.0 Hz)	7.41 (d, 8.0 Hz)	—	3.05 (s)
(+)-**28**	8.08 (t, 7.0 Hz)	8.02 (d, 7.0 Hz)	6.60 (d, 7.0 Hz)	—	—
(+)-**24**	8.08 (s)	2.49 (s)	6.39 (s)	—	—
(+)-**27**	N/A	N/A	N/A	—	N/A
(+)-**29**	7.98 (d, 8.5 Hz)	2.69 (s)	6.34 (s)	—	—
30	8.19 (dd, 5.0, 1.5 Hz)		6.46 (dd, 5.0, 1.5 Hz)		—
31	9.06 (d, 8.0 Hz)		7.19 (d, 8.0 Hz)		2.94 (s)
33	8.05 (t, 7.0 Hz)		6.75 (d, 7.0 Hz)		—
9	7.94 (d, 7.0 Hz)	2.51 (s)	6.52 (d, 3.0 Hz)	6.62 (dd, 7.0, 3.0 Hz)	—
32	8.57 (d, 8.0 Hz)	2.69 (s)	6.72 (d, 3.0 Hz)	6.95 (dd, 8.0, 3.0 Hz)	2.80 (s)
34	7.93 (t, 7.0 Hz)	2.60 (s)	6.50 (d, 2.0 Hz)	6.65 (dd, 7.0, 2.0 Hz)	—

non-α-methylated analogue (−)-**1** at 0 °C. On the basis of NMR data it is proposed that the α-methyl group may enforce a non-planar conformation on the derived acylpyridinium salt, leading to the notion that the reduced stereoselectivity of α-methyl-DMAP (−)-**24** may reflect an increased susceptibility to ketene formation.

Experimental

General

All reactions were performed under anhydrous conditions and an inert atmosphere of nitrogen in oven-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise indicated. Reagents were used as obtained from commercial sources or purified according to known procedures.[63] Flash chromatography was carried out using Merck Kiesegel 60 F_{254} (230–400 mesh) silica gel. Only distilled solvents were used as eluents. Thin layer chromatography (TLC) was performed on Merck DC-Alufolien or glass plates pre-coated with silica gel 60 F_{254} which were visualised either by quenching of ultraviolet fluorescence (λ_{max} = 254 nm) or by charring with 5% w/v phosphomolybdic acid in 95% EtOH, 10% w/v ammonium molybdate in 1 M H_2SO_4, or 10% $KMnO_4$ in 1 M H_2SO_4. Observed retention factors (R_f) are quoted to the nearest 0.05. All reaction solvents were distilled before use and stored over activated 4 Å molecular sieves, unless otherwise indicated. Anhydrous CH_2Cl_2 was obtained by refluxing over CaH_2. Anhydrous THF and Et_2O were obtained by distillation, immediately before use, from sodium–benzophenone ketyl under an inert atmosphere of nitrogen. Anhydrous DMF was obtained by distillation from CaH_2 under reduced pressure. Petrol refers to the fraction of light petroleum boiling between 40–60 °C. High resolution mass spectrometry (HRMS) measurements are valid to ±5 ppm.

1-Methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine 3[15]

To a stirred solution of alcohol **2**[15] (0.45 g, 2.9 mmol) in CH_2Cl_2 (15 cm^3) was added Et_3N (1.23 cm^3, 8.7 mmol) and the mixture was cooled to 0 °C. *p*-Nitrobenzenesulfonyl chloride (0.98 g, 4.35 mmol) was then added over 10 min and the reaction was stirred for 1 h. The mixture was then warmed to room temperature, stirred for a further 2 h and then washed with sat. $NaHCO_3$ (15 cm^3). The organic phase was then dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography (Et_3N–EtOAc, 1 : 19) to give *pyridine* **3** (0.39 g, 98%) as a white solid. R_f 0.15 (EtOAc–Et_3N, 19 : 1); δ_H ($CDCl_3$) 2.74 (3H, s, CH_3), 2.92 (2H, t, J = 8.5 Hz, CH_2), 3.37 (2H, t, J = 8.5 Hz, CH_2), 6.20 (1H, d, J = 5.5 Hz, CH), 7.95 (1H, s, CH) and 8.05 (1H, d, J = 5.5 Hz, CH); *m*/*z* (EI^+) (rel. intensity) 134 (75%, M^+) and 133 (100).

2-Methyl-4-(dimethylamino)pyridine·BF_3 7 and 2-ethyl-4-(dimethylamino)pyridine·BF_3 8

Method I. To a stirred solution of DMAP·BF_3 **6**[53] (0.10 g, 0.53 mmol) in THF (3 cm^3) at −78 °C was added LTMP (0.26 M in THF, 2 cm^3, 0.53 mmol). After 30 min MeI (0.75 cm^3, 5.3 mmol) was added and the mixture stirred for 30 min. The reac-

tion mixture was then warmed to room temperature, carefully quenched with water (15 cm^3) and extracted with chloroform (2 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (EtOAc–petrol, 2 : 3) to give the following compounds.

2-Methylpyridine·BF_3 7. White solid (0.065 g, 60%). Mp 143 °C; R_f 0.40 (EtOAc–CH_2Cl_2–petrol, 1 : 3 : 3); ν_{max}/cm^{-1} ($CHCl_3$) 1636, 1548, 1440, 1386, 1290, 1108, 1037 and 912; δ_H ($CDCl_3$) 2.60 (3H, s, CH_3), 3.12 (6H, s, 2 × CH_3), 6.37–6.46 (2H, m, 2 × CH) and 8.17 (1H, br d, J = 5.5 Hz, CH); δ_C ($CDCl_3$) 21.31 (CH_3), 39.50 (2 × CH_3), 104.04 (CH), 107.92 (CH), 142.87 (CH), 154.58 (C_q) and 156.42 (C_q); *m/z* (CI^+) (rel. intensity) 222 (11%, MNH_4^+), 185 (7) and 137 (100). HRMS calcd. for $C_8H_{16}N_3B_1F_3$ (MNH_4^+) 221.1426, found 221.1427.

2-Ethylpyridine·BF_3 8. White solid (0.020 g, 17%). R_f 0.50 (EtOAc–CH_2Cl_2–petrol, 1 : 3 : 3); ν_{max}/cm^{-1} ($CHCl_3$) 1637, 1551, 1535, 1442, 1393, 1109, 1073 and 903; δ_H ($CDCl_3$) 1.29 (3H, t, J = 7.6 Hz, CH_3), 3.05 (2H, q, J = 7.6 Hz, CH_2), 3.15 (6H, s, 2 × CH_3), 6.42–6.48 (2H, m, 2 × CH) and 8.25 (1H, d, J = 7.0 Hz, CH); δ_C ($CDCl_3$) 14.12 (CH_3), 31.68 (CH_2), 39.12 (2 × CH_3), 104.39 (2 × CH), 149.05 (CH), 154.95 (C_q) and 163.35 (C_q); *m/z* (CI^+) (rel. intensity) 151 (100%, MH^+) and 122 (6). Found: C, 49.49; H, 6.44; N, 12.69. Calcd. for $C_9H_{14}N_2B_1F_3$: C, 49.58; H, 6.47; N, 12.85%.

