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Rapid, room-temperature acylative kinetic resolution of *sec*-alcohols using atropisomeric 4-aminopyridine/triphenylphosphine catalysis

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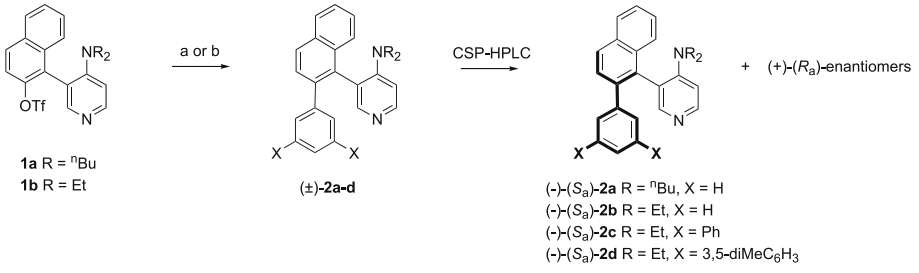
Abstract—Two new atropisomeric 4-aminopyridine-based nucleophilic catalysts containing terphenyl 'blocking groups' have been prepared and evaluated for kinetic resolution (KR) of aryl alkyl *sec*-alcohols. One of these biaryls is shown to be the most selective atropisomeric catalyst yet prepared for several *sec*-alcohols but its low reactivity makes it non-optimal for use at room temperature (rt). Optimisation of the conditions for conducting KRs at rt using a previously described catalyst (containing a phenyl blocking group) at the 1 mol% level indicates that PPh_3 (1 equiv) is beneficial for enantioselectivity and allows KR of (±)-1-(naphthyl)ethanol in less than 30 min with $s > 15$ (i.e., ~40% recovered alcohol with >95% ee). These conditions constitute a convenient and practical method for rapid KR of *sec*-alcohols and are anticipated to facilitate a detailed kinetic study of this catalytic manifold by calorimetry.

1. Introduction

The kinetic resolution (KR) of alcohols by enantioselective esterification using small-molecule nucleophilic chiral catalysts in combination with acid anhydrides or chlorides has been studied by an increasing number of groups over the past decade.[1–3] Indeed, this research area has been in the vanguard of the contemporary 'organocatalysis' renaissance,[4] and a number of attractive and practical KR protocols for a range of *sec*-alcohols have resulted.[5–9] Research from our laboratory has focused on the development of axially chiral, atropisomeric derivatives of 4-aminopyridine and, in particular, 4-dialkylaminopyridines **2a** and **2b** (Scheme 1) as catalysts for the KR of



Scheme 1. Synthesis of catalysts **2a–d** from triflates **1a** and **1b**. Reagents and conditions: For **2a** and **2b** see Refs. 11 and 12, respectively. For **2c** and **1b**: (a) i. 3,5-diPh(C_6H_3)Br, Mg, THF; ii. $PdCl_2$ (dppp) [23%]; (b) 3,5-diPh(C_6H_3)$B(OH)_2$, $Pd(OAc)_2$, P(biph)Cy_2, LiCl, K_3PO_4, toluene [50%]. For **2d** from **1b**: (a) 3,5-di-(3,5-diMeC_6H_3)$C_6H_3B(OH)_2$ (**3**), P(biph)Cy_2, LiCl, K_3PO_4, toluene [39%].

Keywords: Nucleophilic catalysis; Asymmetric catalysis; Organocatalysis; Atropisomerism; Esterification; Acylation; *sec*-Alcohols.
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sec-alcohols.[10,11] A drawback to using these catalysts to date has been the requirement to conduct the experiments for relatively long durations (typically ~10 h) at low temperature (−78 °C). We describe herein our endeavours to achieve rapid KR at ambient temperature. This stemmed from our desire to make the transformation more practical on a process scale and to define conditions under which we could conveniently study the detailed kinetics of such KR processes by calorimetry.

2. Results and discussion

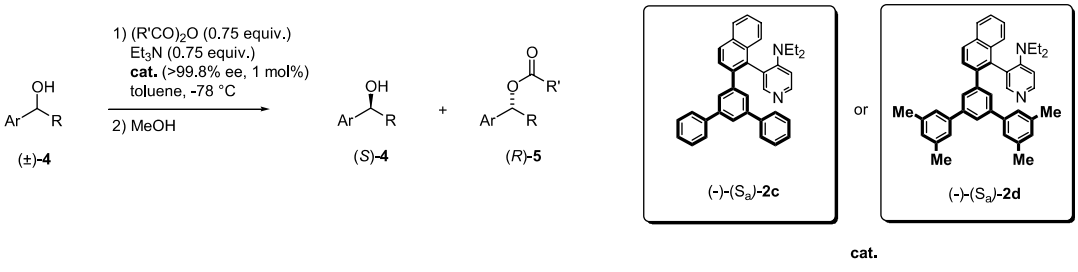
During the course of our studies towards the development of catalysts **2a** and **2b**, we prepared a related series of biaryls having an *N*-methyl-5-azaindoline catalytic core in place of the 4-dialkylaminopyridine.[12] Although this series of compounds give modest levels of enantioselectivity relative to **2b**, it was found that the presence of a terphenyl group at the 2-position of the naphthyl ring attached to the catalytic core gave improved enantioselectivity relative to its phenyl analogue. Reasoning that the improved stereoselectivity reflected more efficient facial discrimination between the front and back faces of the pyridine ring leading to increased $\Delta\Delta G^{\#}$ between the diastereomeric transition states for esterification, we were keen to investigate the performance of terphenyl-containing catalysts **2c** and **2d** relative to the parent compound **2b**. In particular, we were hopeful that these catalysts might allow for good levels of selectivity in KRs run at ambient temperature.

The synthesis of these two new catalysts **2c** and **2d** was achieved from triflate **1b** by either Kharasch or Suzuki-type coupling of the appropriate terphenyl Grignard reagent or boronic acid, respectively, followed by semi-preparative CSP-HPLC (Scheme 1). The absolute configurations of the atropisomeric axes were assigned using circular dichroism spectroscopy (see Section 4).[11]

Using the enantiomerically pure terphenyl catalysts **2c** and **2d**, a series of KR experiments were performed with an array of (±)-*sec*-alcohols **4a–f** as substrates (Table 1).

To allow direct comparison with results obtained with catalysts **2a** and **2b**, initial reactions were run at −78 °C in toluene under previously optimised conditions with the exception that acetic anhydride rather than isobutyric anhydride was employed as acyl donor.[10,12] Preliminary studies revealed that this led to higher levels of stereoselectivity across the board (e.g., $s=39$ vs $s=17$, respectively, for the use of catalyst **2c** with alcohol **4c**, entries 3 and 5; other data not shown). It can be seen that, despite their similar structures, terphenyl-containing catalyst **2c** is significantly more stereoselective than terphenyl-containing catalyst **2d** despite their similar structures. Catalyst **2c** is more stereoselective than phenyl-containing catalysts **2a** and **2b** for alcohols **4a**, **4c** and **4d** and similarly selective for the other alcohols. The rates of reactions catalysed by terphenyl-containing catalysts **2c** and **2d** are, however, lower by a factor of ~2 as compared to those catalysed by phenyl-containing catalysts **2a** and **2b**.

Table 1. KR of alcohols **4a–f** using enantiomerically pure biaryls **2c** and **2d**



Entry	Cat.	Alcohol, ester	**4**, **5**	Anhydride	Time (h)	(*S*)-**4**	(*R*)-**5**	C (%)[a]	s[b]	(s^{ref})[c]
			Ar, R	R′		ee_A (%)[d]	ee_E (%)[e]			
1[f]	**2c**	**4a**, **5a**	Ph, Me	Me	6.0	5.7	90.3	6	22	(13)
2	**2c**	**4b**, **5b**	Ph, Et	Me	9.0	17.1	83.2	17	13	(13)
3	**2c**	**4c**, **5c**	1-Nap, Me	Me	6.6	16.8	94.1	15	39	(29)
4	**2c**	**4c**, **5c**	1-Nap, Me	Me[g]	11.3	94.2	76.9	55	27	
5[f]	**2c**	**4c**, **5c**	1-Nap, Me	*i*-Pr	8.2	11.6	87.8	12	17	
6[f]	**2c**	**4d**, **4d**	2-MeC_6H_4, Me	Me	6.6	21.5	92.3	19	31	(25)
7	**2c**	**4e**, **5e**	2-$MeOC_6H_4$, Me	Me	6.6	5.8	90.8	6	22	(25)
8	**2c**	**4f**, **5f**	2,6-diMeC_6H_3, Me	Me	7.0	13.7	89.9	13	22	(25)
9[f]	**2d**	**4a**, **5a**	Ph, Me	Me	6.7	4.5	73.1	6	6.7	
10[f]	**2d**	**4c**, **5c**	1-Nap, Me	Me	6.8	10.6	85.1	11	14	
11	**2d**	**4d**, **4d**	2-MeC_6H_4, Me	Me	6.2	6.2	82.1	7	11	
12	**2d**	**4f**, **5f**	2,6-diMeC_6H_3, Me	Me	6.2	3.8	72.8	5	6.5	

[a] Conversion $C=100\times ee_A/(ee_A+ee_E)$.
[b] Selectivity factor[13] reproducible to ±2 in parallel runs.
[c] The s values in parentheses are those obtained for this substrate using catalyst **2b** with (^{i}PrCO)$_2$O (taken from Ref. 11).
[d] ee Of recovered alcohol, established by CSP-HPLC.
[e] ee Of ester, established by CSP-HPLC on derived alcohol following saponification.
[f] The dextrorotatory enantiomer of catalyst was employed giving enantiomeric products to those shown.
[g] Ac_2O (2.5 equiv) used.