2-Methyl-4-(dimethylamino)pyridine·BF_3 7

Method II. To a stirred solution of DMAP·BF_3 **6**[53] (0.15 g, 0.79 mmol) in THF (4 cm^3) was added freshly sublimed *t*-BuOK (0.106 g, 0.95 mmol). The mixture was cooled to −78 °C and *n*-BuLi (1.63 M in hexanes, 0.58 cm^3, 0.95 mmol) was added dropwise. After 10 min, MeI (0.5 cm^3, 7.9 mmol) was added and stirred for 30 min. The mixture was warmed to −40 °C, quenched with water (10 cm^3) and then warmed to room temperature. The reaction mixture was extracted with CH_2Cl_2 (3 × 10 cm^3), the organic extracts were combined and dried over $MgSO_4$. Evaporation and purification by flash chromatography (CH_2Cl_2–petrol, 4 : 1) gave *2-methylpyridine·BF_3* **7** (0.14 g, 87%) as a white solid. Spectroscopic data as above.

2-Methyl-4-(dimethylamino)pyridine 9

A stirred solution of 2-methylpyridine·BF_3 **7** (0.14 g, 0.69 mmol) in MeOH (8 cm^3) was heated at reflux for 2 h. The solution was cooled to room temperature and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc–MeOH saturated with NH_3, 97 : 3) to give *2-methylpyridine* **9** (0.092 g, 99%) as a white solid. R_f 0.40 (NH_3 saturated MeOH–CH_2Cl_2, 7 : 93); ν_{max}/cm^{-1} (Nujol) 1644, 1608, 1560 and 1077; δ_H ($CDCl_3$) 2.51 (3H, s, CH_3), 3.17 (6H, s, 2 × CH_3), 6.52 (1H, d, J = 3.0 Hz, CH), 6.62 (1H, dd, J = 7.0, 3.0 Hz, CH) and 7.94 (1H, d, J = 7.0 Hz, CH); δ_C ($CDCl_3$) 24.70 (CH_3), 39.10 (2 × CH_3), 104.24 (CH), 105.58 (CH), 148.98 (CH), 154.84 (C_q) and 158.07 (C_q); *m/z* (EI^+) (rel. intensity) 136 (83%, M^+), 135 (100), 121 (24) and 92 (20); HRMS calcd. for $C_8H_{12}N_2$ (M^+) 136.1000, found 136.1002.

1-Methyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine·BF_3 10

To a stirred solution of pyridine **3** (0.1 g, 0.75 mmol) in Et_2O (3 cm^3) at 0 °C was added BF_3·Et_2O (0.1 cm^3, 0.825 mmol). After 30 min a white precipitate formed which was collected by filtration, washed with cold Et_2O (1 cm^3) and the filtrate concentrated *in vacuo* to give *pyridine·BF_3* **10** (0.12 g, 80%) as a white amorphous solid. R_f 0.30 (EtOAc–CH_2Cl_2–petrol, 1 : 3 : 3); ν_{max}/cm^{-1} ($CHCl_3$) 1649, 1596, 1535, 1478, 1430, 1409 and 1085; δ_H ($CDCl_3$) 3.00 (3H, s, CH_3), 3.15 (2H, t, J = 8.5 Hz, CH_2), 3.80 (2H, t, J = 8.5 Hz, CH_2), 6.30 (1H, d, J = 6.7 Hz, CH), 7.85 (1H, br s, CH) and 8.03–8.11 (1H, br s, CH); δ_C ($CDCl_3$) 24.78 (CH_2), 32.68 (CH_3), 54.16 (CH_2), 99.23 (CH), 126.14 (C_q), 135.21 (CH), 143.58 (CH) and 160.31 (C_q); *m/z* (CI^+) (rel. intensity) 220 (81%, MNH_4^+) and 135 (100); HRMS calcd. for $C_8H_{14}N_3B_1F_3$ (MNH_4^+) 219.1269, found 219.1278.

1,6-Dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine·BF_3 4 and 1,4-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine·BF_3 11

To a stirred solution of pyridine·BF_3 **10** (0.1 g, 0.5 mmol) in THF (2 cm^3) at −78 °C was added LTMP (0.25 M in THF, 2 cm^3) and the mixture was stirred vigorously for 1 h. The mixture was then warmed to −60 °C and MeI (0.3 cm^3, 5.0 mmol) was added dropwise. After 10 min at −60 °C, the mixture was allowed to warm to room temperature, diluted with water (10 cm^3) and then CH_2Cl_2 (10 cm^3). The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 cm^3). The organic layers were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by flash chromatography (CH_2Cl_2–petrol, 7 : 13) to give a mixture of *pyridines* **4** and **11** (~1 : 3 by ^1H NMR) as a white solid (0.078 g, 73%). R_f 0.40 (EtOAc–CH_2Cl_2–petrol, 1 : 3 : 3); δ_H ($CDCl_3$) [*pyridine* **11**] 2.63 (3H, s, CH_3), 2.95 (3H, s, CH_3), 3.07 (2H, t, J = 8.9 Hz, CH_2), 3.75 (2H, t, J = 8.9 Hz, CH_2), 6.10 (1H, s, CH) and 7.97 (1H, br s, CH); [*pyridine* **4**] 2.47 (3H, s, CH_3), 2.95 (3H, s, CH_3), 3.05 (2H, t, J = 8.9 Hz, CH_2), 3.77 (2H, t, J = 8.9 Hz, CH_2), 6.15 (1H, d, J = 9.1 Hz, CH) and 8.13–8.25 (1H, br s, CH); *m/z* decomplexed ions found: (EI^+) (rel. intensity) 148 (74%, M^+), 147 (100), 133 (17), 106 (10) and 79 (9).

7-Bromo-1,6-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine 5 and 7-bromo-1,4-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]-pyridine 12

A mixture of pyridines **4** and **11** (0.093 g, 0.63 mmol) in MeOH (5 cm^3) was heated at reflux for 4 h and then concentrated *in vacuo* to give a white solid. The crude mixture was passed through a short silica column (EtOAc), concentrated *in vacuo* and dissolved in DMF (5 cm^3). The solution was cooled to 0 °C and NBS (0.117 g, 0.64 mmol) was added slowly. After 2 h the solvent was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (10 cm^3), and washed successively with sat. $NaHCO_3$ (7 cm^3) and water (2 × 5 cm^3). The organic phase was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (EtOAc) to give the following compounds.

Pyridine 5. Brown solid (0.024 g, 17%), R_f 0.15 (EtOAc–petrol, 1 : 1); ν_{max}/cm^{-1} ($CHCl_3$) 1601, 1492, 1467, 1415, 1311, 1207, 1093 and 906; δ_H ($CDCl_3$) 2.49 (3H, s, CH_3), 2.87 (2H, t, J = 8.9 Hz, CH_2), 3.20 (3H, s, CH_3), 3.47 (2H, t, J = 8.9 Hz, CH_2) and 7.75 (1H, s, CH); δ_C ($CDCl_3$) 24.79 (CH_2), 25.47 (CH_3), 37.00 (CH_3), 56.79 (CH_2), 99.59 (C_q), 126.00 (C_q), 140.99 (CH), 154.96 (C_q) and 157.21 (C_q); *m/z* (EI^+) (rel. intensity) 226/228 (100%, MH^+), 146 (38), 132 (8), 118 (9), 77 (12) and 52 (12); HRMS calcd. for $C_9H_{11}N_2Br^{79}$ (M^+) 226.0106, found 226.0104.

Pyridine 12. Brown solid (0.076 g, 53%), R_f 0.20 (EtOAc–petrol, 1 : 1); ν_{max}/cm^{-1} ($CHCl_3$) 1596, 1567, 1492, 1463, 1446, 1409, 1288 and 1014; δ_H ($CDCl_3$) 2.12 (3H, s, CH_3), 2.74 (2H, t, J = 8.9 Hz, CH_2), 3.30 (3H, s, CH_3), 3.35 (2H, t, J = 8.9 Hz, CH_2) and 7.90 (1H, s, CH); δ_C ($CDCl_3$) 20.58 (CH_3), 25.89 (CH_2), 36.06 (CH_3), 55.62 (CH_2), 96.10 (C_q), 125.27 (C_q), 150.32 (C_q), 151.37 (CH) and 153.57 (C_q); *m/z* (EI^+) (rel. intensity) 226/228 (100%, MH^+), 146 (44), 132 (10) and 77 (9); HRMS calcd. for $C_9H_{11}N_2Br^{79}$ (M^+) 226.0106, found 226.0095.

1,4-Dimethyl-7-(1-naphthyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]-pyridine 13

To a stirred solution of pyridine **12** (0.27 g, 1.17 mmol) in ethanol (1 cm^3) and toluene (2.5 cm^3) was added aqueous

Na_2CO_3 (2 M, 2.5 cm^3) followed by $Pd(PPh_3)_4$ (0.041 g, 0.035 mmol) and 1-naphthylboronic acid (0.24 g, 1.4 mmol). The mixture was heated at reflux overnight, cooled to room temperature and partitioned between CH_2Cl_2 (20 cm^3) and sat. $NaHCO_3$ (20 cm^3). The phases were separated and the aqueous phase was extracted with further portions of CH_2Cl_2 (2 × 20 cm^3). The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc → EtOAc–MeOH saturated with NH_3, 49 : 1) to give *pyridine* **13** (0.31 g, 98%) as a white solid. R_f 0.45 (NH_3 saturated MeOH–CH_2Cl_2, 7 : 93); ν_{max}/cm^{-1} ($CHCl_3$) 1600, 1576, 1490, 1462, 1405 and 1280; δ_H ($CDCl_3$) 2.05 (3H, s, CH_3), 2.42 (3H, s, CH_3), 2.98 (2H, t, J = 8.3 Hz, CH_2), 3.27–3.53 (2H, m, CH_2), 7.37–7.52 ($4H_{arom}$, m), 7.60–7.72 ($1H_{arom}$, m), 7.70–7.89 ($2H_{arom}$, m) and 7.95 (1H, s, CH); δ_C ($CDCl_3$) 21.21 (CH_3), 26.23 (CH_2), 35.89 (CH_3), 55.52 (CH_2), 114.55 (C_q), 122.91 (C_q), 125.31 (CH), 125.97 (CH), 126.37 (CH), 128.12 (CH), 128.21 (CH), 128.41 (CH), 132.01 (CH), 132.162 (CH), 133.22 (C_q), 135.20 (C_q), 150.77 (CH), 151.05 (C_q) and 155.93 (C_q); *m/z* (EI^+) (rel. intensity) 274 (100%, M^+), 259 (7), and 189 (8); HRMS calcd. for $C_{19}H_{18}N_2$ (M^+) 274.1470, found 274.1481.

3-Bromo-2-methyl-4-dimethylaminopyridine 14 and 3-bromo-6-methyl-4-dimethylaminopyridine 15

To a stirred solution of 2-methylpyridine **9** (0.3 g, 2.2 mmol) in DMF (15 cm^3) at 0 °C was slowly added NBS (0.4 g, 2.3 mmol). After 2 h, the solvent was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2 (25 cm^3), this was then washed successively with sat. $NaHCO_3$ (20 cm^3) and water (2 × 15 cm^3). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (CH_2Cl_2) to give the following compounds.

Bromopyridine 14. Yellow oil (0.2 g, 43%), R_f 0.30 (CH_2Cl_2–EtOAc, 3 : 2); ν_{max}/cm^{-1} ($CHCl_3$) 1751, 1719, 1687, 1580, 1481, 1457, 1430, 1342, 1156 and 1029; δ_H ($CDCl_3$) 2.63 (3H, s, CH_3), 2.82 (6H, s, 2 × CH_3), 6.66 (1H, d, J = 5.5 Hz, CH) and 8.16 (1H, d, J = 5.5 Hz, CH); δ_C ($CDCl_3$) 26.09 (CH_3), 43.08 (2 × CH_3), 112.26 (CH), 114.85 (C_q), 147.39 (CH), 158.37 (C_q) and 158.82 (C_q); *m/z* (EI^+) (rel. intensity) 213/215 (100%, M^+), 135 (13) and 55 (15); HRMS calcd. for $C_8H_{11}N_2Br^{79}$ (M^+) 214.0106, found 214.0111.

Bromopyridine 15. Yellow oil (0.18 g, 38%), R_f 0.25 (CH_2Cl_2–EtOAc, 3 : 2); ν_{max}/cm^{-1} ($CHCl_3$) 1707, 1580, 1521, 1485, 1453, 1441, 1386, 1295, 1160 and 1025; δ_H ($CDCl_3$) 2.37 (3H, s, CH_3), 2.85 (6H, s, 2 × CH_3), 6.58 (1H, s, CH) and 8.28 (1H, s, CH); δ_C ($CDCl_3$) 23.95 (CH_3), 42.40 (2 × CH_3), 109.85 (C_q), 113.22 (CH), 152.33 (CH), 157.04 (C_q) and 157.71 (C_q); *m/z* (EI^+) (rel. intensity) 213/215 (100%, M^+), 135 (16) and 56 (50); HRMS calcd. for $C_8H_{11}N_2Br^{79}$ (M^+) 214.0106, found 214.0097.