The modest increase in stereoselectivity and significant decrease in reactivity displayed by terphenyl-containing catalyst **2c** relative to phenyl-containing catalyst **2b** persuaded us to focus further studies on the more readily prepared and resolved catalyst **2b**. Our aim was to find optimal conditions for running rapid KR reactions with this catalyst at ambient temperature. Using (±)-1-(naphthyl)ethanol **4c** as a test substrate and isobutyric anhydride (0.5 equiv) as acyl donor we first surveyed the influence of the reaction solvent and auxiliary base on the KR process (Table 2).

Solvent screening (entries 1–7) in the absence of an auxiliary base revealed that the reactions conducted in *t*-amyl alcohol[14] (*t*-AmOH) and toluene (entries 1 and 2) reached completion (i.e., $C\sim50\%$, as limited by the amount of anhydride present) within 1 h and gave the highest levels of stereoselectivity. The reactions also reached completion in cyclohexane and THF but the stereoselectivities were reduced (entries 3 and 4). The reactions did not reach completion in DMF, CH_2Cl_2, or DMPU and, additionally, gave poor levels of enantioselectivity (entries 5–7).

Using both *t*-AmOH and toluene as solvents, Et_3N, pyridine, P4-*t*-Bu phosphazine [Schwessinger's base, *t*-BuN=P-(N=PNMe$_2$)$_3$],[15] 2,6-di-*t*-butylpyridine, 1,2,2,6,6-pentamethylpiperidine (PMP), K_2CO_3 and K_3PO_4 were surveyed as auxiliary bases (entries 8–21). With the exception of the reactions carried out using P4-*t*-Bu phosphazine base (entries 12 and 13), all the reactions reached completion and, although the levels of stereoselectivity did not vary dramatically, the use of 2,6-di-*t*-butyl pyridine gave the most stereoselective KRs in both solvent systems (entries 14 and 15).

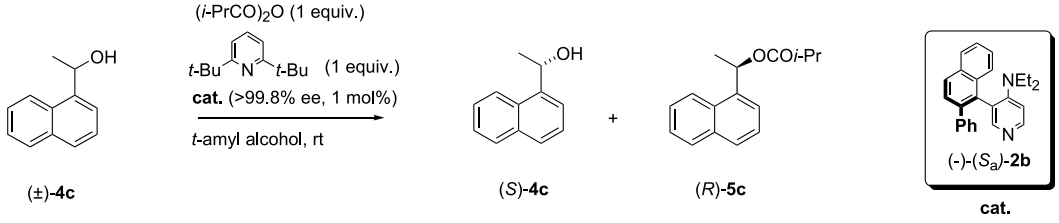
In order to determine the performance of these optimised conditions for KR at rt we conducted a larger scale KR of (±)-1-(naphthyl)ethanol **4c** using 1.0 rather than 0.5 equiv of isobutyric anhydride and removed aliquots for analysis by CSP-HPLC every 2 min (to 10 min), every 5 min (to 45 min) and at increasing intervals thereafter (to 20 h; Graphs 1 and 2) (Scheme 2).

The data show that the reaction reaches ~60% conversion in ~25 min under these conditions, and that at this point the ee of the recovered starting material is >95%.

Finally, we surveyed a number of achiral additives in order to optimise the selectivity further.[16] The reactions were performed using 0.5 equiv of isobutyric anhydride, 0.5 equiv of 2,6-di-*t*-butyl pyridine and 1 equiv of the additive in both *t*-amyl alcohol and toluene (Table 3).

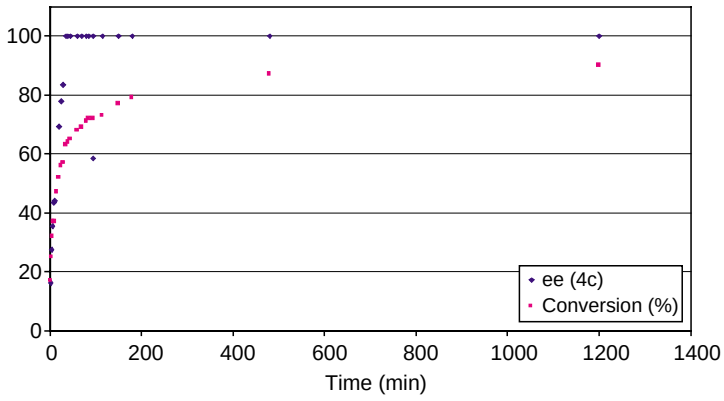
Surprisingly, given that Sc(OTf)$_3$ has been reported to act synergistically with 4-DMAP to accelerate esterification reactions,[17] this additive completely inhibited the reaction

Table 2. Effect of the solvent and auxiliary base on the KR of alcohol **4c** using catalyst **2b**

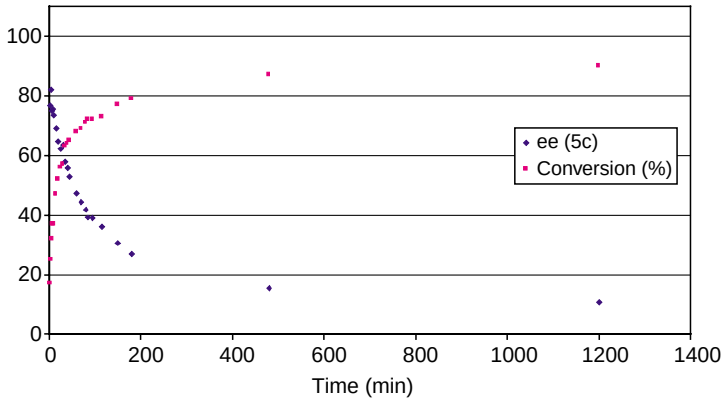


Entry	Base	Solvent	(*S*)-**4c**	(*R*)-**5c**	C (%)[a]	*s*[b]
			ee$_A$ (%)[c]	ee$_E$ (%)[d]		
1	None	*t*-AmOH	72.8	70.6	51	12.6
2		Toluene	68.4	68.6	50	10.8
3		Cyclohexane	46.0	45.4	50	4.1
4		THF	52.0	56.0	48	5.8
5		DMF	31.0	39.0	44	3.0
6		CH_2Cl_2	47.2	63.6	43	7.1
7		DMPU	16.0	34.0	32	2.4
8	NEt_3	*t*-AmOH	71.8	70.8	50	12.2
9		Toluene	69.7	63.7	52	9.1
10	Pyridine	*t*-AmOH	67.4	72.2	48	12.2
11		Toluene	64.0	66.6	49	9.5
12	P4-*t*-Bu-Phosphazene	*t*-AmOH	22.6	46.6	33	3.4
13		Toluene	10.4	17.2	38	1.6
14	2,6-di-(*t*-Bu)-Pyridine	*t*-AmOH	79.8	69.2	54	13.5
15		Toluene	71.0	68.4	51	11.1
16	1,2,2,6,6-PMP	*t*-AmOH	80.0	69.0	54	13.3
17		Toluene	69.0	65.2	51	9.5
18	K_2CO_3	*t*-AmOH	63.4	73.8	46	12.5
19		Toluene	62.6	66.4	49	9.4
20	K_3PO_4	*t*-AmOH	73.6	71.0	51	12.8
21		Toluene	68.0	65.6	51	9.6

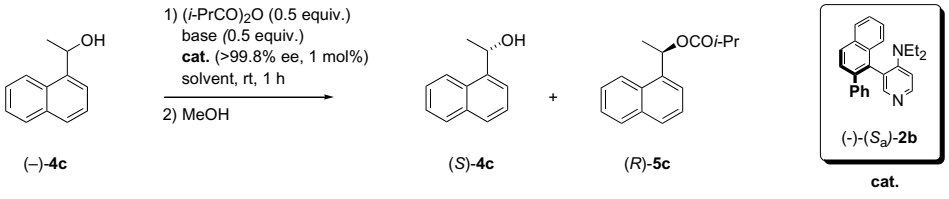
[a] Conversion $C=100\times ee_A/(ee_A+ee_E)$.
[b] Selectivity factor[13] reproducible to ±1 in parallel runs.
[c] ee Of recovered alcohol, established by CSP-HPLC.
[d] ee Of ester, established by CSP-HPLC on derived alcohol following saponification.



Graph 1. ee Of **4c** and % conversion versus time.



Graph 2. ee Of **5c** and % conversion versus time.



Scheme 2.

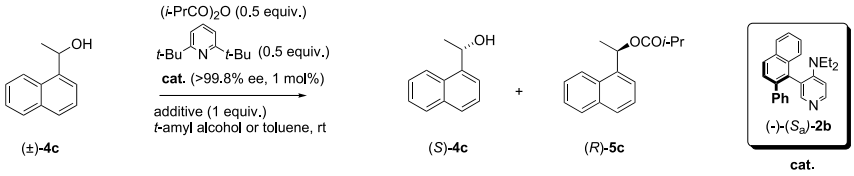
in both solvents (entries 1 and 2). The presence of 4 Å molecular sieves appeared to have no effect on the reaction (entries 3 and 4) and *n*-Bu_4NBr, 1-hydroxypyridine and HMPA were deleterious to the levels of selectivity in both solvents (entries 5–10). However, a small but reproducible increase in selectivity was observed in both solvents when using PPh_3 as an additive giving a selectivity of 15.5 in *t*-amyl alcohol and 13.5 in toluene (entries 11 and 12) compared to 13.5 and 11.1, respectively, when no additive was used (Table 2, entries 14 and 15). However, use of $P(O)Ph_3$, PEt_3, $P(4\text{-}FC_6H_4)_3$, $AsPh_3$ or $BiPh_3$ in place of the PPh_3 did not promote similar or further increases in stereoselectivity (entries 13–20).