1,4-Dimethyl-7-(1-naphthyl)-2,3-dihydro-1*H*-pyrro lo[3,2-*c*]-pyridine·BF_3 17

To a stirred solution of 1-methyl-7-(1-naphthyl)-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine **16**[15] (0.15 g, 0.58 mmol) in THF (4 cm^3) at 0 °C was added BF_3·THF (0.064 cm^3, 0.58 mmol). After 1 h, the mixture was cooled to −78 °C and *n*-BuLi (2.5 M in hexanes, 0.46 cm^3, 1.16 mmol) was added dropwise. After an additional 1 h, MeI (0.37 cm^3, 5.8 mmol) was added, the mixture was stirred at −78 °C for 30 min, then 0 °C for 30 min and finally warmed to room temperature. The reaction mixture was carefully diluted with water (10 cm^3) and then extracted with CH_2Cl_2 (3 × 15 cm^3). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc–petrol, 1 : 1) to give *pyridine·BF_3* **17** (0.14 g, 71%) as a pale yellow foam. R_f 0.24 (EtOAc–petrol, 2 : 3); ν_{max}/cm^{-1} ($CHCl_3$) 1658, 1596, 1533, 1413, 1355, 1296, 1234 and 1055; δ_H ($CDCl_3$) 2.12 (3H, s, CH_3), 2.41 (3H, s, CH_3), 3.07 (2H, t, J = 9.1 Hz, CH_2), 3.59–3.84 (2H, m, CH_2), 7.27–7.33 ($1H_{arom}$, m), 7.40–7.50 ($4H_{arom}$, m), 7.77 (1H, s, CH) and 7.79–7.89 ($2H_{arom}$, m); δ_C ($CDCl_3$) 16.46, 16.97, 24.22, 25.37, 34.40, 34.47, 55.18, 55.54, 113.51, 124.38, 124.98, 125.185, 125.21, 125.36, 126.42, 126.59, 126.97, 127.28, 128.52, 128.64, 128.75, 129.21, 129.66, 130.39, 131.83, 132.57, 132.84, 133.11, 142.72, 143.03, 146.10, 157.47 and 158.54 (more peaks than expected, presumably due to atropisomerism around the N–B bond); *m/z* decomplexed ions found: (EI^+) (rel. intensity) 274 (100%, M^+), 239 (8), 189 (6) and 137 (7); HRMS calcd. for $C_{19}H_{18}N_2$ (M^+) 274.1470, found 274.1474.

3-(1-Naphthyl)-4-pyrrolidinopyridine·BF_3 18

To a stirred solution of the 3-(1-naphthyl)-4-pyrrolidinopyridine[15] (1.2 g, 4.38 mmol) in THF (35 cm^3) at 0 °C was added BF_3·THF (0.58 cm^3, 5.26 mmol). After 15 min, the mixture was warmed to room temperature and stirred for a further 25 min. The reaction mixture was concentrated *in vacuo* and purified by flash chromatography to give (0.29 g, 24%) as a white solid and *pyridine·BF_3* **18** (1.08 g, 72%) as a yellow foam. R_f 0.25 (EtOAc–CH_2Cl_2–petrol, 1 : 3 : 3); ν_{max}/cm^{-1} ($CHCl_3$) 1632, 1523, 1454, 1385, 1344, 1308, 1235, 1129, 1105, 1004 and 919; δ_H ($CDCl_3$) 1.4–2.0 (4H, br s, 2 × CH_2), 2.07–3.87 (4H, m, 2 × CH_2), 6.74 (1H, d, J = 7.3 Hz, CH), 7.36–7.54 ($5H_{arom}$, m), 7.87–7.96 ($2H_{arom}$, m), 8.05 (1H, s, CH) and 8.19 (1H, br d, J = 6.7 Hz, CH); δ_C ($CDCl_3$) 24.70 (br, 2 × CH_2), 50.19 (2 × CH_2), 108.15 (CH), 120.24 (C_q), 124.82 (CH), 125.29 (CH), 126.35 (CH), 127.14 (CH), 128.57 (CH), 128.70 (CH), 129.18 (CH), 132.78 (C_q), 132.93 (C_q), 134.19 (C_q), 140.70 (CH), 144.20 (CH) and 153.80 (C_q). Found: C, 66.54; H, 5.19; N, 8.12. Calcd. for $C_{19}H_{18}N_2B_1F_3$: C, 66.70; H, 5.30; N, 8.19%.

2-Methyl-5-(1-naphthyl)-4-pyrrolidinopyridine–boron trifluoride complex 19

To a solution of pyridine·BF_3 **18** (0.11 g, 0.32 mmol) in THF (10 cm^3) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 0.26 cm^3, 0.64 mmol). After 30 min, MeI (0.1 cm^3, 1.6 mmol) was added and the mixture was stirred for a further 30 min. The reaction was quenched with water (10 cm^3), allowed to warm to room temperature and then extracted with CH_2Cl_2 (3 × 10 cm^3). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromatography (CH_2Cl_2–EtOAc–petrol, 3 : 1 : 4) to give *2-methylpyridine·BF_3* **19** (0.078 g, 68%) as a yellow foam. R_f 0.35 (EtOAc–CH_2Cl_2–petrol, 1 : 3 : 3); δ_H ($CDCl_3$) 1.62–1.79 (4H, m, 2 × CH_2), 2.65 (3H, s, CH_3), 2.73–2.92 (2H, m, CH_2), 3.04–3.22 (2H, m, CH_2), 6.56 (1H, s, CH), 7.35–7.55 ($5H_{arom}$, m) and 7.85–7.97 (1H + $2H_{arom}$, m); δ_C ($CDCl_3$) 19.61 (CH_3), 25.12 (2 × CH_2), 50.51 (2 × CH_2), 107.86 (CH), 119.07 (C_q), 124.943 (CH), 125.08 (CH), 126.49 (CH), 127.33 (CH), 128.66 (CH), 128.81 (CH), 129.44 (CH), 132.76 (C_q), 132.98 (C_q), 133.19 (C_q), 141.85 (CH), 150.16 (C_q) and 154.59 (C_q); δ_F ($CDCl_3$) −146 (BF_3); *m/z* decomplexed ions found: (EI^+) (rel. intensity) 288 (15%, M^+), 86 (65) and 84 (100); HRMS calcd. for $C_{20}H_{20}N_2$ (M^+) 288.1626, found 288.1620.

2-Deuterio-4-dimethylaminopyridine·BF_3 20

To a stirred solution of DMAP·BF_3 **6**[53] (0.3 g, 1.58 mmol) in THF (15 cm^3) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 0.98 cm^3, 3.16 mmol). After 1 h, deuterium oxide (0.3 cm^3, 15.8 mmol) was added and stirring continued for 30 min. The reaction mixture was warmed to room temperature and extracted with CH_2Cl_2 (3 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) gave *2-deuteriopyridine·BF_3* **20** (0.29 g, 97%) as a white solid. R_f 0.25 (EtOAc–CH_2Cl_2–petrol, 1 : 3 : 3); ν_{max}/cm^{-1} ($CHCl_3$) 1621, 1550, 1438, 1388, 1363 and

1292; δ_H ($CDCl_3$) 3.31 (6H, s, 2 × CH_3), 6.37 (2H, m, 2 × CH) and 8.21 (1H, br d, CH); δ_C ($CDCl_3$) 39.63 (2 ×CH_3), 106.19 (2 × CH), 141.45 (t, $^1J_{C-D}$ = 27 Hz, C_q), 141.72 (CH) and 156.53 (C_q); *m*/*z* decomplexed ions found: (EI^+) (rel. intensity) 123 (100%, M^+), 112 (49) and 83 (19); HRMS calcd. for $C_7H_9D_1N_2$ (M^+) 123.0907, found 123.0902.