Although the role of the PPh_3 is not clear at this time, its use in conjunction with 2,6-di-*t*-butyl pyridine/*t*-amyl alcohol allows for significantly more stereoselective KRs than under the conditions used as a starting point for this investigation (cf. Table 3, entry 11, $s=15.5$ and Table 2, entry 9, $s=9.1$).

3. Conclusions

Two approaches towards the development of efficient conditions for the rapid acylative KR of aryl alkyl *sec*-alcohols using atropisomeric 4-aminopyridine-based nucleophilic catalysts have been explored. Two new catalysts, **2c** and **2d**, containing terphenyl 'blocking groups' have been prepared and evaluated for this purpose. Catalyst **2c** was found to be more enantioselective than **2d**, and is the most selective atropisomeric catalyst yet described for KR of several *sec*-alcohols. The low reactivity of this catalyst, however, militates against its use for rapid KR at rt. Optimisation of the conditions for conducting KRs at rt using previously described catalyst **2b** at the 1 mol% level indicate that PPh_3 (1 equiv) is beneficial for selectivity and allows KR of (±)-1-(naphthyl)ethanol **4c** to occur in <30 min to give $\sim$40% recovered alcohol with $>95\%$ ee (i.e., $s\sim15$). This rapid KR process is expected to facilitate detailed kinetic studies by calorimetry; studies that we hope

Table 3. Effect of some additives on the KR of alcohol **4c** using catalyst **2b**



Entry	Additive	Solvent	(*S*)-**4c**	(*R*)-**5c**	C (%)[a]	*s*[b]
			ee_A (%)[c]	ee_E (%)[d]		
1	$Sc(OTf)_3$	*t*-AmOH	—	—	—	—
2		Toluene	—	—	—	—
3	MS (4 Å)	*t*-AmOH	73.8	72.4	50	13.3
4		Toluene	74.6	68.0	52	11.4
5	*n*-Bu_4NBr	*t*-AmOH	64.2	65.2	50	9.1
6		Toluene	61.4	60.6	50	7.4
7	2-Hydroxypyridine	*t*-AmOH	61.6	68.0	47	9.6
8		Toluene	50.2	56.4	47	5.8
9	HMPA	*t*-AmOH	76.2	69.0	52	11.1
10		Toluene	65.4	64.0	50	8.6
11	PPh_3	*t*-AmOH	81.4	72.4	53	15.5
12		Toluene	82.4	69.2	54	13.5
13	$P(O)Ph_3$	*t*-AmOH	71.0	70.1	50	12.3
14		Toluene	66.0	68.4	49	10.5
15	$AsPh_3$	*t*-AmOH	74.4	66.0	53	10.6
16		Toluene	62.2	63.4	50	7.9
17	$BiPh_3$	*t*-AmOH	69.2	66.3	51	10.0
18		Toluene	57.4	59.8	49	7.0
19	PEt_3	Toluene	64.2	71.0	47	11.1
20	$P(4\text{-}FC_6H_4)$	Toluene	74.0	62.0	54	9.0

[a] Conversion $C=100\times ee_A/(ee_A+ee_E)$.
[b] Selectivity factor[13] reproducible to ± 1 in parallel runs.
[c] ee Of recovered alcohol, established by CSP-HPLC.
[d] ee Of ester, established by CSP-HPLC on derived alcohol following saponification.

will help unravel the complex interplay of factors responsible for catalysis and chirality transfer in these reactions,[18,19] and reveal the role of the PPh_3 additive.

4. Experimental

4.1. General procedures

All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in oven-dried glassware. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogenous materials. Reagents were used as obtained from commercial sources or purified according to known procedures.[20] 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 plates pre-coated with silica gel 60 F_{254}, which were visualised either by quenching of ultraviolet fluorescence ($\lambda_{max}=254$ nm) or by charring with 10% $KMnO_4$ in 0.1 M NaOH. All reaction solvents were distilled immediately before use. Anhydrous CH_2Cl_2 was obtained by refluxing over CaH_2, toluene by refluxing over Na, and THF by refluxing over Na/benzophenone ketyl. Petrol refers to the fraction of light petroleum boiling between 40–60 °C. High-resolution mass spectrometry (HRMS) measurements are valid to ± 5 ppm. CSP-HPLC was performed on a Hewlett Packard Series 1100 instrument. CD spectra were recorded between 280 and 380 nm in CH_3CN ($\sim$1 mg/5 mL) with a Jasco J600 spectropolarimeter using 10 mm quartz cuvettes at 20 °C.

4.1.1. ($\pm$)-Diethyl[3-(2-[1,1′;3′,1″]terphenyl-5′-yl-naphthalen-1-yl)pyridin-4-yl]amine (2c). *Method 1*. To a suspension of 3-bromo-1,5-diphenylbenzene[21] (420 mg, 1.36 mmol) and Mg (49 mg, 2.0 mmol) in THF (6 mL) was added a crystal of I_2 and the mixture sonicated at 20–30 °C for 1 h. The resulting arylmagnesium bromide was transferred via syringe to a solution of 1-(4-diethylaminopyridin-3-yl)naphthalen-2-yl trifluoromethanesulfonate **1b**[12] (192 mg, 0.45 mmol) and $PdCl_2$(dppp) (13 mg, 23 μmol) in THF (2 mL). The resulting brown solution was stirred at rt for 30 min and refluxed for 21 h. After cooling to rt, the reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2. The combined extracts were dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash chromatography ($CH_2Cl_2\rightarrow$EtOAc) to give the recovered triflate **1b**[12] (83 mg, 43%) and the title compound **2c** (52 mg, 23%) as a pale yellow oil. $R_f=0.60$ (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 2976, 1586, 1498, 1265; δ_H ($CDCl_3$, 250 MHz) 0.49 (t, $J=7.0$ Hz, 6H), 2.57–2.91 (4H), 6.57 (d, $J=6.0$ Hz, 1H), 7.30–7.69 (16H), 7.89–8.00 (3H), 8.31 (d, $J=6.0$ Hz, 1H), and 8.32 (s, 1H); δ_C ($CDCl_3$, 63 MHz) 12.1 ($2\times CH_3$), 44.8 ($2\times CH_2$), 112.1 (CH), 122.9 (C_q), 124.2 (CH), 126.1 (CH), 126.6 (CH), 126.8 (CH), 127.2 ($4\times$CH), 127.4 ($2\times$CH), 127.5 (CH), 127.5 (CH), 128.2 (CH), 128.4 (CH), 128.8 ($4\times$CH), 132.4 (C_q), 133.3 (C_q), 134.2 (C_q), 138.4 (C_q),

141.0 (2×C_q), 141.1 (2×C_q), 142.5 (2×C_q), 148.8 (CH), 154.4 (CH), 155.0 (C_q); *m/z* (EI^+) (rel intensity) 504 (50%, MH^+), 503 (95%, M^+), 488 (100), 231 (25), 57 (50); HRMS calculated for $C_{37}H_{32}N_2$ (MH^+) 504.2565, found 504.2555 (Δ=−2.0 ppm).

Method 2. To a solution of 1-(4-diethylaminopyridin-3-yl)naphthalen-2-yl trifluoromethanesulfonate **1b**[12] (0.65 g, 1.5 mmol) in toluene (12 mL) was added K_3PO_4 (0.66 g, 3.0 mmol), LiCl (0.133 g, 3.0 mmol), $Pd(OAc)_2$ (0.035 g, 0.15 mmol), biphenyl-2-yl-dicyclohexylphosphane (0.22 g, 0.6 mmol) and 3,5-diphenylbenzeneboronic acid[22] (0.64 g, 2.3 mmol). The resulting orange solution was stirred vigorously at 80 °C for 20 h and then at reflux for 4 h. After cooling to rt, the reaction mixture was diluted with satd Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3×35 mL). The organic extracts were dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash chromatography (CH_2Cl_2→EtOAc) to give terphenylnaphthylpyridine **2c** (0.39 g, 50%) as a pale yellow oil. Analytical data as above.

4.2. General procedure for the optical resolution of (±)-2

The atropisomers were separated using semipreparative CSP-HPLC by repeated injection of ~2 mg of the racemate in 15 μL of CH_2Cl_2. In all cases the levorotatory enantiomer (−)-**2** eluted first. The enantiomers were further purified by flash chromatography (EtOAc). Analytical CSP-HPLC revealed >99.8% ee for both the levorotatory and the dextrorotatory enantiomers. Assignment of the absolute configuration of the atropisomeric axes follows from correlation of the sign of the Cotton-effect peaks in their CD spectra at ~320 nm with that of biaryl (−)-**2b** for which the absolute configuration has been unambiguously established by X-ray crystallography [as its salt with *N*-Boc-*O*-benzyl-(*S*)-tyrosine].[10,12]

4.2.1. (−)-(S_a) and (+)-(R_a)-Diethyl[3-(2-[1,1′;3′,1″]-terphenyl-5′-yl-naphthalen-1-yl)pyridin-4-yl]amine (2c).

CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/EtOAc/Et_2NH, 85:14.4:0.6; 3 mL min^{-1}; 35 °C; UV detection at 250 nm, reference at 525 nm. (−)-(S_a)-**2c**, white solid. Mp 80.5–82.0 °C, spectroscopic data as above; retention time 20.3 min; $[\alpha]_D^{25}$ −113 (*c* 1.4 in $CHCl_3$); CD λ_{max}/nm 320 (−ive). (+)-(R_a)-**2c**, white solid. Mp 81.0–82.0 °C, spectroscopic data as above; retention time 26.9 min; $[\alpha]_D^{25}$ +112 (*c* 1.4 in $CHCl_3$); CD λ_{max}/nm 320 (+ive).

4.2.2. 3,5-Bis(3,5-dimethylphenyl)benzeneboronic acid (3).