2-Deuterio-6-methyl-4-dimethylaminopyridine·BF_3 21

To a stirred solution of pyridine·BF_3 **20** (0.15 g, 0.81 mmol) in THF (7 cm^3) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 0.65 cm^3, 1.62 mmol). After 1 h, MeI (0.4 cm^3, 6.48 mmol) was added and stirring continued for 1 h. The reaction mixture was carefully quenched with water (20 cm^3), warmed to room temperature and extracted with CH_2Cl_2 (3 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) gave *6-methylpyridine·BF*$_3$ **21** (0.12 g, 72%) as a white solid. R_f 0.40 (EtOAc–CH_2Cl_2–petrol, 5 : 15 : 15); ν_{max}/cm^{-1} ($CHCl_3$) 1627, 1540, 1444, 1365, 1095 and 904; δ_H ($CDCl_3$) 2.61 (3H, s, CH_3), 3.13 (6H, s, 2 × CH_3) and 6.43 (2H, d, *J* = 5.2 Hz, 2 × CH); δ_C ($CDCl_3$) 21.28 (CH_3), 39.50 (2 × CH_3), 103.90 (CH), 107.91 (CH), 141 (t, $^1J_{C-D}$ = 27 Hz, C_q), 154.49 (C_q) and 156.43 (C_q); *m*/*z* decomplexed ions found: (EI^+) (rel. intensity) 137 (100%, M^+), 122 (18) and 93 (12); HRMS calcd. for $C_8H_{11}N_2D_1$ (M^+) 137.1063, found 137.1065.

2-Deuterio-5-(1-naphthyl)-4-pyrrolidinopyridine·BF_3 22

To a stirred solution of pyridine·BF_3 **18** (0.31 g, 0.9 mmol) in THF (15 cm^3) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 0.72 cm^3, 1.8 mmol). After 1 h, deuterium oxide (0.5 cm^3, 28 mmol) was added and stirring continued for 30 min. The reaction mixture was warmed to room temperature and extracted with CH_2Cl_2 (3 × 20 cm^3). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography (CH_2Cl_2) gave *1-deuteriopyridine·BF*$_3$ **22** (0.19 g, 61%) as a pale yellow foam. R_f 0.25 (EtOAc–CH_2Cl_2–petrol, 1 : 3 : 3); ν_{max}/cm^{-1} ($CHCl_3$) 1621, 1529, 1513, 1446, 1355, 1301, 1138, 1105, 1001 and 914; δ_H ($CDCl_3$) 1.48–1.96 (4H, m, 2 × CH_2), 2.63–3.80 (4H, m, 2 × CH_2), 6.73 (1H, s, CH), 7.37–7.60 (5H_{arom}, m), 7.88–7.99 (2H_{arom}, m) and 8.07 (1H, s, CH); δ_C ($CDCl_3$) 24–26 (br, 2 × CH_2), 50.29 (2 × CH_2), 108.154 (CH), 120.37 (C_q), 124.93 (CH), 125.38 (CH), 126.45 (CH), 127.23 (CH), 128.67 (CH), 128.79 (CH), 129.28 (CH), 132.90 (C_q), 133.06 (C_q), 134.32 (C_q), 140.51 (t, $^1J_{C-D}$ = 27 Hz, C_q), 144.25 (CH) and 153.95 (C_q). Found: C, 66.08; H, 5.23; N, 8.03. Calcd. for $C_{19}H_{17}D_1N_2B_1F_3$: C, 66.50; H, 4.99; N, 8.16%.

(±)-Diethyl[3-(2-phenyl-1-naphthyl)-4-pyridyl]amine·BF_3 23

To a stirred solution of pyridine (±)-**1**[16] (397 mg, 1.13 mmol) in THF (10 cm^3) at 0 °C was added BF_3·THF. The resulting solution was stirred for 1 h at this temperature and then allowed to warm to room temperature. The solution was then concentrated *in vacuo*, and purified by flash chromatography (EtOAc–petrol, 1 : 1) to give the *pyridine·BF*$_3$ (±)-**23** as a white solid (294 mg, 0.70 mmol, 62%). R_f 0.75 (EtOAc–petrol, 1 : 1); mp 150–152 °C; ν_{max}/cm^{-1} ($CHCl_3$) 2978, 1636, 1526 and 1115; δ_H ($CDCl_3$) 0.65 (6H, t, *J* = 7.2 Hz, 2 × CH_3), 2.79–2.88 (2H, m, CH_2), 3.05–3.10 (2H, m, CH_2), 6.54 (1H, d, *J* = 7.3Hz, CH), 7.03–7.06 (2H_{arom}, m), 7.20–7.25 (3H_{arom}, m), 7.51–7.58 (3H_{arom}, m), 7.74 (1H, d, *J* = 7.9 Hz, CH), 7.94 (1H, d, *J* = 7.1 Hz, CH), 7.99 (1H, d, *J* = 8.5 Hz, CH), 8.06 (1H, s, CH) and 8.10 (1H, d, *J* = 7.2 Hz, CH); δ_C ($CDCl_3$) 12.22 (2 × CH_3), 45.49 (2 × CH_2), 109.54 (CH), 120.10 (C_q), 125.85 (CH), 126.57 (CH), 127.17 (CH), 127.58 (CH), 128.16 (3 × CH), 128.53 (CH), 129.28 (2 × CH), 129.49 (CH), 131.51 (C_q), 131.67 (C_q), 133.06 (C_q), 139.46 (C_q), 140.51 (C_q), 140.57 (CH), 146.50 (CH), and 156.59 (C_q); *m*/*z* decomplexed ions found: (CI^+) (rel. intensity) 353 (MH^+, 100%), 337 (15); HRMS calcd. for $C_{25}H_{24}BF_3N_2$ (NH_4 adduct) 438.233, found 438.233.

(±)-Diethyl[2-methyl-5-(2-phenyl-1-naphthyl)-4-pyridyl]amine 24 and (±)-diethyl[2-ethyl-5-(2-phenyl-1-naphthyl)-4-pyridyl]-amine 25

To a stirred solution of pyridine·BF_3 (±)-**23** (185 mg, 0.44 mmol) in THF (7 cm^3) at −78 °C was added *t*-BuLi (0.590 cm^3, 1.65 M, 0.97 mmol) dropwise. After 2 h, MeI (0.275 cm^3, 626 mg) was added at −78 °C and the reaction mixture was allowed to warm to room temperature over 18 h. The mixture was then diluted with water (15 cm^3) and extracted with CH_2Cl_2 (3 × 15 cm^3). The organic extracts were combined, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was then heated at reflux in MeOH (5 cm^3) for 2 h. The resulting solution was allowed to cool to room temperature and concentrated *in vacuo*. Purification by flash chromatography (EtOAc) gave the following compounds.

α-Methylpyridine (±)-24. Yellow oil (40 mg, 0.11 mmol, 25%), R_f 0.20 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2979, 2254, 1593, 1381 and 918; δ_H ($CDCl_3$) 0.52 (6H, t, *J* = 7.2, 2 × CH_3), 2.49 (3H, s, CH_3), 2.57–2.85 (4H, m, 2 × CH_2), 6.39 (1H, s, CH), 7.11–7.19 (5H_{arom}, m), 7.40–7.55 (3H_{arom}, m), 7.81–7.93 (3H_{arom}, m) and 8.08 (1H, s, CH); δ_C ($CDCl_3$) 12.06 (2 × CH_3), 24.36 (CH_3), 44.49 (2 × CH_2), 110.99 (CH), 120.41 (C_q), 125.90 (CH), 126.34 (CH), 126.47 (CH), 126.66 (CH), 127.56 (2 × CH), 128.02 (2 × CH), 128.58 (CH), 129.56 (2 × CH_2), 132.51 (C_q), 133.07 (C_q), 133.97 (C_q), 138.81 (C_q), 141.80 (C_q), 153.32 (CH), 155.52 (C_q) and 156.94 (C_q); *m*/*z* (EI^+) (rel. intensity) 366 (M^+, 77%), 351 (100); HRMS calcd. for $C_{26}H_{26}N_2$ 366.2096, found 366.2096.

α-Ethylpyridine (±)-25. Yellow oil (19 mg, 0.05 mmol, 11%), R_f 0.30 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2976, 2257, 1591, 1382 and 918; δ_H ($CDCl_3$) 0.51 (6H, t, *J* = 7.0, 2 × CH_3), 1.31 (3H, t, *J* = 7.6, CH_3), 2.56–2.84 (6H, m, 3 × CH_2), 6.38 (1H, s, CH), 7.08–7.16 (5H_{arom}, m), 7.41–7.56 (3H_{arom}, m), 7.84–7.94 (3H_{arom}, m) and 8.10 (1H, s, CH); δ_C($CDCl_3$) 12.04 (2 × CH_3), 14.09 (CH_3), 31.27 (CH_2), 44.56 (2 × CH_2), 109.77 (CH), 120.61 (C_q), 125.90 (CH), 126.29 (CH), 126.47 (CH), 126.70 (CH), 127.49 (2 × CH), 128.00 (2 × CH), 128.57 (CH), 129.59 (2 × CH), 132.52 (C_q), 133.07 (C_q), 134.05 (C_q), 138.83 (C_q), 141.80 (C_q), 153.37 (CH), 155.65 (C_q), and 162.32 (C_q); *m*/*z* (EI^+) (rel. intensity) 380 (M^+, 85%), 365 (100); HRMS calculated for $C_{27}H_{28}N_2$ 380.2253, found 380.2260.

Optical resolution of biaryl (±)-24

The enantiomers of biaryl **24** were separated using semi-preparative CSP HPLC (Chiralcel OD column, 1 × 25 cm; hexanes–EtOAc–Et_2NH, 90 : 9.6 : 0.4; 4 cm^3 min^{-1}; 30 °C). UV detection was performed at 250 nm. Injections of ~0.5 mg of the racemate in 5 μL of CH_2Cl_2 were made every 12 min. Enantiomer (−)-**24** was collected from 9.0 to 10.5 min, and enantiomer (+)-**24** was collected from 14.0 to 15.5 min. Both enantiomers were pale yellow oils. Analytical CSP HPLC revealed >99.9% ee for the levorotatory {$[a]_D^{25}$ −107 (*c* 0.15 in $CHCl_3$)} and >97.9% for the dextrorotatory {$[a]_D^{25}$ +100 (*c* 0.20 in $CHCl_3$)} enantiomer.

Representative procedure for rate experiments using 1-phenylethanol. The experiment employing 2-methyl-DMAP 9

To a stirred solution of 2-methyl-DMAP **9** (0.007 g, 0.05 mmol), 1-phenylethanol (0.122 g, 1.0 mmol) and Et_3N (0.209 cm^3, 1.5 mmol) in THF (2 cm^3) was added Ac_2O (0.094 cm^3, 1.0 mmol). After 5 min, ~0.5 cm^3 of the reaction mixture was removed and quickly filtered through a short plug of silica

(CH_2Cl_2–EtOAc, 19 : 1). After 15 min, 4 h and 24 h this sampling procedure was repeated. After evaporation of the solvent, the extent of reaction was determined by HPLC (Chiralcel OD column, 0.46 × 25 cm; hexanes–propan-2-ol, 99 : 1; 1 cm^3 min^{-1}; 0 °C): R_t [(*R*)- and (*S*)-acetates] 7.4 and 8.4 min; R_t [(*R*) and (*S*)-alcohol] 31 and 49 min.[16]

Representative procedure for catalytic KR of alcohol (±)-1-(1-naphthyl)ethanol. The experiment employing catalyst (−)-24

A solution of (±)-1-(1-naphthyl)ethanol (172 mg, 1.00 mmol), Et_3N (104 μL, 0.75 mmol), and catalyst (−)-**24** (3.7 mg, 10 μmol, >99.9% ee) in toluene (2.0 cm^3) was cooled to 0 °C. During vigorous stirring, ($^iPrCO)_2O$ (331 μL, 2.00 mmol) was added dropwise. After 24 h at 0 °C, the reaction was quenched by addition of MeOH (10 cm^3) at 0 °C. The mixture was allowed to warm to room temperature over 15 min and the solvents were evaporated *in vacuo*. 1-(1-Naphthyl)ethanol and its isobutyric ester were separated by flash chromatography (petrol–CH_2Cl_2, 1 : 1 → CH_2Cl_2). The ester was hydrolyzed by heating to reflux in 5% NaOH–MeOH (2 cm^3) for 5 min.[18] After evaporation of the solvent, the residue was passed through a short flash silica column eluting with EtOAc. The enantiomeric excess for the unreacted alcohol and the alcohol obtained by the ester saponification was established by analytical CSP HPLC (Chiralcel OD column, 0.46 × 25 cm; hexanes–propan-2-ol, 90 : 10; 1 cm^3 min^{-1}; 30 °C): R_t [(*S*)-alcohol] 12.4 min; R_t [(*R*)-alcohol] 21.1 min.[16]

^{1}H NMR data for compounds in Table 3

(±)-Diethyl[3-(2-phenyl-1-naphthyl)-4-pyridyl]amine 1. δ_H ($CDCl_3$, 400 MHz) 0.52 (6H, t, *J* = 7.0 Hz, 2 × CH_3), 2.60–2.69 (2H, m, CH_2), 2.74–2.83 (2H, m, CH_2), 6.50 ($1H_{arom}$, d, *J* = 6.0 Hz), 7.09–7.19 ($5H_{arom}$, m), 7.43–7.55 ($3H_{arom}$, m), 7.83 ($1H_{arom}$, d, *J* = 8.5 Hz), 7.92 ($2H_{arom}$, t, *J* = 8.5 Hz), 8.18 ($1H_{arom}$, s) and 8.22 ($1H_{arom}$, d, *J* = 6.0 Hz).