To a solution of 1,5-bis(3,5-dimethylphenyl)-3-bromobenzene[12] (1.0 g, 2.7 mmol) in Et_2O (25 mL) was added *n*-BuLi (1.20 mL, 2.5 M, 3.0 mmol) in hexanes at −78 °C. The reaction was stirred for 0.5 h at −78 °C, warmed to 0 °C over 15 min and then stirred at this temperature for a further 1.5 h. After re-cooling to −78 °C, the reaction mixture was treated with $B(OMe)_3$ (0.9 mL, 3.3 mmol) and allowed to warm to rt over 1.5 h. The reaction mixture was then treated with 1 M HCl (20 mL) and extracted with CH_2Cl_2 (3×30 mL). The organic extracts were dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash chromatography (hexane→EtOAc/hexane, 1:1) to give boronic acid **3** (0.73 g, 81%) as a white powder. Mp 106.5–107.0 °C; R_f=0.50 (EtOAc/hexane, 1:5); ν_{max}/cm^{-1} ($CHCl_3$) 2911, 1603, 1403, 1354, 1263, 844; δ_H ($CDCl_3$, 250 MHz) 2.38 (12H, s), 6.12 (2H, br s), 7.02 (2H, s), 7.30 (4H, s), 7.94 (1H, t, *J*=2.0 Hz), 8.05 (d, *J*=2.0 Hz); δ_C ($CDCl_3$, 63 MHz) 21.4 (4×CH_3), 125.3 (4×CH), 129.1 (3×CH), 132.4 (2×CH), 138.2 (4×C_q), 141.2 (2×C_q), 141.6 (2×C_q) [C_q-B not seen]; *m/z* (CI^+) (rel intensity) 331 (0.5%, MH^+), 304 (50%), 286 [100%, $MH^+ - B(OH)_2$]; HRMS calculated for $C_{22}H_{22}$ {$MH^+ - [B(OH)_2]$} 286.1722, found 286.1711 (Δ=−3.7 ppm).

4.2.3. Diethyl{3-[2-(3,5,3″,5″-tetramethyl[1,1′;3′,1″]-terphenyl-5′-yl)naphthalen-1-yl]pyridin-4-yl}-amine (2d).

To a solution of 1-(4-diethylaminopyridin-3-yl)-naphthalen-2-yl trifluoromethanesulfonate **1b**[12] (0.215 g, 0.5 mmol) in toluene (4 mL) was added K_3PO_4 (0.215 g, 1.0 mmol), LiCl (0.043 g, 1.0 mmol), $Pd(OAc)_2$ (0.011 g, 0.05 mmol), biscyclohexylbiphenylphosphine (0.071 g, 0.2 mmol) and boronic acid **3** (0.25 g, 0.75 mmol). The resulting orange solution was stirred vigorously at 80 °C for 20 h and then at reflux for 4 h. After cooling to rt, the reaction mixture was diluted with satd Na_2CO_3 (20 mL) and extracted with CH_2Cl_2 (3×35 mL). The organic extracts were dried ($MgSO_4$), concentrated in vacuo and the residue purified by flash chromatography (CH_2Cl_2→EtOAc) to give the title compound **2d** (0.110 g, 39%) as a pale yellow oil. R_f=0.65 (EtOAc); ν_{max}/cm^{-1} ($CHCl_3$) 3008, 2931, 1589, 1502, 1379, 909, 850, 824; δ_H ($CDCl_3$, 250 MHz) 0.41 (6H, t, *J*=7.0 Hz), 2.31 (12H, s), 2.56 (2H, dq, *J*=7.0, 7.0 Hz), 2.73 (2H, dq, *J*=7.0, 7.0 Hz), 6.55 (1H, d, *J*=6.0 Hz), 6.91 (2H, s), 6.98 (4H, s), 7.25 (2H, d, *J*=1.0 Hz), 7.39–7.51 (3H), 7.63 (1H, d, *J*=8.0 Hz), 7.80–7.92 (3H), 8.25 (1H, s), 8.30 (1H, d, *J*=6.0 Hz); δ_C ($CDCl_3$, 63 MHz) 12.0 (2×CH_3), 21.4 (4×CH_3), 44.7 (2×CH_2), 112.1 (CH), 122.9 (C_q), 124.3 (CH), 125.1 (4×CH), 126.0 (CH), 126.6 (CH), 126.6 (CH), 127.3 (2×CH), 128.1 (CH), 128.3 (CH), 128.5 (CH), 128.9 (2×CH), 132.4 (C_q), 133.2 (C_q), 134.0 (C_q), 138.2 (4×C_q), 141.1 (2×C_q), 141.2 (2×C_q), 142.1 (C_q), 148.6 (CH), 154.3 (CH), 154.9 (C_q); *m/z* (EI^+) (rel intensity) 561 (MH^+, 50%), 560 (100%, M^+), 545 (60), 531 (23); HRMS calculated for $C_{41}H_{40}N_2$ (M^+) 560.3191, found 560.3204 (Δ=+2.3 ppm).