(±)-Diethyl[1-acetyl-3-(2-phenyl-1-naphthyl)pyridin-4(1*H*)-ylidene]ammonium chloride 26. δ_H ($CDCl_3$, 400 MHz) 0.51 (3H, t, *J* = 7.0 Hz, CH_3), 1.06 (3H, t, *J* = 7.0 Hz, CH_3), 2.89–2.94 (1H, m, C*H*H), 3.05 (3H, s, $COCH_3$), 3.26–3.39 (2H, m, CH_2), 3.72–3.78 (1H, m, CH*H*), 7.03–7.06 ($2H_{arom}$, m), 7.29–7.35 ($3H_{arom}$, m), 7.41 ($1H_{arom}$, d, *J* = 8.0 Hz), 7.55–7.61 ($4H_{arom}$, m), 7.98–8.07 ($2H_{arom}$, m), 8.30 ($1H_{arom}$, d, *J* = 2.0 Hz) and 9.91 ($1H_{arom}$, dd, *J* = 8.0, 2.0 Hz).

(±)-Diethyl[3-(2-phenyl-1-naphthyl)pyridin-4(1*H*)-ylidene]-ammonium chloride 28. δ_H ($CDCl_3$, 400 MHz) 0.66 (6H, t, *J* = 7.0 Hz, 2 × CH_3), 2.82–2.91 (2H, m, CH_2), 3.05–3.14 (2H, m, CH_2), 6.60 ($1H_{arom}$, d, *J* = 7.0 Hz), 7.03–7.05 ($2H_{arom}$, m), 7.21–7.23 ($3H_{arom}$, m), 7.50–7.66 ($4H_{arom}$, m), 7.92–7.97 ($2H_{arom}$, m), 8.02 ($1H_{arom}$, d, *J* = 7.0 Hz) and 8.08 ($1H_{arom}$, t, *J* = 7.0 Hz).

(±)-Diethyl[2-methyl-5-(2-phenyl-1-naphthyl)-4-pyridyl]amine 24. Data as above.

(±)-Diethyl[2-methyl-5-(2-phenyl-1-naphthyl)pyridin-4(1*H*)-ylidene]ammonium chloride 29. δ_H ($CDCl_3$, 400 MHz) 0.65 (6H, t, *J* = 7.0 Hz, 2 × CH_3), 2.69 (3H, s, CH_3), 2.81–2.90 (2H, m, CH_2), 3.09–3.18 (2H, m, CH_2), 6.34 ($1H_{arom}$, s), 7.03–7.06 ($2H_{arom}$, m), 7.20–7.24 ($4H_{arom}$, m), 7.48–7.63 ($4H_{arom}$, m), 7.84 ($1H_{arom}$, d, *J* = 6.0 Hz), 7.92 ($1H_{arom}$, d, *J* = 7.5 Hz) and 7.98 ($1H_{arom}$, d, *J* = 8.5 Hz).

4-(Dimethylamino)pyridine 30. δ_H ($CDCl_3$, 400 MHz) 2.96 (6H, s, 2 × CH_3), 6.46 (2H, dd, *J* = 5.0, 1.5 Hz, 2 × CH) and 8.19 (2H, dd, *J* = 5.0, 1.5 Hz, 2 × CH).

Dimethyl[1-acetylpyridin-4(1*H*)-ylidene]ammonium chloride 31. δ_H ($CDCl_3$, 400 MHz) 2.94 (3H, s, $COCH_3$), 3.41 (6H, s, 2 × CH_3), 7.19 (2H, d, *J* = 8.0 Hz, 2 × CH) and 9.06 (2H, d, *J* = 8.0 Hz, 2 × CH).

Dimethyl[pyridin-4(1*H*)-ylidene]ammonium chloride 33. δ_H ($CDCl_3$, 400 MHz) 3.18 (6H, s, 2 × CH_3), 6.75 (2H, d, *J* = 7.0 Hz, 2 × CH) and 8.05 (2H, t, *J* = 7.0 Hz, 2 × CH).

2-Methyl-4-(dimethylamino)pyridine 9. Data as above.

Dimethyl[1-acetyl-2-methylpyridin-4(1*H*)-ylidene]ammonium chloride 32. δ_H ($CDCl_3$, 400 MHz) 2.69 (3H, s, CH_3), 2.80 (3H, s, $COCH_3$), 3.31 (3H, s, CH_3), 3.33 (3H, s, CH_3), 6.72 (1H, d, *J* = 3.0 Hz, CH), 6.95 (1H, dd, *J* = 3.0, 8.0 Hz, CH) and 8.57 (1H, d, *J* = 8.0 Hz, CH).

Dimethyl[2-methylpyridin-4(1*H*)-ylidene]ammonium chloride 34. δ_H ($CDCl_3$, 400 MHz) 2.60 (3H, s, CH_3), 3.18 (6H, s, 2 × CH_3), 6.50 (1H, d, *J* = 2.0 Hz, CH), 6.65 (1H, dd, *J* = 7.0, 2.0 Hz, CH) and 7.93 (1H, t, *J* = 7.0 Hz, CH).

Acknowledgements

Grateful acknowledgement is made to the ESPRC, the BBSRC, and GlaxoSmithKline for financial support. We thank Mr Teyrnon Jones and Mr Fujiang Zhu (Sheffield University) for assistance with NMR experiments.

References

1 A. Einhorn and F. Hollandt, *Annalen*, 1898, **301**, 95.
2 S. L. Bafna and V. Gold, *J. Chem. Soc.*, 1953, 1406.
3 V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1953, 1409.
4 V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1953, 1416.
5 M. L. Bender, *Chem. Rev.*, 1960, **60**, 53, and references therein.
6 A. R. Butler and V. Gold, *J. Chem. Soc.*, 1961, 4362.
7 L. M. Litvinenko and A. I. Kirichenko, *Dokl. Chem. (Engl. Transl.)*, 1967, 763; L. M. Litvinenko and A. I. Kirichenko, *Dokl. Akad. Nauk SSSR Ser. Khim.*, 1967, **176**, 97.
8 W. Steglich and G. Höfle, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 981.
9 G. Höfle, W. Steglich and H. Vorbruggen, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 569.
10 A. Hassner, L. R. Krepski and V. Alexanian, *Tetrahedron*, 1978, **34**, 2069.
11 F. V. Scriven, *Chem. Soc. Rev.*, 1983, **12**, 129.
12 A. Hassner, in *Encyclopedia of Reagents for Organic Synthesis*, ed. L. A. Paquette, Wiley, New York, 1995, Vol. 3, pp. 2022–2024.
13 U. Ragnarsson and L. Grehn, *Acc. Chem. Res.*, 1998, **31**, 494.
14 A. C. Spivey, T. Fekner and H. Adams, *Tetrahedron Lett.*, 1998, **39**, 8919.
15 A. C. Spivey, T. Fekner, S. E. Spey and H. Adams, *J. Org. Chem.*, 1999, **64**, 9430.
16 A. C. Spivey, T. Fekner and S. E. Spey, *J. Org. Chem.*, 2000, **65**, 3154.
17 A. C. Spivey, A. Maddaford, T. Fekner, A. J. Redgrave and C. S. Frampton, *J. Chem. Soc., Perkin Trans. 1*, 2000, 3460.
18 E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1996, **118**, 1809.
19 E. Vedejs and X. Chen, United States Patent No. 5,646,287, 1997 (July 8th).
20 E. Vedejs and X. Chen, *J. Am. Chem. Soc.*, 1997, **119**, 2584.
21 K. Fuji, T. Kawabata, M. Nagato and K. Tasasu, *J. Am. Chem. Soc.*, 1997, **119**, 3169.
22 J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1996, **61**, 7230.
23 J. C. Ruble, H. A. Latham and G. C. Fu, *J. Am. Chem. Soc.*, 1997, **119**, 1492.
24 J. C. Ruble, J. Tweddell and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 2794.
25 J. Liang, J. C. Ruble and G. C. Fu, *J. Org. Chem.*, 1998, **63**, 3154.
26 C. E. Garrett and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 7479 and erratum: C. E. Garrett and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 10276.
27 J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1998, **120**, 11532.
28 B. L. Hodous, J. C. Ruble and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 2637.
29 B. Tao, J. C. Ruble, D. A. Hoic and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 5091 and erratum: B. Tao, J. C. Ruble, D. A. Hoic and G. C. Fu, *J. Am. Chem. Soc.*, 1999, **121**, 10452.
30 Y. Ie and G. C. Fu, *Chem. Commun.*, 2000, 119.
31 S. Bellemin-Laponnaz, J. Tweddell, J. C. Ruble, F. M. Breitling and G. C. Fu, *Chem. Commun.*, 2000, 1009 and references therein.

32 S. J. Taylor and J. P. Morken, *Science*, 1998, **280**, 267.
33 G. Naraku, N. Shimomoto, T. Hanamoto and J. Inanaga, *Enantiomer*, 2000, **5**, 135.
34 H. Kotsuki, H. Sakai and T. Shinohara, *Synlett*, 2000, 116.
35 G. C. Fu, *Acc. Chem. Res.*, 2000, **33**, 412.
36 S. Arai, S. Bellemin-Laponnaz and G. C. Fu, *Angew. Chem., Int. Ed.*, 2001, **40**, 234.
37 H. B. Kagan and J. C. Fiaud, *Top. Stereochem.*, 1988, **18**, 249.
38 W. C. Willis, *J. Chem. Soc., Perkin Trans. 1*, 1999, 1765.
39 A. C. Spivey, A. Maddaford and A. Redgrave, *Org. Prep. Proced. Int.*, 2000, **32**, 331.
40 R. Adams and H. C. Yuan, *Chem. Rev.*, 1933, **12**, 261.
41 E. L. Eliel and S. H. Wilen, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994.
42 M. Slany and P. J. Stang, *Synthesis*, 1996, 1019 and references therein.
43 N. W. Alcock, J. M. Brown and D. I. Hulmes, *Tetrahedron: Asymmetry*, 1993, **4**, 743.
44 H. Zhang, F. Xue, T. C. W. Mak and K. S. Chan, *J. Org. Chem.*, 1996, **61**, 8002.
45 H. Brunner, G. Olschewski and B. Nuber, *Synthesis*, 1999, 429.
46 R. Gallo, C. Roussel and U. Berg, *Adv. Heterocycl. Chem.*, 1988, **43**, 173.
47 C. W. Bird, *Tetrahedron*, 1962, **18**, 1.
48 L. I. Bondarenko, A. I. Kirichenko, L. M. Litvinenko, I. N. Dmitrenko and V. D. Kobets, *Zh. Org. Khim.*, 1981, **17**, 2588.
49 T. Sammakia and T. B. Hurley, *J. Org. Chem.*, 1999, **64**, 4652.
50 S. V. Kessar, P. Singh, K. N. Singh and M. Dutt, *J. Chem. Soc., Chem. Commun.*, 1991, 570.
51 S. V. Kessar and P. Singh, *Chem. Rev.*, 1997, **97**, 721.
52 K. C. Nicolaou, A. E. Koumbis, S. A. Snyder and K. B. Simonsen, *Angew. Chem., Int. Ed.*, 2000, **39**, 2529.
53 M. J. G. Lesley, A. Woodward, N. J. Taylor, T. B. Marder, I. Cazenobe, I. Ledoux, J. Zyss, A. Thornton, D. W. Bruce and A. K. Kakkar, *Chem. Mater.*, 1998, **10**, 1355.
54 S. Choppin, P. Gros and Y. Fort, *Chem. Lett.*, 2000, **2**, 803.
55 R. A. Abramovitch, E. M. Smith, E. Knaus and M. Saha, *J. Org. Chem.*, 1972, **37**, 1690.
56 R. A. Abramovitch, R. T. Coutts and E. M. Smith, *J. Org. Chem.*, 1972, **37**, 3584.
57 H. L. Yale, in *Pyridine and its Derivatives*, ed. R. A. Abramovitch, Wiley, New York, 1974, vol. 14, supplement II, ch. VII.
58 R. J. Ife, C. A. Dyke, D. J. Keeling, E. Meenan, M. L. Meeson, M. E. Parsons, C. A. Price, C. J. Theobald and A. H. Underwood, *J. Med. Chem.*, 1989, **32**, 1970.
59 D. R. Anderson, N. C. Faibish and P. Beak, *J. Am. Chem. Soc.*, 1999, **121**, 7553 and references therein.
60 J. A. Zoltewicz and J. D. Meyer, *Tetrahedron Lett.*, 1968, 421.
61 M. Oki, *Top. Stereochem.*, 1983, **14**, 1.
62 A. K. Sheinkman, S. I. Suminov and A. N. Kost, *Russ. Chem. Rev.*, 1973, **42**, 642.
63 D. D. Perrin and W. C. F. Armarego, *Purification of Laboratory Chemicals*, 3rd edn., Pergamon Press, Oxford, 1988.