4.2.4. (−)-(S_a) and (+)-(R_a)-Diethyl{3-[2-(3,5,3″,5″-tetramethyl[1,1′;3′,1″]terphenyl-5′-yl)naphthalen-1-yl]-pyridin-4-yl}amine (2d).

CSP-HPLC conditions: Chiralcel OD (1 cm×25 cm); hexanes/EtOAc/Et_2NH, 89:10.6:0.4; 3 mL min^{-1}; 30 °C; UV detection at 254 nm, reference at 360 nm. (−)-(S_a)-**2d**, colourless oil, spectroscopic data as above; retention time 13.1 min; $[\alpha]_D^{25}$ −90 (*c* 1.6 in $CHCl_3$); CD λ_{max}/nm 320 (−ive). (+)-(R_a)-**2d**, colourless oil, spectroscopic data as above; retention time 21.4 min; $[\alpha]_D^{25}$ +89 (*c* 1.4 in $CHCl_3$); CD λ_{max}/nm 320 (+ive).

4.3. General procedure for catalytic acylative KR (Table 1; except entry 5)

A solution of (±)-alcohol **4** (1.00 mmol), Et_3N (104 μL, 0.75 mmol) and catalyst (−)-(S_a)-**2** (0.01 mmol, >99.8% ee) in toluene (2 mL) was cooled to −78 °C. Ac_2O (83 μL, 0.75 mmol) was then added dropwise with vigorous stirring.

After 6.0–11.3 h (see table) at −78 °C the reaction was quenched by the dropwise addition of MeOH (3 mL), the reaction mixture was allowed to warm to rt over 15 min, and the solvents were evaporated in vacuo. The alcohol and its ester were separated by flash chromatography (petrol/CH_2Cl_2, 2:1→CH_2Cl_2). The ester was hydrolysed by heating at reflux in a solution of 5% NaOH/MeOH (2 mL) for 5 min. After removal of the solvent the residue was passed through a small plug of flash silica eluting with EtOAc. The enantiomeric excesses for the unreacted alcohol and alcohol obtained from hydrolysis of the ester were established by CSP-HPLC.

4.4. Optimal procedure for catalytic acylative KR of (±)-1-(1-naphthyl)ethanol 4c at rt using catalyst 2b (Table 3, entry 11)

To a solution of (±)-alcohol **4c** (600 mg, 3.48 mmol), 2,6-di-*t*-butylpyridine (391 μL, 1.74 mmol), triphenylphosphine (915 mg, 3.48 mmol) and catalyst (−)-(S_a)-**2b** (12.3 mg, 3.5 μmol, >99.8% ee) in *t*-amyl alcohol (7 mL) was added (i-PrCO)$_2$O (263 μL, 1.74 mmol) dropwise with vigorous stirring. After 1 h the solvent was evaporated in vacuo and the residue purified by flash chromatography (petrol/CH_2Cl_2, 2:1→CH_2Cl_2) to give alcohol **4c** as a colourless oil (280 mg, 47, 81.4% ee by CSP-HPLC) and its ester **5c** as a colourless oil (438 mg, 52, 72.4% ee as determined following hydrolysis then CSP-HPLC, as above).

4.5. CSP-HPLC analysis of chiral alcohols (Tables 1–3).

4.5.1. 1-Phenylethanol 4a. Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 99:1; 1 mL min^{-1}; 0 °C; UV detection at 211 nm, reference at 525 nm. Retention times: 31 min (*R*), 49 min (*S*). Assigned by comparison with authentic samples supplied by Aldrich.[23]

4.5.2. 1-Phenylpropanol 4b. Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 97:3; 1 mL min^{-1}; 25 °C; UV detection at 211 nm, reference at 525 nm. Retention times: 15 min (*S*), 17 min (*R*).[24]

4.5.3. 1-(1-Naphthyl)ethanol 4c. Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 90:10; 1 mL min^{-1}; 25 °C; UV detection at 211 nm, reference at 525 vnm. Retention times: 12 min (*S*), 24 min (*R*).[23]

4.5.4. 1-(2-Tolyl)ethanol 4d. Chiralcel OD (1 cm×25 cm); hexanes/*i*-PrOH, 99:1; 3 mL min^{-1}; 30 °C; UV detection at 220 nm, reference at 360 nm. Retention times: 6.1 min (*S*), 26.4 min (*R*).[25]

4.5.5. 1-(2-Methoxyphenyl)ethanol 4e. Chiralcel OD (0.46 cm×25 cm); hexanes/*i*-PrOH, 90:10; 1 mL min^{-1}; 25 °C; UV detection at 211 nm, reference at 525 nm. Retention times: 12 min (*S*), 19 min (*R*).[23]

4.5.6. 1-(2,6-Dimethylphenyl)ethanol 4f. Chiralcel OD (1 cm×25 cm); hexanes/*i*-PrOH, 93:7; 3 mL min^{-1}; 30 °C; UV detection at 210 nm, reference at 360 nm. Retention times: 8.6 min (*R*), 10.3 min (*S*).[23]

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